Review

Clinical review: Devices and drugs for cardiopulmonary resuscitation – opportunities and restraints

Max Harry Weil[1] and Shijie Sun[2]

[1]President and Distinguished University Professor, Institute of Critical Care Medicine, Palm Springs, Keck School of Medicine, University of Southern California, Los Angeles, California, and Northwestern University Medical School, Chicago, Illinois, USA
[2]Director of Laboratories, Institute of Critical Care Medicine, Palm Springs, and Associate Clinical Professor, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

Corresponding author: Max Harry Weil, weilm@911research.org

Abstract

The science and technology of CPR is only just emerging from its infancy. However, substantial improvements are anticipated, including the ability of lay rescuers to identify cardiac arrest promptly, the availability of additional measurements, and expanded intelligence provided by expanded AEDs with which to more effectively prompt the rescuer through the resuscitation procedure. Most important in our view is the ability to maintain uninterrupted precordial compression. Better timing and better waveforms for defibrillation are emerging. The recognition of the importance of postresuscitation myocardial dysfunction and the selection of better vasopressor agents to minimize the adverse inotropic and chronotropic actions of adrenergic drugs are also likely to improve outcomes of CPR.

Introduction

Successful reversal of cardiac arrest is contingent on prompt identification of the absence of an effective heart beat and interventions that will restore effective ventilation and circulation. Typically, cardiopulmonary resuscitation (CPR) is only successful if it is instituted within 5 min after the heart stops beating. Survival rates for out-of-hospital cardiac arrest are remarkably low [1]. Especially in large cities and in rural communities, survival ranges from less than 2% to 5%, which projects the magnitude of the problem [2,3]. In communities in which there is early response by bystanders who initiate CPR or by minimally trained rescuers, including fire and police personnel, and in which there is early response by an effective professional emergency medical response system such as in Seattle, Washington [4,5] or Rochester, Minnesota [6], survival from out-of-hospital cardiac arrest may be increased as much as 10-fold.

Cardiac arrest detector

Among major changes in the guidelines from the American Heart Association [7], lay rescuers are no longer taught or expected to perform a 'pulse check'. The early diagnosis of cardiac arrest by laypersons is therefore based solely on lack of cerebral responsiveness and failure to detect breathing. Accordingly, resuscitation is initially delayed for confirmation of cardiac arrest. With the introduction of external automated defibrillators (AEDs) [8] there are even longer delays, and especially so when a pulseless rhythm prompts repetitive rhythm analyses by the AED, during which interventions must be suspended [9]. This prompted the development of a cardiac arrest detector that is based on impedance measurements [10]. The cardiac arrest detector prompts the rescuer to intervene more rapidly with chest compression, protection of the airway and ventilation – not just defibrillation. The AED therefore becomes a more comprehensive measuring device because it detects and quantifies both heart beat and breathing, and it provides an estimate of the cardiac output produced by chest compression. It therefore expands measurements to beyond those provided by the ECG, and allows more comprehensive automated decision making and therefore prompting of the rescuer.

Defibrillation

Perhaps among the greatest advances of the past decade has been the introduction of AEDs. These devices 'jump start' the heart by allowing rapid conversion of ventricular tachycardia and ventricular fibrillation when applied by minimally trained laypersons [7]. The results of the recently published Public Access Defibrillation Study in North America [11] provides additional evidence of the benefit of

---

AED = external automated defibrillator; CPR = cardiopulmonary resuscitation.

early defibrillation by lay rescuers in settings in which there is large public exposure. Unfortunately, the same study suggested little benefit in home settings. In addition, much has been learned with respect to the biology and technology, which will form the basis for improved defibrillation in the future. Repetitive electrical shocks are injurious to the arrested heart [12]. Biphasic waveforms have major advantages over monophasic waveforms and allow lower energy defibrillation, which minimizes myocardial injury and the severity of the newly identified condition 'post-resuscitation myocardial dysfunction' [13,14].

Postresuscitation myocardial dysfunction

The global myocardial ischemia of cardiac arrest partially explains the large fall-off in meaningful survival of victims of cardiac arrest. As many as 40% of victims are initially resuscitated, but fewer than an average of 5% leave the hospital alive and neurologically intact. After resuscitation a progressive reduction in cardiac output and in myocardial contractility has been demonstrated, such that the heart produces lesser systemic and coronary blood flows [15–18]. This form of heart failure is similar to the 'stunning' of the myocardium in settings of acute coronary obstruction [19]. During cardiac arrest there is global myocardial ischemia during the 'no-flow' interval in which the myocardium is not perfused. Like stunning, the function of the heart is progressively impaired over an interval of 4 hours, with gradual recovery over the following days [20]. The severity of postresuscitation myocardial dysfunction is minimized by early resuscitation with restoration of an effective rhythm, cardiac output, and coronary blood flow; by reducing the numbers and the energy levels of shocks delivered by the defibrillator; and by the use of biphasic rather than monophasic waveform shocks [13,14].

Precordial compression

Precordial compression produces between 20% and 25% of the normal cardiac output. Because blood flow is preferentially delivered to the coronary and cerebral circuits, it allows these vulnerable organs to survive. The lesser importance of ventilation in contrast to the essential role of maintaining forward blood flow prompted the revision of the American Heart Association international guidelines in the year 2000 to reduce interruptions for ventilation from 5/1 to 15/2 [7]. The compression to ventilation ratios were therefore reduced in adults.

A major shortcoming of cardiac resuscitation following the introduction of AEDs has been the interruption of precordial compression, during which there is a decline in coronary perfusion and an exacerbation of myocardial injury, together with persistent ectopic ventricular arrhythmias and recurrent cardiac arrest [9,21]. Precordial compression is also interrupted following onset of cardiac arrest for endotracheal intubation. Experimental data suggest that as little as 10 s of interruption to precordial compression compromises

outcomes. Efforts to improve the forward flow generated by precordial compression have prompted the use of a series of manual, pneumatic, and electrically powered mechanical devices, including the Thumper® (Michigan Instruments Inc., Grand Rapids, MI, USA) the CardioPump®, the Pneumatic Vest®, and the Revivant® Compressor (Revivant Corp., Sunnyvale, CA, USA), and re-examination of the potential benefits of open chest internal cardiac massage [22–25].

These discoveries prompted several new developments at our Institute. The first of these is the resuscitation blanket, which isolates the rescuer from electrical shocks, allowing for continuous chest compression independent of delivery of a shock [26]. Second, repetitive shocks are minimized by identifying and reacting to optimal timing of defibrillation [27] by a technique of amplitude frequency analysis. Finally, we developed a compact chest compressor so that interruption to chest compression can be avoided during transport. Such a device is likely to be essential, not only for transport through stairways, in ambulances, and through the halls of hospitals, but also because of the ability to maintain effective and uninterrupted precordial compression.

Monitoring the effectiveness of precordial compression

End-tidal carbon dioxide has emerged as a very good measure for quantifying the 'cardiac output' produced by chest compression [28,29]. Such a monitor detects operator fatigue during human resuscitation, which occurs as early as 2 min after a rescuer starts chest compression. As an additional benefit, end-tidal carbon dioxide provides almost immediate detection of return of spontaneous circulation, without interrupting chest compression to interpret the ECG or palpate for a potentially pulsatile rhythm.

Limitations and alternatives to epinephrine (adrenaline)

Epinephrine has been the vasopressor of choice because of its α-adrenergic effects, which increase systemic vascular resistance and therefore myocardial and cerebral blood flows, and consequently the success of initial resuscitation. However, epinephrine also has β-adrenergic effects by which it increases myocardial oxygen consumption and the severity of postresuscitation myocardial dysfunction. The β-adrenergic effects of epinephrine also account for increases in ventricular ectopy and the recurrence of ventricular tachycardia and ventricular fibrillation. In addition, epinephrine produces arteriovenous shunting through the lung, and therefore causes a very profound although transient reduction in the arterial oxygen content [30]. Experimentally, when the β-adrenergic effects of epinephrine are blocked by the rapid acting β-adrenergic blocker esmolol, the outcomes of advanced life support are substantially improved [31]. Optimism that vasopressin would minimize the adverse effects of epinephrine was not supported by a recently completed European Multicenter Study [32]. The prolonged

vasoconstrictor action of vasopressin, we suspect, adversely effects postresuscitation myocardial dysfunction [18].

More recently, our group's attention has been focused on more selective adrenergic agents for treatment of cardiac arrest. Primary α-adrenergic drugs, including phenylephrine and methoxamine, have predominant α_1-adrenergic actions. Unfortunately, α_1-adrenergic receptors are desensitized during the myocardial ischemia of cardiac arrest, such that these drugs are minimally effective in increasing peripheral resistance. In addition, α_1-adrenergic receptors also reside in the heart, although to a much lesser extent than β-adrenergic receptors [33]. Accordingly, α_1-agonists also have inotropic effects that increase the severity of myocardial ischemia. Our attention has therefore turned to a selective α_2-adrenergic agonist and specifically to α-methylnorepinephrine, which has yielded significantly better outcomes experimentally because of its relatively pure peripheral vasopressor action [34,35].

Therapeutic hypothermia after cardiac arrest

Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. Recent studies have shown that induced hypothermia for 12–24 hours improves outcome in patients who are resuscitated from out-of-hospital cardiac arrest [36,37]. The rapid infusion of large volume, ice-cold crystalloid fluid results in a significant decrease in median core temperature from 35.5°C to 33.8°C, and is associated with beneficial hemodynamic, renal, and acid–base effects. Further studies are ongoing to improve this technique [38].

Conclusion

Although laboratory research on CPR cannot directly be applied to clinical management, insights gained in the laboratory led to the extraordinary discovery of CPR itself by Kouwenhoven and coworkers [39] and, in our experience, accounted for essentially every subsequent major advance in the field, including that in adverse effects of automated defibrillation [40]. The importance thereof is even greater in light of the restraints that preclude human studies in the USA when informed consent of the patient is not possible.

Competing interests

Financial reimbursements: MHW has received non-personal support of the Institute of Critical Care Medicine from Philips Heartstream, Zoll Medical, Medtronic Physiocontrol and Laerdal Medical

Stocks or shares: MHW is a Trustee of entity which includes Phillips and Zoll stock invested in insignificant amounts.

Patents: The Institute of Critical Care Medicine has patents on instrumentation related to resuscitation. MHW receives no personal benefit. The Institute receives royalties for patents from Optical Sensors and has received research and/or meeting support from each defibrillation company and from the Laerdal Foundation.

Non-financial competing interests: American Heart Association Emergency Cardiac Care Committee member and planning committee for international guidelines for CPR/AED

References

1. Weil MH, Tang W (editors): *CPR: Resuscitation of the Arrested Heart*. Philadelphia: W.B. Saunders; 1998.
2. Becker LB, Ostrander MP, Barrett J, Kondos GT: **Outcome of cardiopulmonary resuscitation in a large metropolitan area: where are the survivors?** *Ann Emerg Med* 1991, **20:**355-361.
3. Caffrey SL, Willoughby PJ, Pepe PE, Becker LB: **Public use of automated external defibrillators.** *N Engl J Med* 2002, **347:** 1242-1247.
4. Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP: **Predicting survival from out-of-hospital cardiac arrest: a graphic model.** *Ann Emerg Med* 1993, **22:**1652-1658.
5. Rea TD, Eisenberg MS, Culley LL, Becker L: **Dispatcher-assisted cardiopulmonary resuscitation and survival in cardiac arrest.** *Circulation* 2001, **104:**2513-2516.
6. White RD: **Optimal access to – and response by – public and voluntary services, including the role of bystanders and family members, in cardiopulmonary resuscitation.** *New Horizons* 1997, **5:**153-157.
7. American Heart Association: **AHA 2000 guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.** *Circulation* 2000, **Suppl 8:**I-1-I-358.
8. Weaver DW, Hill D, Fahrenbruch CR, Copass MK, Martin JS, Cobb LA, Hallstrom AP: **Use of the automatic external defibrillation in the management of out-of-hospital cardiac arrest.** *N Engl J Med* 1988, **319:**661-666.
9. Yu T, Weil MH, Tang W, Sun S, Klouche K, Povoas H, Bisera J: **Adverse outcomes of interrupted precordial compression during automated defibrillation.** *Circulation* 2002, **106:**368-372.
10. Pellis T, Bisera J, Tang W, Weil MH: **Expanding automatic external defibrillators to include automated detection of cardiac, respiratory, and cardiorespiratory arrest.** *Crit Care Med* 2002, **Suppl:**S176-S178.
11. Ornato JP, McBurnie MA, Nichol G, Salive M, Weisfeldt M, Riegel B, Christenson J, Terndrup T, Daya M, for the PAD Trial Investigators: **The Public Access Defibrillation (PAD) trial: study design and rationale.** *Resuscitation* 2003, **56:**135-147.
12. Xie J, Well MH, Sun S, Tang W, Sato Y, Jin X, Bisera J: **High-energy defibrillation increases the severity of postresuscitation myocardial dysfunction.** *Circulation* 1997, **96:**683-688.
13. Tang W, Weil MW, Sun S, Yamaguchi H, Povoas HP, Marn Pernat A, Bisera J: **The effects of biphasic and conventional monophasic defibrillation on postresuscitation myocardial function.** *J Am Coll Cardiol* 1999, **34:**815-822.
14. Tang W, Weil MH, Sun S, Povoas HP, Klouche K, Kamohara T, Bisera J: **A comparison of biphasic and monophasic waveform defibrillation after prolonged ventricular fibrillation.** *Chest* 2001, **120:**948-954.
15. Brown CG, Martin DR, Pepe PE, Stueven H, Cummins RO, Gonzalez E, Jastremski M and the Multicenter High-Dose Epinephrine Study Group: **A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital.** *N Engl J Med* 1992, **327:**1051-1055.
16. Tang W, Weil MH, Sun S, Gazmuri RJ, Bisera J: **Progressive myocardial dysfunction after cardiac resuscitation.** *Crit Care Med* 1993, **21:**1046-1050.
17. Gazmuri RJ, Weil MH, Bisera J, Tang W, Fukui M, McKee D: **Myocardial dysfunction after successful resuscitation from cardiac arrest.** *Crit Care Med* 1996, **24:**992-1000.
18. Kern KB: **Postresuscitation myocardial dysfunction.** *Cardiol Clin* 2003, **20:**89-101.
19. DeAntonio HJ, Kaul S, Lerman BB: **Reversible myocardial depression survivors of cardiac arrest.** *Pacing Clin Electrophysiol* 1990, **13:**982-985.
20. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, Cariou A, Rozenberg A, Carli P, Weber S, *et al.*: **Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest.** *J Am Coll Cardiol* 2002, **40:**2110-2116.
21. Wik L, Jansen TB, Fylling F, Steen T, Vaagenes P, Auestad BH, Steen PA: **Delaying defibrillation to give basic cardiopul-**

monary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. *JAMA* 2003, **289:**1434-1436.

22. Babbs CF, Voorhees WD, Fitzgerald KR, Holmes HR, Geddes LA: **Relationship of blood pressure and flow during CPR to chest compression amplitude: evidence for an effective compression threshold.** *Ann Emerg Med* 1983, **12:**527-532.

23. Cohen TJ, Goldner BG, Maccaro PC, Ardito AP, Trazzera S, Cohen MB, Dibs SR: **A comparison of active compression-decompression cardiopulmonary resuscitation with standard cardiopulmonary resuscitation for cardiac arrests occurring in the hospital.** *N Engl J Med* 1993, **329:**1918-1921.

24. Halperin H, Berger R, Chandra N, Ireland M, Leng C, Lardo A, Paradis N: **Cardiopulmonary resuscitation with a hydraulic-pneumatic band.** *Crit Care Med* 2000, **28:**N203-N206.

25. Kern KB, Sanders AB, Badylak SF, Janas W, Carter AB, Tacker WA, Ewy GA: **Long-term survival with open-chest cardiac massage after ineffective closed-chest compression in a canine preparation.** *Circulation* 1987, **75:**498-503.

26. Yu T, Weil MH, Young C, Tang W, Klouche K, Bisera J: **Resuscitation blanket [abstract].** *Crit Care Med* 2000, **Suppl:**A66.

27. Marn-Pernat A, Weil MH, Tang W, Pernat A, Bisera J: **Optimizing timing of ventricular defibrillation.** *Crit Care Med* 2001, **29:** 2360-2365.

28. Weil MH, Bisera J, Trevino RP, Rackow EC: **Cardiac output and end-tidal carbon dioxide.** *Crit Care Med* 1985, **13:**907-909.

29. Falk JL, Rackow EC, Weil MH: **End-tidal carbon dioxide concentration during cardiopulmonary resuscitation.** *N Engl J Med* 1988, **318:**607-611.

30. Tang W, Weil MH, Sun SJ, Gazmuri RJ: **The effects of epinephrine and vasopressor agents on ETCO$_2$ during CPR.** In *Recent Advances in Anaesthesia, Pain, Intensive Care and Emergency*. Edited by Gullo A. Trieste, Italy: A.P.I.C.E.; 1992:263-267.

31. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ: **Epinephrine increases the severity of postresuscitation myocardial dysfunction.** *Circulation* 1995, **92:**3089-3093.

32. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadhbauer KH, Lindner KH, European Resuscitation Council: **A comparison of vasopressin and epinephrine for out-of-hospital cardiopuolmonary resuscitation.** *N Engl J Med* 2004, **350:**105-113.

33. Pellis T, Weil MH, Tang W, Sun S, Xie J, Song L, Checchia P: **Evidence favoring the use of an alpha$_2$-selective vasopressor agent for cardiopulmonary resuscitation.** *Circulation* 2003, **108:**2716-2721.

34. Sun S, Weil MH, Tang W, Kamohara T, Klouche K: **Alpha-methylnorepinephrine, a selective alpha$_2$-adrenergic agonist for cardiac resuscitation.** *J Am Coll Cardiol* 2001, **37:**951-956.

35. Klouche K, Weil MH, Sun S, Tang W, Zhao DH: **A comparison of alpha-methylnorepinephrine, vasopressin and epinephrine for cardiac resuscitation.** *Resuscitation* 2003, **57:**93-100.

36. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K: **Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.** *N Engl J Med* 2002, **346:**557-563.

37. The Hypothermia after Cardiac Arrest Study Group: **Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.** *N Engl J Med* 2002, **346:**549-556.

38. Sterz F, Holzer M, Roine R, Zeiner A. Losert H, Eisenburger P, Uray T, Behringer W: **Hypothermia after cardiac arrest: a treatment that works.** *Curr Opin Crit Care* 2003, **9:**205-210.

39. Kouwenhoven WB, Jude JR, Knickerbocker GG: **Closed chest cardiac massage.** *JAMA* 1960, **173:**1064-1067.

40. Yu T, Weil MH, Tang W, Sun S, Klouche K, Povoas H, Bisera J: **Adverse outcomes of interrupted precordial compression during automated defibrillation.** *Circulation* 2002, **106:**368-372.