Title
Sudden cardiac death: Directing the scope of resuscitation towards the heart and brain

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Full Title: Sudden Cardiac Death: Expanding the Scope of Resuscitation Toward the Heart and Brain

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Short Title: Aggressive Integrated Resuscitation

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ABSTRACT

Background. The fundamental goal of cardiopulmonary resuscitation (CPR) is recovery of the heart and the brain. This is best achieved by 1) immediate CPR for cerebral perfusion, 2) correction of the cardiac cause of cardiac arrest, and 3) controlled cardioplegic cardiac reperfusion. Failure of such an integrated therapy may cause permanent brain damage despite cardiac resuscitation.

Methods. This strategy was applied at 4 centers to 34 sudden cardiac death patients a) after acute myocardial infarction (n=20), b) "intraoperatively" following successful discontinuation of cardiopulmonary bypass (n=4), and c) "postoperatively" in surgical ICU (n=10). Each witnessed arrest patient failed conventional CPR with ACLS interventions, including defibrillation. Cardiac arrest interval was 72±43 minutes, (20-150 minutes). Compression and drugs maintained BP>60 mmHg to avoid cerebral hypoperfusion. OR transfer was delayed until blood pressure was monitored. In 4 patients femoral bypass maintained perfusion while angiographic diagnosis was made.

Results. Management principles included no repeat defibrillation after 10 minutes of unsuccessful CPR, catheter-monitored peak BP>60 mmHg during diagnosis and OR transit, left ventricular venting during cardiopulmonary bypass and 20 minutes global and graft substrate enriched blood cardioplegic reperfusion. Survival was 79.4% with two neurological complications (5.8%).

Conclusions. Recovery without adverse neurological outcomes is possible in a large number of cardiac arrest victims following prolonged manual CPR. Therapy is directed toward maintaining a monitored peak BP above 60mmHg, determining the culprit cardiac cause, and correcting it with controlled reperfusion to preserve function.

Condensed Abstract. This study reports an aggressive approach to sudden death from witnessed arrest in 34 patients, undergoing CPR for 72±43 minutes. There was 79.4% survival and only 5.8% permanent neurological damage. This salvage of heart and brain was due to integration of a) insuring brain perfusion during CPR, b) providing early body and brain perfusion with CPB while defining cardiac pathology, and c) applying specific cardioplegic management during revascularization of the injured heart.

KEYWORDS

sudden death; cardiopulmonary resuscitation; coronary angiography; cardiopulmonary bypass; controlled myocardial reperfusion

TEXT

Each year in the United States, approximately 450,000 persons die of unexpected sudden death in an emergency department or before reaching a hospital (1). Cardiac causes have been identified in 50% to 78% of cases(2-5). Dysrhythmia accounts for 47% of these, acute ischemia or infarction for 43%, and myocardial failure for the remainder (6). Ventricular fibrillation (VF) or tachycardia (VT) has been observed in 30% to 43% of cardiac arrest victims and asystole in 15% to 48% (2; 7-9). Survival to discharge with out-of-hospital cardiopulmonary resuscitation (CPR) ranges between 5% and 21%.(4; 7; 10; 11). In-hospital cardiac arrest also carries a poor prognosis in spite of trained personnel to initiate defibrillation. CPR restores blood flow in 44% of patients but only 15% survive to discharge.(12-16).

The etiology of cardiac arrest and the secondary organ effects after resuscitation are factors that influence survival (17). Successful defibrillation often results in a stunned heart with low cardiac output. The brain is particularly sensitive to poor perfusion and is often injured. A third of patients who are resuscitated have evidence of significant neurological dysfunction (18). If coma follows successful cardiac resuscitation, 73% of patients are significantly impaired neurologically (19).

We have developed an aggressive strategy to witnessed death of presumed cardiac origin. Our approach involves three key components. The first is CPR with monitoring and treatment of blood pressure to insure brain perfusion. The second is conversion to cardiopulmonary bypass as rapidly as possible to insure both brain and total body perfusion. This can be achieved via femoral (femoral bypass) or great vessel cannulation via sternotomy. The third is prompt diagnosis and coronary revascularization utilizing a myocardial protection strategy that both limits further damage during the requisite period of aortic clamping needed for coronary grafting and restores global cardiac function (20). This is accomplished by the infusion of amino acid enhanced warm blood cardioplegia, which has been shown to recover function of the acutely ischemic or infarcted myocardium despite prolonged CPR (21; 22).

Four centers applied these resuscitation methods. Patients in this review experienced witnessed sudden death (1) in or out of the hospital after acute myocardial infarction, (2) in the operating room immediately following cardiac surgery, and (3) in the postoperative intensive care unit following cardiac surgery. Witnessed death was defined as the onset of patient collapse in the out-of-hospital setting, or the onset of ventricular fibrillation, or asystole in the hospital setting.

Methods.

A total of 34 sudden death victims were treated between 1992 and 2001. Mean age was 63±9.3 years. Immediate CPR was applied to all patients. Defibrillation and drug infusion per ACLS protocol failed to restore perfusion in every case. Acute evolving myocardial infarction was seen in 20 patients. Three arrived by helicopter in full arrest undergoing CPR. Coronary anatomy was defined in the catheterization laboratory during arrest and chest compression. One of these three patients with out of the hospital infarction was placed on cardiopulmonary bypass via femoral cannulation in the catheterization laboratory. The remaining 17 patients arrested in the catheterization laboratory following elective percutaneous coronary intervention and two of these were placed on femoro-femoral bypass in the catheterization laboratory. A second group of 4 patients experienced cardiac arrest in the operating room following cardiac surgery and the discontinuation of cardiopulmonary bypass (CPB). After chest closure, ventricular fibrillation required return of CPB. The third group of 10 patients arrested in the intensive care unit (ICU) after coronary bypass surgery (CABG). They were taken to the operating room or placed on CPB in the intensive care (one patient) unit prior to transfer to the operating room (Table 1).

Excluded from this study were 15 cardiogenic shock patients who had acute infarction at home, in the hospital, or in the catheterization laboratory where successful defibrillation was achieved prior to transit to the operating room.

Controlled myocardial reperfusion was applied in all cases. CPB was instituted with mild systemic hypothermia (34 degrees C) and left ventricular venting through the right superior pulmonary vein. The aorta was clamped and warm (37º C) enriched (aspartate and glutamate) blood cardioplegia was infused antegrade into the aortic root and then retrograde into the coronary sinus in a manner that is detailed in prior publications (Table2) (23). If primary coronary bypass was performed, or if a prior graft was revised, a maintenance dose of low potassium cold blood cardioplegia (4º C) was then administered through the same routes. Coronary bypass grafts were constructed and maintenance cardioplegia delivered in a sequence previously described as the "integrated method" (20). A 20-minute infusion of warm enriched blood cardioplegia was delivered followed by antegrade warm blood perfusion until adequate cardiac contractility resumed. Finally, the aortic clamp was removed and the patient weaned from cardiopulmonary support after 30 more minutes of CPB support.

Myocardial management was the same among patients who arrested in the ICU following CABG even if patency of the grafts was established by inspection and palpation. Warm enriched blood cardioplegia was administered antegrade at a flow of 150ml/min for a total period of 20 minutes. Left ventricular venting was used to prevent distension and increased oxygen utilization. The aortic clamp was released and the patient weaned from cardiopulmonary bypass after 30 minutes.

Results.

The period of cardiac arrest averaged 72±43 minutes (range 20-150 minutes). At the time CPB was initiated, ventricular fibrillation was present in 26 patients and asystole in 8. A peak blood pressure of approximately 60 mmHg was achieved via CPR, and transfer to the operating room was deferred until the blood pressure was monitored. For example, we once delayed transfer to the operating room for 30 minutes until a satisfactory arterial blood pressure was confirmed by arterial cannulation. An average of 3.0±0.1 grafts were constructed in patients undergoing coronary bypass grafting. All 10 postoperative patients who developed sudden cardiac arrest had satisfactory hemodynamics prior to the onset of sudden intractable ventricular dysrhythmia. Intraoperatively, only one patient required regrafting due to acute graft occlusion. Intra-aortic balloon pumping (IABP) was used peri operatively in 20 patients (58%). There were no specific indications for IABP use. This was left to the discretion of the operating surgeon. In most cases, however, it was placed after the discontinuation of cardiopulmonary bypass to assist in cardiac recovery.

Seven patients died yielding a survival to discharge from hospital of 79.4%. Cardiogenic shock was the cause of death in 5 patients. One patient had reoperation for sternal dehiscence, required colectomy for perforation, developed mediastinitis and died 87 days postoperatively. Another patient had a massive cerebrovascular accident and died early postoperatively.

Neurological complications were rare. One patient had seizures for two days possibly related to lidocaine required for control of dysrhythmias. There were two permanent adverse neurological outcomes (5.8%). As described above, one patient with a history of stroke and severe peripheral vascular disease recovered cardiac function but suffered a massive stroke postoperatively and died. Another patient became paraplegic postoperatively. This patient presented by helicopter following infarction in shock. CPR was sustained for one hour during transport during unsuccessful attempts to cardiovert ventricular fibrillation. Femoral bypass was established in the catheterization laboratory while coronary pathology was defined. Three coronary grafts were constructed and an IABP placed in the ascending aorta due to severe peripheral vascular disease. The patient recovered full cardiac function but suffered from spinal cord ischemia and has remained hemiplegic in the lower extremities five years later. The remaining patients had grossly normal neurological function and ambulated normally at the time of hospital discharge. Extensive neuro-cognitive function was not done in any patient.

Discussion.

About 40% of cardiac arrest patients respond acutely to resuscitative measures but approximately 15% survive to hospital discharge (17). Long-term survival data following discharge from successful resuscitation demonstrate a poor prognosis. One-year mortality of 25% has been reported following cardiopulmonary resuscitation and discharge from hospital (24). The mortality

rose to 46% at 2.5 years (25). The underlying cause of cardiac arrest was not corrected in these series and may have impacted the long-term outcomes.

Even more troubling are the neurological sequelae; one third of those surviving have evidence of significant dysfunction (18). Investigators of the Brain Resuscitation Clinical Trials I and II reported that among 774 patients who were initially comatose after successful resuscitation, only 27% recovered good neurological function (19).

These adverse neurological outcomes suggest that conventional treatment may sometimes save the heart but brain injury is common. Our strategy was devised to a) assure adequate brain perfusion at the onset of witnessed arrest, b) maintain systemic and brain perfusion as the diagnosis and management of the underling event that produces arrest is discovered and corrected, and c) provide return of cardiac function following repair to avoid a low output syndrome that can further damage the brain.

CPB SUPPORT DURING ARREST

Sudden death victims placed on CPB without correction of the underlying pathology do not survive as demonstrated in two studies. In one, emergency CPB was applied to 10 cardiac arrest patients in the emergency room. The time of witnessed arrest prior to CPB was 32.0±13.6 minutes. Seven patients were weaned from CPB with intrinsic spontaneous circulation. In spite of successful

hemodynamic resuscitation, there were no long-term survivors (26). A similar experience showed no survivors among 29 cardiac arrest patients placed on portable CPB when the cardiac pathology was not corrected (27).

Despite poor clinical results in patients treated with CPB alone, this modality can preserve brain function during resuscitation. Investigators induced VF in dogs for 4 minutes and then performed closed chest CPR for 30 minutes. CPB was then established for early defibrillation and assisted circulation for one hour. All animals recovered and were neurologically normal (28). In another study, dogs underwent 15 minutes of normothermic ventricular fibrillation without CPR followed by femoral cannulation and CPB. This support restored cerebral blood and myocardial blood flow, even in the absence of spontaneous cardiac contractions. Electroencephalographic intermittent burst waves appeared 90±25 min after the start of resuscitation. At 131±28 min continuous waves returned. The mean neurological deficit score was 100.6 (normal: 0, brain death: 500) (29). This recovery is surprising in light of the perception that irreversible damage follows 4 minutes of arrest, and illustrates the effective use of CPB in maintaining cerebral blood flow.

Our findings in this study suggest that CPB may be useful as part of an integrated strategy to assure brain perfusion until correction of the underlying cardiac defect. In the future, the duration of cerebral anoxia that is tolerated in

humans may be further extended by controlling the whole body reperfusate after cardiopulmonary collapse, as has been shown in our recent animal studies (30).

CORRECTION OF UNDERLYING PATHOLOGY

Correction of the underlying pathology is crucial for survival when emergency percutaneous CPB support is applied. One series reported 11 patients in cardiac arrest refractory to conventional resuscitation measures. All 7 patients with correctable disease treated by emergency angioplasty or bypass grafting survived to discharge. Patients with unsuitable anatomy for correction died (31). One of the largest series of emergency femoral bypass included 144 patients over a 4-year period. A total of 31% of patients were discharged from the hospital. Among 55 patients who were surgically corrected, 24 (44%) were discharged from the hospital. Only 3 patients (10%) were discharged among the 30 patients in whom no corrective action was taken (32). Similar findings were noted in a multi-institutional review of emergency portable CPB in the treatment of cardiac arrest among 187 patients in 17 centers. Survival was 77% among patients in whom corrective action could be taken vs. 50% among those in whom the underlying cause of arrest was not repaired (33). Another series examined the outcome of 36 patients treated with emergency CPB who suffered cardiac arrest outside of the hospital and showed the value of correcting the cause of cardiac arrest. CPB, coronary reperfusion therapy and mild hypothermia were used. Patients with suspected acute coronary syndrome underwent immediate coronary angiography (34). Successful coronary reperfusion was achieved in

about 90% of cases. Mild hypothermia (34º C) with coil cooling for two days resulted in good recovery in 52% of patients demonstrating the protective effect of this method. However, hypothermia contributed to significant morbidity. These approaches were not used in our patients because cardiac resuscitation with a warm reperfusate allowed prompt cardiac recovery.

CONTROLLED REPERFUSION

Substrate-enhanced warm blood cardioplegic reperfusion is called "controlled reperfusion". It was devised and verified in our laboratory.(35; 36). In one study, dogs were subjected to 2 hours of irreversible ischemic fibrillation (22). We showed that adequate perfusion pressure during CPR improves both subendocardial and possibly cerebral flow, which may reduce brain ischemia during manual circulatory support (37). Restoration of coronary blood flow alone after temporary support by CPB with no effort to control reperfusion allowed 80% survival and moderate residual cardiac dysfunction. In contrast, delivery of controlled cardioplegic reperfusion, as is done during elective coronary bypass grafting, allowed 100% survival and recovery of normal stroke work index.

The contents and methods of controlled reperfusion have been previously described in detail (38). The components (Table 2) and their effect are presently reviewed. High potassium blood cardioplegia maintains cardiac arrest avoiding the sudden cellular calcium accumulation and disruption of the sarcolemma, which are observed when re-oxygenation allows premature myocardial

shortening to resume. Low calcium is used to limit calcium loading during the conditions of impaired ionic balance in the early period of reperfusion. Diltiazem is added to further limit ionic calcium entry into the cells. Amino acid substrates, aspartate and glutamate, increase the energy-depleted heart's ability to utilize oxygen and hasten ionic recovery. Normothermia provides the correct environment for the return of enzymatic function. Hyperosmolarity reduces edema. Alkalosis with tromethamine (THAM) is used to hasten enzymatic recovery vs. bicarbonate, which yields more CO_2 and acidosis. Such acidification accentuates subsequent calcium accumulation via the energy independent sodium calcium exchanger that is blocked by limiting sodium hydrogen exchange (39).

Sustained perfusion and immediate correction of the underlying cardiac pathology were applied in all of our patients based on the effectiveness of these strategies from our prior clinical studies (23; 40). We studied controlled reperfusion in both cardiac surgery and acute infarction (35; 41). In 1978 we described blood cardioplegia for reperfusion and this method is now used as a standard cardioplegic solution in the majority of centers worldwide (42). In 1986, we reported immediate recovery of regional contractility up to 6 hours after infarction by controlling the conditions of reperfusion and the reperfusate composition (22).

Our findings also applied to ventricular fibrillation induced by coronary occlusion. Controlled myocardial reperfusion following infarction resulted in excellent survival and restoration of cardiac function (43). In 1992 we reported 14 patients with intractable ventricular fibrillation (30–50 minutes) who underwent emergency CPB and controlled reperfusion. Complete hemodynamic recovery was seen in 13 patients. Survival was 79% with only two neurological events (40). Our multi-institutional experience with controlled reperfusion for acute coronary occlusion among 156 patients was reported in 1993 and included a subset of 12 patients brought to the operating room with irreversible ventricular fibrillation (23). Ten of these patients had complete cardiac and neurological recovery. Controlled reperfusion achieved 87% recovery of contractility in the infarcted segment confirming the usefulness of this practice.

Other investigators have demonstrated the value of controlled reperfusion in patients who had VF unresponsive to CPR after CABG (44). Among a group of 9 survivors, 3 received a cardioplegic reperfusate, while none of 7 non-survivors was given controlled reperfusion. Conversely, a recent report describes 167 patients who underwent emergency CABG in cardiogenic shock (n=167) or during CPR (n=92) (45). These patients were not placed on temporary CPB and did not undergo controlled reperfusion. Hospital mortality was 43% among CPR patients (46). There was only 27% freedom from alive hospital discharge after 30 days, presumably from ongoing cardiac failure.

In the current study, we found only one occluded graft among patients returned to the surgery from operating room or the intensive care unit following coronary bypass. The native coronary artery was regrafted. In the remaining 13 patients, the grafts were assessed and found to be patent. Immediate CPB support with warm enhanced blood cardioplegia resulted in cardiac recovery in all but one patient who died of cardiogenic shock. We recommend that patients who arrest in the intensive care unit be promptly returned to the operating room even if defibrillation attempts fail. Continued monitored CPR assuring a peak blood pressure of 60 mmHg should be sustained en route to the operating room where CPB can be instituted. As we have shown, femoral cannulation in the intensive care unit can also be effective prior to transport if available. Often patients in the intensive care unit have antecedent hemodynamic deterioration, electrocardiographic evidence of ischemia, or intractable dysrhythmia. Angiographic diagnosis can delay recovery and is not advised. Rapid CPB, reconstruction of occluded grafts if necessary, and myocardial reperfusion with warm controlled substrate enhanced cardioplegia, provides an excellent opportunity for successful weaning from support. Even in the absence of an occluded or twisted graft, such an approach has been shown to salvage myocardial function.(43)

AGGRESSIVE CPR

We believe that aggressive monitored CPR is vital to sustain cerebral perfusion. One patient was not moved from the intensive care unit during CPR

until it was established by catheter monitoring that the peak blood pressure was at least 60 mmHg. This was considered a requirement to prevent neurological injury from poor perfusion. This strategy resulted in adverse neurological outcome in only 2 of our 34 patients in spite of relatively long arrest times that averaged 72±43 minutes (range 20-150 minutes).

The 79.4% survival and minimal permanent neurological damage in our patients is a dramatic improvement from results reported in the past. In most instances, ongoing CPR is abandoned when asystole (occurring in 8 of our patients) follows unsuccessful cardioversion. We attribute this success to an approach that salvages both the heart and brain by a) insuring brain perfusion during CPR, b) providing early body and brain perfusion with CPB while defining cardiac pathology, and c) applying specific cardioplegic management during revascularization of the injured heart. We believe that failure to integrate these treatment phases may have contributed to the unsuccessful results enumerated in our literature review, and credit the synthesis of these integrating factors for these unprecedented outcomes.

LIMITATIONS OF STUDY

The study population was heterogeneous. Patients selected for this therapy were those in whom the cause of sudden death was thought to be cardiac in origin. Only the three patients who presented with sudden death via helicopter had no known cause of sudden death. Diagnosis of cardiac cause

was urgently confirmed in these cases during catheterization. The remaining 31 patients were already hospitalized with the diagnosis of coronary disease. Therefore, application of our therapy cannot be recommended to all victims of sudden cardiac death. We excluded patients in an irreversible status, where arrest became the terminal event.

Institutional Review Board (IRB) approval was not obtained. This was not a prospective study with strict inclusion or exclusion criteria. Patients were treated by our method when absolute failure was noted by all conventional methods of resuscitation. Table 1 shows that 8 patients were asystolic and 26 patients had ventricular fibrillation which could not be cardioverted. The operators then proceeded with a method which had been described in prior literature and shown to have a chance at recovery. No patient was subjected to this therapy if CPR and defibrillation returned cardiac activity.

During resuscitation, we maintained a peak pressure of 60mmHg to maintain adequate brain flow. The optimal perfusion pressure and adjunctive measures must be further evaluated. Hence the only criteria for inclusion was witnessed death with CPR, monitored BP≥60 mmHg, accurate diagnosis, and reperfusion with substrate enriched cardioplegia previously described for treatment of acute myocardial infarction.

Postoperative outcomes are limited to survival and neurological outcome. The hemodynamic response of our therapy has been previously described (23). The main emphasis of this report is to demonstrate the feasibility of aggressive intervention in patients who fail conventional CPR measures by prompt extracorporeal circulation and controlled myocardial reperfusion.

Conclusions.

Our additions to conventional CPR therapy for sudden death victims have resulted in improved survival with few adverse neurological outcomes. This strategy, based on experimental and clinical evidence employs external chest compression until CPB can be instituted. Diagnosis of a reversible cardiac cause mandates emergency angiography even during life support by CPB. Correction of the underlying cardiac pathology by surgical revascularization and controlled reperfusion offers hope for these patients.

TABLE 1: Arrest Site, Rhythm and CPB Method

	Hospital MI or MI in Catheterization Laboratory	Operating Room	Postoperatively in ICU
Site of arrest	20	4	10
Rhythm			
VF	14	4	8
Asystole	6	0	2
CPB method			
femoral bypass	3	0	1
sternotomy	17*	4*	9*

*in operating room

**** femoral bypass: Cannulation of femoral vessels to institute cardiopulmonary bypass**

***** Cannulation of the aorta and right atrium to institute cardiopulmonary bypass**

TABLE 2: Warm Blood Cardioplegia Reperfusate *

Cardioplegia Additive	Volume added (ml)	Component Modified	Final Concentration
KCl (2 mEq/mL)	40	K^+	20-25 mEq/L
THAM (o.3 mol/L)	225	pH	7.5-7.6
CPD	225	Ca^+	0.1-0.25mmol/L
Glucose	40D50W	Glucose	>400 mg%
Osmolarity	-----	Osmolarity	380-400 mOsm
Glutamate	125	Substrate	13 mmol/L
Aspartate	125	Substrate	13 mmol/L
5% dextrose and H_2O	250	-----	-----
Diltiazem	300µg/kg body weight		

*This crystalloid component is mixed with blood in a 4:1 ratio (Blood / Cardioplegia), and delivered at 150ml/min for 20 minutes

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