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作成者（著者）	Lurie, Keith G / Metgzer, Anja / Yannopoulos, Demetris / Nakamura, Yuji / Yoshihara, Katsunori / Sugiyama, Atsushi
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Review Article

Harnessing Biphasic Changes in Intrathoracic Pressure to Improve Cardiac Arrest Outcomes

Keith G. Lurie[1, 2)*] Anja Metgzer[1)] Demetris Yannopoulos[2)]
Yuji Nakamura[3)] Katsunori Yoshihara[4)] and Atsushi Sugiyama[3)*]

[1)]Department of Emergency Medicine, University of Minnesota
[2)]Cardiovascular Division, Department of Medicine, University of Minnesota
[3)]Department of Pharmacology, Scool of Medicine, Faculty of Medicine, Toho University
[4)]Department of General Medicine and Emergency Care, School of Medicine, Faculty of Medicine, Toho University

ABSTRACT: Understanding the physiology of blood flow to the brain and heart during cardiopulmonary resuscitation (CPR) is an essential first step in improving outcomes after cardiac arrest. Over the past 20 years much has been learned about the importance of carefully modulating pressures inside the thorax to optimize perfusion to the heart and brain during CPR. When compressions are too fast, too slow, too deep, or too shallow, outcomes are worsened. Full chest wall recoil is also essential to refill the heart after each compression.

Furthermore, changes in intrathoracic pressure are immediately transmitted to the brain: elevated thoracic pressures increase intracranial pressure and thus reduce brain perfusion. The opposite is also true. New devices such as the impedance threshold device (ITD) have been designed to harness the recoil of the chest during CPR and thereby lower intrathoracic pressures. The small vacuum that develops with conventional CPR is augmented by the ITD during conventional CPR, active compression-decompression (ACD) CPR, and when CPR is delivered by automated chest compression devices. Use of the combination of ACD CPR plus the ITD has been shown to significantly improve short- and long-term outcomes, with favorable brain function, after cardiac arrest. This approach is synergistic with advances in therapeutic hypothermia, mechanical means to provide continuous chest compressions, and other improvements in post-resuscitation care. It is now time to move away from conventional CPR with a pair of hands and utilize new approaches.

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KEYWORDS: cardiac arrest, cardiopulmonary resuscitation, active compression decompression CPR, impedance threshold device

*Corresponding Author; tel: +1-612(626)6911, 03(3762)4151
e-mail: klurie@advancedcirculatory.com
e-mail: atsushi.sugiyama@med.toho-u.ac.jp
1) 717 Delaware Street, SE Suite 508, Minneapolis, MN 55414
2) 401 East River Road, Minneapolis, MN 55455
3) 5–21–16 Omorinishi, Ota, Tokyo 143–8540
4) 6–11–1 Omorinishi, Ota, Tokyo 143–8541

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Cardiac arrest remains the leading cause of death in Japan, Europe, and North America.[1] Given the progress in other medical fields, it is somewhat surprising that, more than 50 years after closed-chest manual chest compressions were first described, the primary medical intervention used to generate perfusion when the heart has stopped is still just a pair of hands.[2] Pressing on the chest with a pair of hands is generally neither efficient nor effective. It is no wonder that survival rates after cardiac arrest are typically less than 5% outside the hospital and less than 20% for in-hospital cardiac arrest. Indeed, the science of resuscitation is still in its infancy.

Understanding the physiology of blood flow to the brain and heart during cardiopulmonary resuscitation (CPR) is an essential first step in improving outcomes after cardiac arrest. This review article focuses on new insights into the mechanisms of blood flow to the brain and heart during CPR and on improved ways to circulate blood during CPR. Our goal is to increase understanding of new clinical opportunities to improve outcomes by enhancing circulation during CPR, which includes new insights related to common errors that often reduce the effectiveness of CPR.

Conventional Manual Closed-Chest CPR

Conventional CPR is performed with a pair of hands. Chest compressions should be 5 cm in depth. With each chest compression, intrathoracic pressure is increased, and the heart is often squeezed between the sternum and spine. Blood is propelled forward from the non-beating heart toward the brain, coronary arteries, and the rest of the body due to the presence of the 1-way cardiac valves and pressure differences between the thorax and nonthoracic structures. During the compression phase, intracranial pressure is increased, which increases resistance to cerebral perfusion, as pressure is transmitted through the paravertebral venous plexus and spinal fluid to the cranium. When the chest is compressed too slowly, too rapidly, too much, or too little, blood flow to the brain and heart is reduced.[3] Interruptions in chest compressions are similarly harmful: without chest compressions there is no forward blood flow. These common errors during CPR adversely affect outcomes. As shown in Fig. 1a, chest compressions during conventional CPR provide the driving force to propel blood forward, and care must be taken to provide this life-saving therapy correctly so as to prevent harm.

The physiology during the decompression or chest recoil phase of CPR is perhaps even more complex, as shown in Fig. 1b. The chest needs to fully recoil after each compression during conventional CPR. It is during the decompression phase that the heart is refilled after being emptied by a chest compression. This refilling process is extremely inefficient when using a pair of hands to noninvasively allow the chest wall structures to recoil. The slight

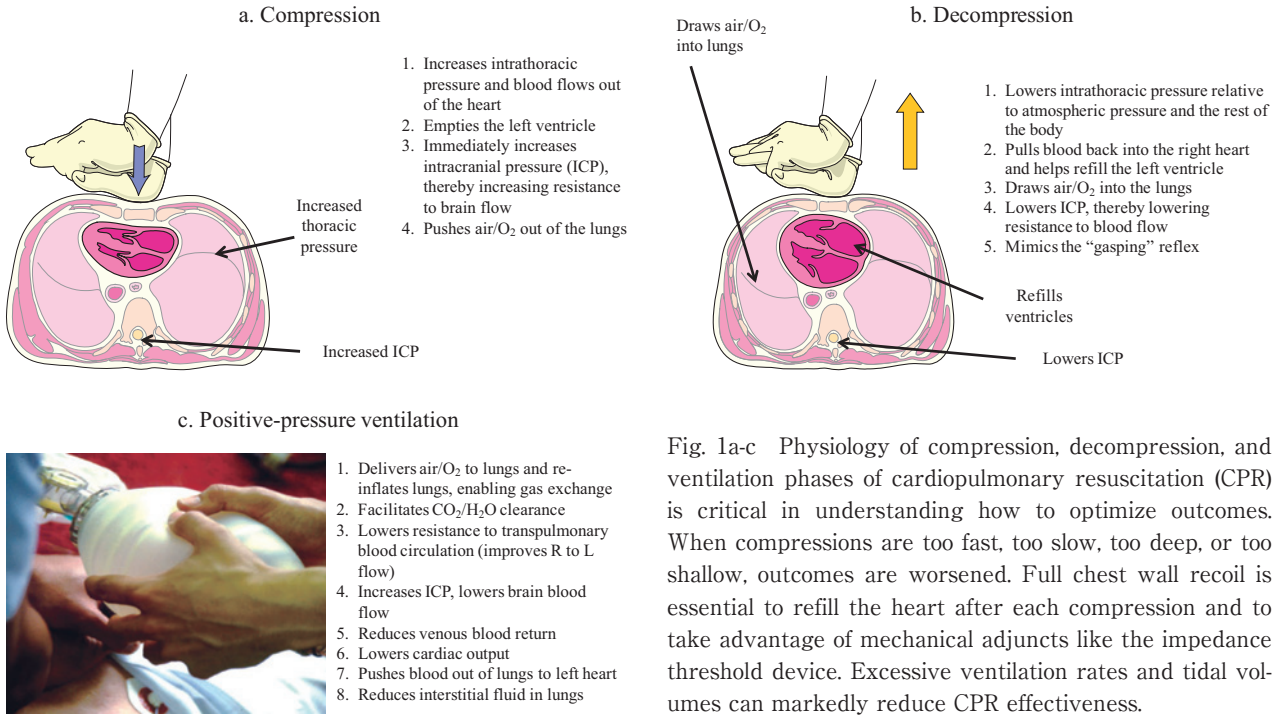


Fig. 1a-c Physiology of compression, decompression, and ventilation phases of cardiopulmonary resuscitation (CPR) is critical in understanding how to optimize outcomes. When compressions are too fast, too slow, too deep, or too shallow, outcomes are worsened. Full chest wall recoil is essential to refill the heart after each compression and to take advantage of mechanical adjuncts like the impedance threshold device. Excessive ventilation rates and tidal volumes can markedly reduce CPR effectiveness.

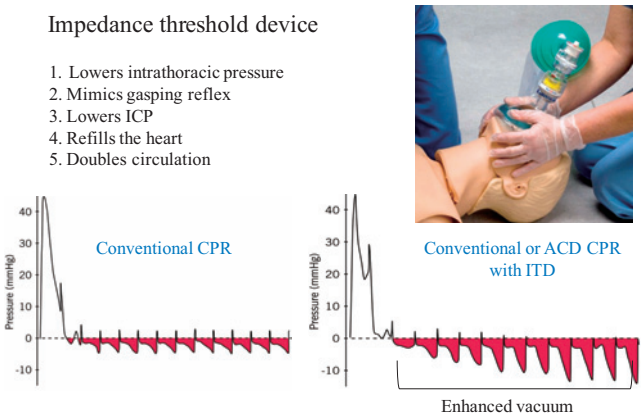


Fig. 2 Effect of inspiratory impedance during cardiopulmonary resuscitation (CPR) on airway pressures. The impedance threshold device (ITD) is designed to harness the recoil of the chest during CPR. The small vacuum that develops with conventional CPR is augmented by the ITD during conventional CPR, active compression-decompression (ACD) CPR, and when CPR is delivered by automated chest compression devices.
ICP: intracranial pressure

vacuum generated inside the thorax draws some blood back into the heart and some air into the lungs. Intracranial pressure (ICP) is minimally reduced with each chest wall recoil, and pressure transference occurs via the same mechanisms that increase ICP during the compression phase. These changes in ICP during the compression and decompression phases have a key role in generating cerebral perfusion.[4] If rescue personnel inadvertently lean on the chest and do not allow the chest to fully recoil after each compression, then intrathoracic pressure remains greater than atmospheric pressure.[5] This common error prevents the refilling of the heart and the reduction in ICP, which in turn markedly reduces blood flow to the brain and myocardium.

Positive pressure ventilation–essential for providing oxygen and removing carbon dioxide during CPR–also affects intrathoracic pressures (Fig. 1c). Each positive-pressure breath increases intrathoracic pressure, which decreases venous blood flow back to the heart and increases ICP, thereby helping to deliver more blood that is pooled in the lungs to the left heart. Excessive ventilation rates and tidal volumes are associated with a marked decrease in cerebral and myocardial perfusion and increased mortality.[6] After the first few minutes of CPR, in the absence of periodic positive-pressure ventilation, blood flow through the lungs is markedly reduced, resulting in profound cerebral oxygenation and perfusion.[7] The balance between too little and too much ventilation is critical to long-term neurologically favorable survival after cardiac arrest.

The coordinated chest compression and decompression components of conventional CPR mimic cardiac systole and diastole, while positive-pressure ventilation provides respiratory gas exchange similar to breathing. Further, the gasping reflex associated with patients in cardiac arrest is associated with a decrease in intrathoracic pressure, which causes entrainment of air into the lungs, venous blood flow back to the heart, and a reduction in ICP.[8] This brief summary of some of the key physiological processes associated with conventional CPR underscores the complexity of the cardiocerebral interactions that must be optimized to enhance circulation when restoring life to a patient in cardiac arrest. A clearer understanding of these mechanisms is critical in order to provide conventional manual CPR and develop new tools to better harness these basic physiological processes.

Beyond Conventional Manual CPR

Inspired by the successful use of a common household plunger instead of a pair of hands to resuscitate a family member in cardiac arrest 25 years ago, CPR researchers have explored new ways to transform the chest from a passive to an active bellows during CPR.[9] These investigations have resulted in new ways to substantially increase blood flow to the heart and brain, reduce ICP during the decompression phase of CPR, and ultimately increase long-term neurologically favorable survival after cardiac arrest.[10–12] Following the index case of the patient and the plunger, a new CPR adjunct was developed to provide active compression-decompression (ACD) CPR. Studies of this new approach in animals and humans were promising, but it soon became clear that more training was needed to perform ACD CPR.[13] Results from large clinical trials of ACD CPR in the 1990s varied from positive to neutral and appeared to depend on several variables.[14] These clinical studies also stimulated additional research on the mechanism of blood flow during ACD CPR and ultimately resulted in a discovery: transient occlusion of the airway during the decompression phase of CPR with a new device reduced intrathoracic pressure during conventional and ACD CPR.[11,15,16] This device, termed an impedance threshold device (ITD), augments circulation during conventional CPR, ACD CPR, and CPR with automated devices. By preventing respiratory gases from rushing into the lungs dur-

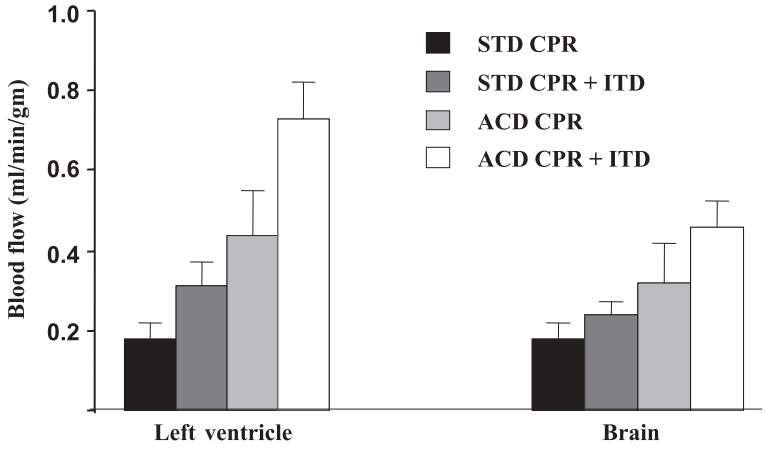


Fig. 3 Blood flow during cardiopulmonary resuscitation (CPR) in a porcine model of ventricular fibrillation. In a pig model of cardiac arrest, radiolabeled microspheres were used to assess blood flow to the heart and brain during conventional or standard (STD) CPR, STD CPR + impedance threshold device (ITD), active compression-decompression (ACD) CPR, and ACD CPR + ITD. Normal baseline blood flow to the heart and brain in pigs is 1.0 ml/min/gm and 0.4 ml/min/gm, respectively.[12]

ing the decompression phase of CPR, the ITD harnesses the thoracic bellows to draw more blood into the thorax and lower ICP during the decompression phase of CPR (Fig. 2).[17] In this manner, it mimics the gasping reflex after each chest compression.[8, 18] Periodic positive-pressure ventilation is provided through the device, which is attached to a facemask or advanced airway. Over the past 2 decades, use of the ITD has been shown to significantly augment cerebral and myocardial perfusion during CPR in animals (Fig. 3),[15, 19] improve hemodynamics in humans,[20] and, more recently, safely and significantly improve long-term survival rates with favorable neurological function in patients after out-of-hospital and in-hospital cardiac arrest.[21–24]

Use of conventional CPR and the ITD has been extensively studied.[15, 19–21, 25] In 1 double-blinded study, arterial blood pressures were nearly doubled with an active versus sham ITD.[20] In studies where the ITD was incorporated into a system of care that included other high-level recommendations in the 2005 American Heart Association Guidelines, survival rates after in-hospital and pre-hospital cardiac arrest nearly doubled.[21, 26] One program, called Take Heart America, is currently implemented in cities across the United States.[26] The use of the ITD and conventional CPR has been reported to improve long-term survival—with favorable neurological outcomes after out-of-hospital cardiac arrest—by approximately 30% overall, with a greater than 50% benefit in patients with a witnessed cardiac arrest and a presenting rhythm of ventricular fibrillation.[21] Outcomes are even better when this new approach is used in patients with an in-hospital arrest, most likely because the time between arrest and start of CPR is reduced. However, 1 large clinical trial of the ITD found no benefit or harm from use of this new technology.[27] The study design was complex and involved examining 2 questions simultaneously in the same patients. One question focused on ITD effectiveness, and the other question focused on the relative benefit of 30 seconds versus 3 minutes of CPR before defibrillation. This study was stopped early for futility, as neither hypothesis could be adequately assessed. While the results were initially puzzling, a more recent analysis from that study has shown that the compression rate during CPR in that study varied widely, from less than 50 to more than 200 compressions per minute.[28, 29] When the investigators analyzed their data, it became clear that when chest compressions were delivered as recommended and intended, *i.e.*, at a rate of approximately 100 per minute, the active ITD was strikingly beneficial. By contrast, when chest compression was too fast the ITD was of no benefit. Once again this trial highlights the need to understand the physiology of conventional CPR and the importance of providing feedback to rescue personnel so they can provide quality CPR. With quality CPR, the ITD was highly beneficial, based on a recent re-analysis by Idris et al., especially in patients with a witnessed arrest and a presenting rhythm of ventricular

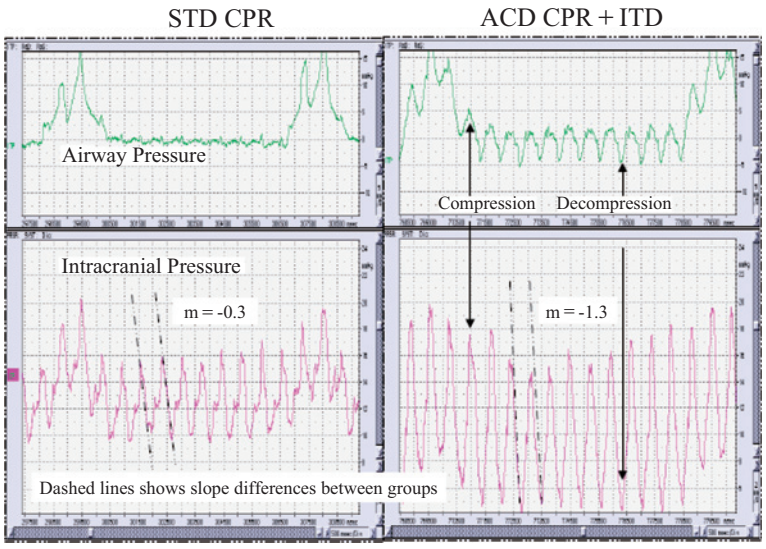


Fig. 4 Mechanism of benefit: active compression-decompression (ACD) cardiopulmonary resuscitation (CPR) + impedance threshold device (ITD) lowers intracranial pressure (ICP) faster, and for a longer duration, during CPR. Airway pressure and intracranial pressure were simultaneously lowered during ACD CPR + ITD. Note the greater rate of ICP reduction in the ACD CPR + ITD figure in comparison to the ICP reduction during standard (STD) CPR at 80 compressions/min. Both figures are from the same animal. ACD CPR + ITD was performed after 5 minutes of STD CPR at 80 compressions/min.

Fig. 5 Two methods of cardiopulmonary resuscitation (CPR) were compared in the ResQTrial. An impedance threshold device (ITD) with a resistance of 16 cm H_2O was used (ResQPOD, Advanced Circulatory Systems, Inc., Minneapolis, MN, USA).
ACD: active compression-decompression

fibrillation.[28]

In parallel with the studies on conventional CPR and the ITD, there have been numerous studies of ACD CPR and the ITD in animals and humans. In animals, blood flow to the brain is restored to normal levels with ACD CPR plus the ITD by optimizing the physiology of the biphasic thoracic pump (Fig. 4).[12] With each decompression, ICP is reduced and circulation to the brain is enhanced.[30] In humans, circulation as assessed by end-tidal carbon dioxide ($ETCO_2$) is significantly augmented with the combination of ACD CPR and an active ITD (versus a sham ITD), coronary perfusion pressures are higher with the device combination versus ACD CPR alone, intrathoracic pressure are lower with the device combination versus ACD CPR alone, and, most importantly, short- and long-term survival rates were significantly improved with ACD CPR and the ITD. To date there have been 5 clinical trials of this device combination.[10,31–34] The largest trial, the ResQTrial, enrolled over 2500 patients and demonstrated that use of the ACD CPR + ITD combination (Fig. 5) resulted in a 53% relative increase in survival to hospital discharge with favorable neurological function as compared with conventional CPR.[10] As in all clinical trials, time is of the essence: a delay in either of the CPR methods resulted in poorer outcomes (Fig. 6). In that study, survivors were followed for a year, and use of ACD CPR + ITD resulted in a 50% relative increase in long-term survival with favorable brain function versus conventional CPR.

Three additional new observations from the most recent and largest clinical trial of the use of ACD CPR + ITD highlight the importance of optimizing circulation during

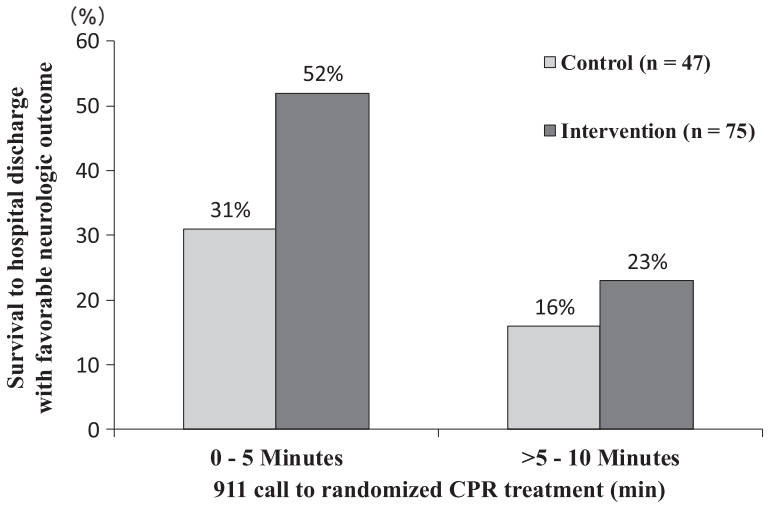
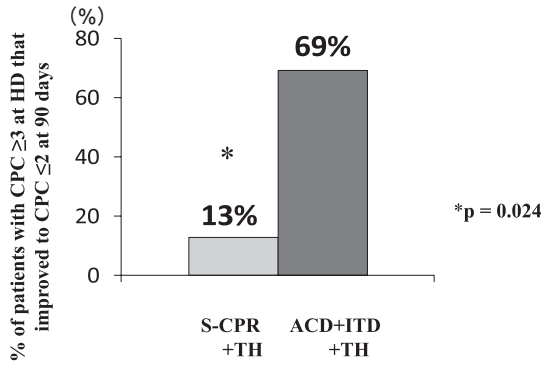


Fig. 6 Time-dependency of interventions. Survival with favorable neurological function at the time of hospital discharge was time- and intervention-dependent in the ResQTrial. When cardiopulmonary resuscitation (CPR) delivered by professional rescue personnel was delayed, survival with favorable neurological status decreased rapidly. Neurological status was considered favorable when the modified Rankin Scale score was 3 or lower at the time of hospital discharge.

CPR. The first is that, in the absence of bystander CPR, the frequency of ventricular fibrillation/pulseless ventricular tachycardia as the first recorded rhythm was 50% higher in the ACD CPR + ITD group.[35] In that trial, all patients received 2 minutes of CPR before activating the automated external defibrillator and analyzing the presenting rhythm. Greater circulation resulted in a 50% greater likelihood of having an initial rhythm that could be treated with defibrillation, which in turn resulted in a 50% higher return of spontaneous circulation rate and a doubling of survival to hospital discharge with favorable neurological function in patients who were not treated with bystander CPR. Those treated with bystander CPR also had higher rates of survival to hospital discharge with good neurological function but similar initial incidence rates of ventricular fibrillation/pulseless ventricular tachycardia as the presenting rhythm. The second observation is that when circulation was enhanced during CPR with the device combination, and therapeutic hypothermia was used post-resuscitation, these interventions had a synergistic benefit (Fig. 7).[36] At the time of hospital discharge approximately 25% in both the conventional CPR group and the ACD CPR + ITD group had poor neurological function, but those treated with ACD CPR + ITD and therapeutic hypothermia had a 6-fold higher likelihood of restoration to normal neurological function 90 days after their cardiac arrest as compared with conventional CPR and therapeutic hypothermia. The third observation was that, for patients who survived to hospital discharge, survival rates up to a year later were significantly higher with the combination of ACD CPR + ITD versus conventional CPR, regardless of the cause of cardiac arrest (Fig. 8).[37] Taken together, these observations underscore how restoring circulation during the first critical minutes of CPR increases the likelihood of better long-term survival.

The Future of CPR

Building upon this improved mechanical platform of CPR, investigators have recently described new ways to enhance circulation with novel pharmacological means and ways to prevent injury associated with reperfusion. While it is beyond the scope of this review article to describe these advances in detail, when coupled with improved mechanical means to enhance circulation, these additional discoveries may provide the keys to future improvement for patients in cardiac arrest. In 1 series of investigations, sodium nitroprusside was used alone or in combination with adenosine to enhance microcirculation and perfusion at the cellular level. Use of nitric oxide donors is thought to improve cell viability and protect against injury associated with reperfusion. Use of this potent vasodilator can be used most effectively when circula-



	S-CPR without TH	S-CPR with TH	ACD+ITD without TH	ACD+ ITD with TH
CPC ≤ 2 at HD	23	30	42	32
CPC ≥ 3 at HD	10	8	11	13
Improved from CPC ≥ 3 at HD to CPC ≤ 2 at 90 days	3/10 (30.0%)	1/8 (12.5%)	3/11 (27.3%)	9/13 (69.2%)

Fig. 7 Active compression-decompression (ACD) cardiopulmonary resuscitation (CPR) + impedance threshold device (ITD) and therapeutic hypothermia (TH) are synergistic. Approximately 25% of all patients who were discharged alive from the ResQTrial had poor neurological function, as determined by a Cerebral Performance Category (CPC) score of 3 or higher, regardless of which CPR method was used. Approximately 45% of all ResQTrial patients admitted to the hospital alive were treated with TH if they were comatose at the time of hospital admission. Post-hoc analysis revealed that the combination of ACD CPR + ITD and TH was synergistic: 90 days after hospital discharge (HD), significantly more patients had a restoration of neurological function, as determined by a CPC of 2 or lower, with the devices plus TH compared with conventional or standard (S) CPR plus TH.

tion is maintained with ACD CPR + ITD, as it causes hypotension with conventional CPR.[38] These new data complement recent findings that suggest that use of epinephrine, a potent vasoconstrictor, is harmful in patients in cardiac arrest. The mechanical adjuncts described above increase both perfusion and blood pressure, whereas epinephrine, especially when used too often or in too high a dose, will increase blood pressure but reduce cerebral and myocardial perfusion.

A second new resuscitation strategy is similarly important. It has been known for many years that reperfusion injury can occur during the first minutes of reperfusion after a period of ischemia, and can be extremely harmful. While the mechanisms are only partially understood, reperfusion of ischemic heart and brain tissue, for example, is associated with mitochondrial damage secondary to a cell membrane transport pore that opens in the setting of ischemia. Use of cyclosporine A before reperfusion is thought to be protective against reperfusion injury, as is limiting flow during the first 1 to 3 minutes of reperfusion.[39] One strategy that has been described in animals is "stutter" CPR, whereby in the first 3 minutes of CPR short, intentional pauses are used to reduce or prevent reperfusion injury. This approach, when coupled with ACD CPR + ITD and sodium nitroprusside, has been shown to significantly improve neurologically intact survival after cardiac arrest in pigs after up to 15 minutes of untreated ventricular fibrillation.[40] To date, experience in humans with this approach is anecdotal and limited.

Recent research on augmenting circulation during resuscitation has been focused on ways to maintain continuous subatmospheric pressure during CPR, except when providing positive-pressure ventilation,[41] and ways to support circulation with extracorporeal devices.[42] As with sodium nitroprusside and strategies to limit reperfusion injury, these new mechanical approaches provide noninvasive and invasive tools to augment and sustain circulation. While no definitive long-term data are available, the authors anticipate these new approaches will provide further benefits to this patient population.

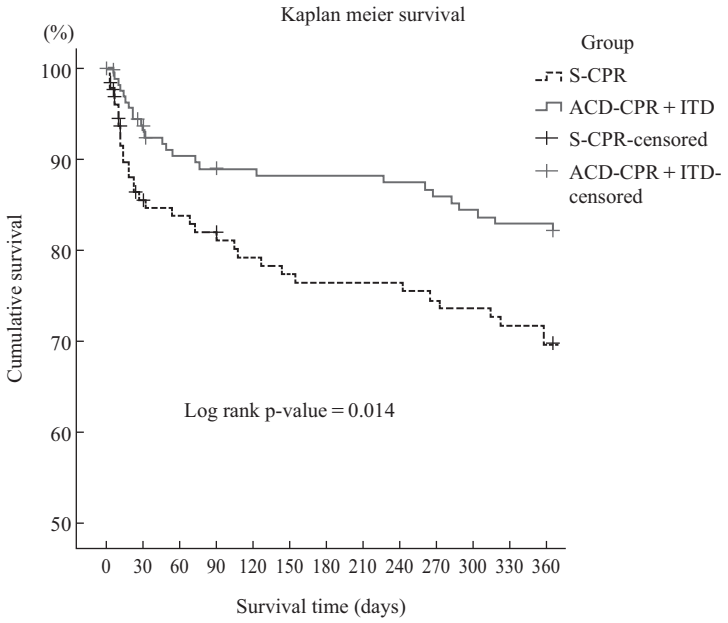


Fig. 8 Kaplan-Meier survival curves for all subjects who were discharged alive or were alive at 30 days. A total of 2738 patients in nontraumatic cardiac arrest were randomized to active compression-decompression (ACD) cardiopulmonary resuscitation (CPR) + impedance threshold device (ITD) or conventional or standard (S) CPR during the ResQTrial. Regardless of the cause of cardiac arrest, survival to 1 year was greater in the ACD CPR + ITD group: 82.1% versus 69.7%, p = 0.014 [log-rank (Mantel-Cox) test of equality of survival distributions for the different groups].

Conclusions

Despite over half a century of practice with conventional CPR, outcomes remain dismal. However, recent progress in this field has provided the physiological blueprint for hope and new ways to improve outcomes. On the basis of our new physiological understanding of CPR, use of combined ACD CPR plus ITD significantly improves short- and long-term outcomes after cardiac arrest. This approach is synergistic with advances in therapeutic hypothermia, mechanical means to provide continuous chest compressions, and other improvements in post-resus citation care. It is now time to move away from conventional CPR with a pair of hands and use new approaches that substantially increase cerebral and myocardial perfusion and improve the likelihood of long-term neurologically favorable survival.

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Keith G Lurie Curriculum vitae

July 1976 Research Assistant, Biochemistry Department, University of Connecticut Medical School
May 1978 Bachelor of Arts (BA) in Architectur, Molecular Biology and Biophysics, Yale University
Sept. 1978 Research Assistant, Cardiology, Department of Medicine, Stanford University
June 1982 Medical Doctor (MD), Stanford University
July 1985 Research Associate, Department of Biophysics and Biochemistry, University of Pennsylvania
July 1989 Assistant Professor of Medicine, Cardiology Division University of California
Sept. 1991 Assistant Professor of Medicine, Cardiovascular Division, University of Minnesota
July 1995 Associate Professor of Medicine, Cardiovascular Division, University of Minnesota
Sept. 2000–present Graduate Faculty, Department of Bioengineering, University of Minnesota
July 2003–present Professor of Emergency Medicine and Internal Medicine, University of Minnesota

Honors and Awards (selected)

Cum Laude; Yale University (1978), Research Fellow; Biophysics and Biochemistry Department Award; University of Pennsylvania (1985–1986), National Institutes of Health (NIH) Physician-Scientist Award "Quantitative Histochemistry of Purkinje Cell Metabolism "Principle Investigator (PI) (1986–1993), Minnesota Heart Association Grant-in-Aid "Aging and the AV node" (1993–1995), American Heart Association Grant-in-Aid "Active Compression-Decompression CPR" (1994–1996), American Heart Association Fellowship "G-Proteins and the AV Node" (W Adkisson) (1996–1998), American Heart Association Fellowship "Adenosine and the AV Node" (B Padanilam) (1999–2000), American Heart Association Fellowship "Novel CPR Therapies" (D Yannopoulos) (2003–2005), US Army Small Business Innovation Research (SBIR) Achievement Award (2008), The US Space Foundation "The Space Technology Hall of Fame"(2008)