

Intravenous Adrenaline or Vasopressin in Sudden Cardiac Arrest: A Literature Review

M E H Ong,*^{MBBS, FRCS (Edin) (A&E)}, S H Lim,**^{FAMS, MBBS, FRCS (Edin) (A&E)}, V Anantharaman,***^{FAMS, MRCP, FRCS (Edin) (A&E)}

Abstract

Introduction: The chain of survival concept implies that provision of early access, early advanced care, including early intravenous drugs would improve survival in sudden cardiac arrest. Intravenous adrenaline (epinephrine) has been used as the drug of choice since 1906. What is the evidence for its effectiveness? Is vasopressin a better alternative? **Methods:** We performed a systematic literature search in order to answer these questions. Evidence from the clinical trials that have been conducted on this subject was reviewed. **Results:** Experimental evidence confirms the beneficial effect adrenaline has on coronary perfusion pressure. However, adrenaline has not been shown conclusively to improve survival in clinical trials. Extensive trials have also failed to show any benefit of high-dose adrenaline over standard doses. Vasopressin seems to be more effective than adrenaline in animal studies for treatment of cardiac arrest due to resistant ventricular fibrillation. However, it has yet to be proven to be superior to adrenaline in clinical trials. **Conclusion:** More research is needed into this area, especially randomised controlled trials studying the effectiveness of vasopressin. Meanwhile, in order to improve survival from sudden cardiac arrest, continuing effort should be made to achieve early initiation of cardiopulmonary resuscitation, early defibrillation and early advanced care.

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Key words: Epinephrine, Pre-hospital arrest, Survival, Ventricular fibrillation

Introduction

Of the approximately 15,000 deaths that occur in Singapore every year, about 25% are from cardiac causes;¹ of which, some 30% to 40% occur suddenly, outside of a hospital. The mechanism of death is usually a fatal arrhythmia, most often ventricular tachycardia or fibrillation.² Similarly, in the USA, 300,000 people die every year from sudden cardiac arrest,³ about one third of all cardiovascular deaths.

In the chain of survival concept,⁴ provision of early access, early cardiopulmonary resuscitation (CPR), early defibrillation and early advanced care, including intravenous drugs, should improve survival in sudden cardiac arrest. Survival rates for pre-hospital cardiac arrest vary in published reports from 2% to over 20%.⁵ Comparison of data from various Emergency Medical Systems (EMS) seems to indicate that early provision of pre-hospital advanced life support, including early intravenous drugs, does improve survival.⁵

Intravenous medications, especially adrenaline (epinephrine), have been used since 1906⁶ to treat cardiac arrest. However, in recent years, the effectiveness of adrenaline in cardiac arrest has been greatly debated and questioned. The International Liaison Committee On Resuscitation (ILCOR) International Emergency Cardiac Care (ECC) and CPR Guidelines 2000 (G2000)⁷ emphasise the importance of a rational, evidence-based approach in selecting drugs for resuscitation. Adrenaline is currently indicated for cardiac arrest from ventricular fibrillation, pulseless ventricular tachycardia, asystole or pulseless electrical activity. These guidelines also introduce a new agent, vasopressin, as an alternative to adrenaline for ventricular fibrillation. The Singapore National Resuscitation Council 2001 guidelines⁸ also list adrenaline and vasopressin as acceptable alternatives for ventricular fibrillation. What is the evidence available regarding these 2 agents?

Currently in Singapore, no intravenous drugs are given to

* Registrar

** Consultant

Department of Emergency Medicine
Singapore General Hospital

*** Senior Consultant and Head

Department of Emergency Medicine, Singapore General Hospital
Clinical Associate Professor

Faculty of Medicine, National University of Singapore

Address for Reprints: Dr Marcus Ong Eng Hock, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

E-mail: gaeoh@sgh.com.sg

cardiac arrest patients pre-hospital. Unpublished data estimate survival for pre-hospital cardiac arrest at between 2% and 3% for Singapore. Plans are underway to incrementally introduce pre-hospital advanced life support, including intravenous drugs in cardiac arrest. However, the question remains, what should be the drug of choice – adrenaline or vasopressin?

Methods

We performed a systematic literature search in order to answer these questions. We conducted an on-line search using PubMed and Ovid search vehicles with the following keywords: adrenaline (epinephrine), vasopressin, cardiac arrest and ventricular fibrillation. Articles selected for review included all human randomised/pseudo-randomised controlled trials, case-controlled studies and case series (more than 5 patients). Other selection criteria were: intravenous route of drug administration, adrenaline or vasopressin was given, patients had to be in cardiac arrest and arrest could be pre-hospital or in-hospital. Each of these trials was carefully studied to assess validity of study results and conclusions.

Results

A total of 811 articles were found using the search words “cardiac arrest/ventricular fibrillation” and “adrenaline/epinephrine”; of these, only 22 fulfilled our selection criteria and were reviewed. These studies are summarised in Table I.

For the search words “cardiac arrest/ventricular fibrillation” and “vasopressin”, 63 articles were found. Of these, only 5 fulfilled our selection criteria and were reviewed (Table I). However, relevant experimental work on vasopressin has also been included in the discussion below.

There were 10 studies comparing high-dose adrenaline against standard dose adrenaline, involving a total of 8467 patients in these studies. There were 4 trials comparing vasopressin and adrenaline with a total of 260 patients, 3 trials comparing methoxamine and adrenaline (327 patients), 1 trial comparing phenylephrine and adrenaline (65 patients) and 1 trial comparing lignocaine and adrenaline (199 patients). There was 1 study comparing noradrenaline, standard dose adrenaline and high-dose adrenaline (816 patients) and 1 study comparing placebo, adrenaline and high-dose adrenaline (194 patients). There were also 2 observational studies on adrenaline (1322 patients) and a case series on vasopressin (8 patients). Further details of these trials are discussed below.

Discussion

Adrenaline

Historically, intravenous adrenaline has been the

recommended drug of choice in cardiac arrest since 1906, when Crile and Dolley⁶ showed that it restored spontaneous circulation in canines having cardiac arrest induced by anaesthetic drugs and hypoxia. In 1963, Redding and Pearson³² also found that 1 mg of adrenaline was effective in resuscitating dogs weighing approximately 10 kg (dose 0.1 mg/kg). Intracardiac injection of adrenaline for cardiac arrest was introduced and widely practiced by 1979.³³ However, concerns with inadvertent cardiac injury³⁴ from this procedure led to the adoption of intravenous adrenaline as the recommended treatment by 1986.³⁵

Adrenaline is thought to aid resuscitation, mainly by its alpha-adrenergic effects. This peaks 2 to 3 minutes following an intravenous bolus and returns to baseline by 5 minutes.³⁶ Several animal studies have shown that adrenaline increases systemic arteriolar constriction, increases vascular tone, improves coronary and cerebral perfusion pressure, and shunting blood to the heart and brain.^{37–40} Coronary perfusion pressure is thought to be one of the best predictors of return of spontaneous circulation in animals^{41–47} and humans.^{48,49}

However, the adverse effects of adrenaline include decreased total forward cardiac output, increased myocardial oxygen consumption and myocardial dysfunction post-resuscitation.^{40–50} Increased intra-pulmonary shunting⁵¹ also contributes to the dose related fall in end-tidal carbon dioxide concentration that has been observed.^{50,52,53} Prolonged muscular and mesenteric vasoconstriction also leads to increased lactic acid production and metabolic acidosis. Both the severity and duration of these physiological impairments have been found to correlate with the total cumulative dose of adrenaline. This has especially been found to be true where high cumulative doses (>15 mg) of adrenaline have been used.¹⁹ Post-resuscitation, compared to patients receiving less than 15 mg adrenaline, those who received >15 mg cumulative dose had significantly lower cardiac index, lower systemic oxygen consumption, lower systemic oxygen delivery ($P < 0.1$) and significantly higher systemic vascular resistance index, higher lactic acid ($P < 0.03$) and lower 24-hour survival (85% versus 41%, $P < 0.002$).

Regarding human clinical studies, we comment first on 2 observational studies. Walraven et al²⁹ found in a prospective observational study of 773 patients with cardiac arrest that the use of adrenaline, atropine, bicarbonate, calcium (all $P < 0.001$) and lignocaine ($P < 0.1$) was associated with a decreased chance of successful resuscitation. Controlling for significant patient factors (age, previous cardiac disease etc) and arrest factors (initial rhythm, cause of arrest etc), multivariate logistic regression showed a significant association between use of adrenaline and unsuccessful resuscitation (OR, 0.08; 95% CI, 0.04–

TABLE I: STUDIES INVOLVING ADRENALINE/VASOPRESSIN IN CARDIAC ARREST

Year	Journal	Author	Patients	Intervention	Method	Results	Comments
1985	Acta Anaesthesiol Scand	Silfvast et al ⁹	Pre-hospital arrest, n = 65	Adrenaline (A) vs phenylephrine (P)	Randomised clinical trial	ROSC; A–10 patients (28%) vs P–9 patients (31%)	Phenylephrine no better
1988	Ann Emerg Med	Turner et al ¹⁰	Inpatient arrest, n = 80	Adrenaline vs methoxamine	Randomised clinical trial	Survival <1 hour, 22 methoxamine, 22 epinephrine	Methoxamine no better
1989	Ann Emerg Med	Olson et al ¹¹	Pre-hospital VF, n = 102	Adrenaline (A) vs methoxamine (M)	Randomised clinical trial	Discharged alive = no difference A (19.6%), M (7.8%) (<i>P</i> >0.05)	Methoxamine no better
1990	Circulation	Weaver et al ¹²	Pre-hospital VF, n = 199	Adrenaline (A) vs lignocaine (L) vs historical controls (bicarbonate only)	Randomised clinical trial	Discharged alive = A vs L no difference Survival to ED = Study (50%) < Historical (64%) (<i>P</i> >0.005)	Adrenaline worse than no treatment
1990	Chest	Roberts et al ¹³	Inpatient arrest, n = 310	Adrenaline	Observational	Strong predictor of mortality (<i>P</i> = 0.0003)	Observational Confounding?
1991	Ann Emerg Med	Goetting et al ¹⁴	Inpatient paediatric arrest, n = 40	High dose vs standard adrenaline	Non-randomised control trial	14 HDE (70%) had ROSC, none of SDE did (<i>P</i> <0.001), 8 survived to discharge	High dose better
1991	Acta Anaesthesiol Scand	Lindner et al ¹⁵	Inpatient arrest, n = 310	High dose vs standard adrenaline	Randomised clinical trial	Higher ROSC (16 of 28) than SDE (6 of 40), no difference in survival	Trend to increased survival in HDE
1992	JAMA	Callaham ¹⁶ et al	Pre-hospital arrest, n = 816	High dose vs noradrenaline vs standard adrenaline	Randomised clinical trial	Discharged alive = no difference in 3 groups	Noradrenaline not better
1992	N Engl J Med	Seill et al ¹⁷	Pre + in-hospital arrest, n = 650	High dose vs standard adrenaline	Randomised clinical trial	Discharged alive = HDE (3%) vs Std A (5%) (<i>P</i> >0.05)	No benefit for high dose
1992	N Engl J Med	Brown et al ¹⁸	Pre-hospital arrest, n = 1280	High dose vs standard adrenaline	Randomised clinical trial	Discharged alive = HDE (5%) vs Std A (4%) (<i>P</i> >0.05)	No benefit for high dose
1994	Chest	Rivers et al ¹⁹	Pre-hospital arrest, n = 49	Adrenaline	Non-randomised control trial	24h mortality higher if cumulative adrenaline >15 mg, adverse physiological effects	Adverse adrenaline effects
1995	Resuscitation	Choux et al ²⁰	Pre-hospital arrest, n = 536	Repeated high doses and repeated standard doses of epinephrine	Randomised clinical trial	Survival to discharge, 3 standard-dose (5.5%), 6 high-dose group (9.2%)	Trend to increased survival in HDE
1995	Resuscitation	Woodhouse et al ²¹	Pre + In-hospital arrest, n = 194	High dose vs placebo vs standard adrenaline (unrandomised)	Randomised clinical trial	No difference in survival in 3 groups	High non-compliance to protocol
1995	Am J Respir Crit Care Med	Patrick et al ²²	In-hospital arrest, n = 145	Adrenaline vs methoxamine	Randomised clinical trial	Successful resuscitation (M 42% versus 53% E)	Methoxamine no better
1996	Prehospital Disaster Med	Carvolth et al ²³	Pre-hospital arrest, n = 1174	High dose vs standard adrenaline	Before and after trial	Survival to discharge SDE 4.9% (29 patients) versus HDE 4.8% (28 patients)	No benefit for high dose

TABLE I: Contd.

Year	Journal	Author	Patients	Intervention	Method	Results	Comments
1996	Ann Intern Med	Lindner et al ²⁴	Inpatient arrest, n = 8	Vasopressin	Case series	ROSC in all, 3 discharged alive	Vasopressin promising
1997	Pharmacotherapy	Sherman et al ²⁵	Inpatient arrest, n = 140	High dose vs standard adrenaline	Randomised clinical trial	None survived to hospital discharge	No benefit for high dose
1997	Acad Emerg Med	Morris et al ²⁶	Inpatient arrest, n = 10	Vasopressin vs adrenaline	Human trial	Coronary perfusion pressure improved with vasopressin and not adrenaline	Vasopressin better
1997	Lancet	Lindner et al ²⁷	Pre-hospital VF, n = 40	Vasopressin (V) vs adrenaline (A)	Randomised clinical trial	ROSC = V (35%) > A (10%) (<i>P</i> < 0.001)	Vasopressin promising
1998	N Engl J Med	Gueugniaud et al ²⁸	Pre-hospital arrest, n = 3327	Repeated high doses and repeated standard doses of epinephrine	Randomised clinical trial	2.3% HDE and 2.8% standard-dose survived to discharge (<i>P</i> = 0.34)	No benefit for high dose
1998	Ann Emerg Med	Walraven et al ²⁹	Inpatient arrest, n = 773	Adrenaline	Observational	Adrenaline associated with unsuccessful resuscitation; OR, 0.08; 95% CI, 0.04-0.14	Observational Confounding?
2000	Ann Emerg Med	Lee et al ³⁰	Inpatient arrest, n = 10	Vasopressin vs adrenaline	Randomised clinical trial	Higher return of circulation and better neurological outcome with vasopressin	Vasopressin better
2001	Lancet	Stiell et al ³¹	Inpatient arrest, n = 200	Vasopressin (V) vs adrenaline (A)	Randomised clinical trial	Survival to discharge (V 12 [12%] vs A 13 [14%], <i>p</i> 50.67; 95% CI, 211.8% to 7.8%)	No difference

ED; emergency department; HDE: high dose epinephrine; ROSC: return of spontaneous circulation; SDE: standard dose epinephrine; VF: ventricular fibrillation

0.14). Based on this, the authors questioned the effectiveness of adrenaline and other drugs in cardiac arrest. However, as patients were not randomised, results could have been confounded by several factors. One confounding factor could be the varying severity and aetiology of cardiac arrest. Patients who received multiple doses of adrenaline could possibly have had a worse prognosis to begin with. Patients who rapidly responded to CPR, defibrillation or a single dose of drug would likely have subsequently good outcomes, whereas patients who remained collapsed would have had repeated doses of multiple drugs in a vain attempt to resuscitate, but still have poor outcomes. The underlying patient and arrest factors would be more important in this case than treatment factors.

Roberts et al,¹³ in a retrospective review of 310 cardiac arrests, found use of adrenaline as a strong early predictor of mortality in cardiac arrest ($P = 0.0316$) and suggested that current widespread belief in the positive effect of adrenaline should be reviewed. However, again, this retrospective study may have the same confounding factors as the previous one. Nevertheless, the fact remains that the use of adrenaline in cardiac arrest had a disappointingly low success rate overall.

In the only 'before and after' trial on adrenaline done so far, Weaver et al¹² studied 199 patients with out-of-hospital cardiac arrest in persistent VF (ventricular fibrillation) who were given adrenaline or lignocaine and compared them with historical controls who were only given bicarbonate. They found that there was no difference in the proportion of patients resuscitated with either adrenaline or lignocaine and lower survival in both groups compared to controls. They concluded that there was no clinical evidence to support the efficacy of drug therapy in persistent VF and recommended that drugs be withheld until several repeated shocks failed to restore circulation. They also suggested a review of current guidelines regarding drug therapy. However, we note that with a 'before and after' type study design, many confounding factors can occur. Also, comparison was not between adrenaline and no treatment, rather with bicarbonate as the historical control. Furthermore, the average time to first defibrillation for this study was 9 ± 4 min. Drug therapy was only initiated after the first defibrillation proved unsuccessful. We know that for cardiac arrest patients defibrillated after 8 min, prognosis is dismal, no matter what subsequent therapy is given.

There has only been 1 placebo controlled trial on adrenaline. Woodhouse et al²¹ compared high-dose adrenaline (10 mg), standard dose adrenaline and placebo in cardiac arrest. This study was originally designed to be a randomised, controlled trial comparing high-dose (10 mg) adrenaline and placebo. However, a large proportion of the eligible study group (45%) were not randomised and

received open 1 mg aliquots of adrenaline due to non-compliance with protocol. This was apparently due to physician reluctance to possibly administer a placebo in a cardiac arrest situation. Those given open, standard doses of adrenaline were included in the final analysis, which showed no significant difference in survival with high dose, standard dose adrenaline or placebo. The patient profile in each group was apparently similar. The authors thus concluded that 1 mg or 10 mg adrenaline does not influence outcomes compared with placebo. Once again, we note that selection bias is likely to have been present, especially for the standard dose adrenaline group. Also this was an in-hospital study, patients who arrested pre-hospital only had interventions on arrival at the emergency department. Treatment intervals are likely to have been long although they were not reported. There have not been any prospective randomised controlled trials comparing standard dose adrenaline with placebo.

Initial studies comparing high-dose adrenaline (>5 mg boluses) with standard-dose adrenaline (1 mg)^{14,15} showed improved rates of return of spontaneous circulation, and by extrapolation, improved survival. However, extensive clinical trials done since^{16-18,20,23,25,28} have now shown that compared to standard dose adrenaline, there is no improvement in survival. A meta-analysis done on the high-dose versus standard-dose adrenaline trials confirms that there is no significant improvement in survival to discharge with escalating doses of adrenaline.⁵⁴ Other drugs that have been assessed include phenylephrine,⁹ noradrenaline¹⁶ and methoxamine,^{10,11,22} but these have not been shown to be superior to adrenaline.

Why has the experimental evidence on the utility of adrenaline in cardiac arrest not been repeated in a clinical setting? There are two possible explanations. Firstly, it could be due to the nature of cardiac arrest trials conducted. Secondly, it could be due to the actual effect of the drug itself. As we have mentioned before, there are many factors affecting outcome in cardiac arrest. These include patient factors, disease factors and event factors such as presence of bystander CPR, EMS response times, time to defibrillation, etc. Furthermore, if time to interventions are long (>8 min),⁴ outcomes are uniformly poor, no matter what intervention is given subsequently. Thus, the need for properly designed randomised controlled trials in this field. However, ethical issues do arise regarding waiver of consent in an emergency situation and the use of placebo in cardiac arrest trials. The second possibility is that although adrenaline may increase return of spontaneous circulation, subsequent delayed effects may adversely affect final outcome, as we have discussed above.

Adrenaline continues till today to be the mainstay treatment in cardiac arrest, possibly due to a lack of

alternatives. The ILCOR G2000 has given adrenaline a Class IIb (possibly helpful) recommendation with an indeterminate level of evidence. However, they have also recommended a new alternative, vasopressin (Class IIb), to adrenaline.

Vasopressin

It was initially observed that patients with cardiac arrest had extremely high circulating levels of endogenous vasopressin.⁵⁵⁻⁵⁷ Vasopressin is a naturally occurring posterior pituitary hormone that acts directly on V1 receptors on contractile elements. It also has an antidiuretic effect.

Subsequent animal studies confirmed that vasopressin improved vital organ perfusion during cardiac arrest.^{58,59} Successful resuscitation with full neurological recovery has been reported.⁶⁰ Compared to the maximum effective dose of 200 µg/kg adrenaline, a dose of 0.8 U/kg of vasopressin achieved significantly higher coronary perfusion pressure, myocardial blood flow and total cerebral blood flow.⁵⁹ Compared with adrenaline, vasopressin was superior in improving ventricular fibrillation mean frequency⁶¹ and cerebral oxygen delivery.⁶² Pharmacological effects also lasted longer after vasopressin than after adrenaline.⁶³ Repeated doses of vasopressin have also been found to maintain coronary perfusion pressure better than adrenaline.⁶⁴⁻⁶⁶ In a randomised swine outcome study (n = 35), return of spontaneous circulation (ROSC) was attained in 67% of vasopressin-treated pigs versus 47% of epinephrine-treated pigs. Twenty-four hour survival with normal neurological status occurred in 61% versus 41%, respectively; however, this difference did not achieve statistical significance ($P = 0.24$).⁶⁷

What about paediatric cardiac arrest? Voelckel et al⁶⁸ found that vasopressin was less effective than adrenaline in the paediatric porcine model (piglets 8 to 11 kg) of cardiac arrest. This observation has not yet been fully explained. This study also showed that a combination of vasopressin and adrenaline was more effective in resuscitation than adrenaline or vasopressin alone. This synergistic effect was found possibly to apply to adult cardiac arrest as well.⁶⁹ Vasopressin has also been shown experimentally to improve survival in cardiac arrest after hypovolaemic shock.⁷⁰

In human studies of the use of vasopressin, Morris et al²⁶ measured coronary perfusion pressure (CPP) in 10 patients with prolonged cardiac arrest. CPP was measured after a dose of adrenaline and again after a dose of vasopressin. They found significantly improved coronary perfusion pressures in patients after vasopressin but not adrenaline. In a case series of 8 patients with in-hospital cardiac arrest, vasopressin was found to restore spontaneous circulation in all patients and 3 were discharged alive.²⁴ Lindner et al,²⁷

in a randomised, double-blind clinical trial compared intravenous vasopressin and adrenaline in refractory ventricular fibrillation. Patients with out-of-hospital cardiac arrest were attended to by a pre-hospital team comprising paramedics and a physician. If patients were found to be in ventricular fibrillation, not responsive to initial defibrillation, 1 dose of study drug was given. This was in identical, precoded syringes and contained either 1 mg adrenaline or 40 U vasopressin. They found a significantly larger proportion of patients were successfully resuscitated with vasopressin compared with adrenaline (40% vs 15%, $P = 0.16$). However, the sample size was small (n = 40) and the authors concluded that more study was needed.

Subsequent results have been mixed. Stiell et al³¹ conducted a randomised trial comparing vasopressin and adrenaline in in-hospital cardiac arrest. They recruited 200 patients who were given 1 dose of either vasopressin 40U or adrenaline 1 mg. The location of arrest was mainly in the wards (> 50%) with others from the Emergency Department or the ICU/CCU. Initial rhythm was usually pulseless electrical activity or asystole, with <20% in ventricular fibrillation. Only about 30% of patients were thought to have a cardiac cause of arrest, with many having non-cardiac current diagnosis (postoperative event, 30%; neoplasm, 14%; circulatory, 40%; respiratory, 14%; digestive, 10%; genitourinary, 7%). They found no significant difference in survival to discharge, 1-hour survival and cerebral outcomes. The authors' conclusion was that they failed to detect any survival advantage for vasopressin over adrenaline. Although there was no statistical difference in outcomes, they added that they did not recommend routine use of vasopressin for in-hospital cardiac arrest, perhaps due to cost considerations. Lee et al,³⁰ however, reported preliminary findings of higher return of spontaneous circulation and better neurological outcomes with vasopressin compared with adrenaline in out-of-hospital cardiac arrest. However, the sample size is small (n = 10) and this trial is still ongoing.

At this point of time, there is insufficient clinical evidence to show whether adrenaline or vasopressin is superior for sudden cardiac arrest. Furthermore, the situation for in-hospital arrest may be different from pre-hospital cardiac arrest, as the underlying aetiology, presenting rhythm and subsequent response to treatment will differ. Vasopressin is currently recommended for refractory ventricular fibrillation, to be given as a single intravenous bolus of 40 U that is not repeated. 40 U of vasopressin costs about S\$42 compared to S\$2.70 for adrenaline.

Conclusion

Although vasopressin has shown promise in animal experimental work, it has yet to be proven in the clinical

setting to be superior to adrenaline in sudden cardiac arrest. Furthermore, there are many factors affecting outcomes in cardiac arrest, and much more research is needed in this critical area. In a review of current treatment of cardiac arrest, Chugh et al⁷¹ issued an appeal for larger clinical trials on cardiac arrest interventions. They argued that the value of assessing vasopressin efficacy in a well-organised clinical trial far outweighs the potential for infringement of patient rights implied in waiver of informed consent. Meanwhile, in order to improve survival from sudden cardiac arrest, continuing effort should be made to address issues we know for certain affect survival: early initiation of CPR, early defibrillation and early advanced care.

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