Harnessing Cardiopulmonary Interactions to Improve Circulation and Outcomes After Cardiac Arrest and Other States of Low Blood Pressure

38

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Abstract

This chapter reviews the traditional therapies used to treat sudden cardiac arrest and shock (cardiopulmonary resuscitation or CPR) and presents modifications of this standard technique to enhance the delivery of oxygenated blood to the heart and brain. In addition, the authors provide descriptions of novel noninvasive technologies that can be used to increase the chance for survival, in particular technologies that provide intrathoracic pressure regulation (IPR) therapy to improve perfusion in profound states of shock. Furthermore, impedance threshold devices and active compression-decompression (ACD) CPR treatment are described, and the results of numerous animal and clinical studies are presented.

Keywords

Cardiac arrest • Sudden cardiac death • Shock • Intrathoracic pressure regulation

Abbreviations

ACD	Active compression-decompression
ACD-CPR	Active compression-decompression cardiopulmonary resuscitation
BLS	Basic life support
CePP	Cerebral perfusion pressure
CPP	Coronary perfusion pressure
CPR	Cardiopulmonary resuscitation
DBP	Diastolic blood pressure
EMS	Emergency medical services
ETP	Endotracheal pressure
FDA	Food and Drug Administration
ICP	Intracranial pressure
IPR	Intrathoracic pressure regulation
ITD	Impedance threshold device
ITP	Intratracheal pressure
ITPR	Intrathoracic pressure regulator
LBNP	Lower body negative pressure
MAP	Mean arterial pressure
PEA	Pulseless electrical activity
RA	Right atrial
ROC	Resuscitation Outcomes Consortium
ROSC	Return of spontaneous circulation
SBP	Systolic blood pressure
VF	Ventricular fibrillation

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38.1 Introduction

Cardiac arrest and life-threatening hypotension typically occur suddenly and without warning. This chapter will briefly review the traditional therapies used to treat sudden cardiac arrest and shock. In addition, we provide descriptions of novel noninvasive technologies that can be used to increase the chance for survival, in particular technologies that provide intrathoracic pressure regulation (IPR) therapy to improve perfusion in profound states of shock.

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38.2 Sudden Cardiac Arrest

Despite the widespread practice of basic and advanced life support, the vast majority of patients in cardiac arrest never survive to hospital discharge. The clinical toll is enormous—more than 1000 adults die each day in the United States alone from an out-of-hospital cardiac arrest, and a similar number of individuals die daily inside the hospital. Many of these patients have no prior warning signs and thus die in the prime of their lives. Sadly, little has changed in the practice of cardiopulmonary resuscitation (CPR) in the past 50 years; thus, it is not surprising that survival rates have remained relatively constant for decades at ~6 % nationwide for all patients with an out-of-hospital cardiac arrest. For patients who present with ventricular fibrillation (VF), survival rates range from 10 to 45 %, depending upon the city where they arrest. Since the frequency of VF is declining, and nearly 70 % of all patients currently present with either pulseless electrical activity (PEA) or asystole, new approaches are desperately needed to decrease mortality from this nation's #1 killer. While the differences in patient outcome between regions are due to many factors, the intrinsic mechanical inefficiency of conventional manual CPR limits the potential of even the most highly skilled rescuers. Moreover, the vast majority of the 300,000+ cardiac arrests that occur annually in the United States occur in the home, and delays to treatment severely limit the chances for patient survival. As a result, even with the most efficient emergency medical services (EMS), less than 20 % of all patients with an out-of-hospital cardiac arrests are discharged from the hospital with intact neurological function [1, 2].

The immediate application of CPR is critical when sudden cardiac arrest occurs. The primary purpose of manual standard CPR is to pump blood from the heart to vital organs during the compression phase and to enhance the return of blood back into the heart (preload) during the chest wall recoil (or decompression) phase. Compression and decompression are illustrated in Fig. 38.1. Devices that optimize this cardiovascular physiology are helpful adjuncts and have been shown to improve outcomes after cardiac arrest. Conversely, there have been several common mistakes identified in standard CPR techniques that result in suboptimal CPR quality, including: (1) not allowing full chest wall recoil, (2) inadequate compression forces, (3) incorrect compression rates, and/or (4) hyperventilation.

It is critical to understand that blood flow to the vital organs is severely reduced during standard CPR, even under the best of circumstances [3, 4]. During standard CPR, chest compression results in an elevation of intrathoracic pressure and indirect cardiac compression. Both of these mechanisms result in forward blood flow out of the chest to perfuse the brain and other vital organs. However, the effectiveness of standard CPR is largely determined by the amount of blood returned to the chest to refill the heart after each compression phase. This process is highly dependent on the degree of chest wall recoil. When the chest recoils, intrathoracic pressures fall relative to extrathoracic pressures, and venous blood returns to the right heart.

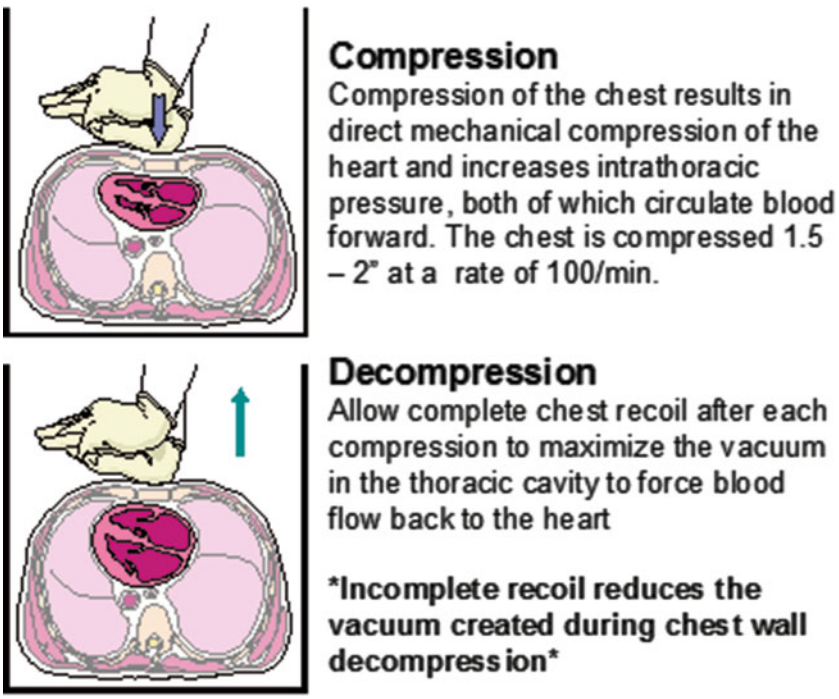


Fig. 38.1 Compression and decompression phases of cardiopulmonary resuscitation

38.3 The Impedance Threshold Device for Cardiac Arrest

Standard CPR by itself has been shown to be inherently inefficient, in large part due to the lack of adequate blood return to the thorax during the chest wall recoil phase [3, 4]. Moreover, the coronary perfusion pressure (CPP), a critical determinant of CPR efficacy, is only marginally adequate as the pressure gradient between the aorta, the right atrium, and left ventricle is far from optimal. During the decompression (or passive relaxation) phase of standard CPR, a small decrease in intrathoracic pressure (relative to atmospheric pressure) develops, which promotes blood flow back to the heart. Myocardial perfusion predominantly occurs during this decompression phase. Uniquely, the impedance threshold device (ITD) (ResQPOD®, Advanced Circulatory, Roseville, MN, USA) was designed to improve venous return to the heart during the decompression phase of CPR [3–9]. In so doing, the ITD increases the CPP during CPR, enhancing delivery of oxygenated blood to both the heart and brain. The ITD shown in Fig. 38.2 works effectively with both a face mask and an advanced airway (e.g., endotracheal tube, supraglottic airway).

The concept underlying the ITD was first discovered when measuring intrathoracic pressures in patients undergoing a new type of CPR, active compression-decompression (ACD) CPR [10]. It was found that if the endotracheal tube was transiently occluded during the active decompression phase, intrathoracic pressures became markedly more negative. This led to the idea of transiently blocking the airway or impeding inspiratory gas exchange during the chest wall decompression phase of CPR to create a greater pressure differential between the thorax and the rest of the body, thereby enhancing blood flow back into the thorax. As such, the ITD harnesses the kinetic energy of the chest wall recoil, thereby augmenting the "bellows-like" action of the chest with each compression-decompression cycle [8, 9]. The ITD contains pressure-sensitive valves that selectively impede the influx of inspiratory gas during chest wall decompression, thereby augmenting the amplitude and duration of the vacuum within the thorax. This vacuum draws more venous blood back into the heart, resulting in increased cardiac preload, followed by improved cardiac output and vital organ perfusion. During chest compression, the one-way valve is open and does not cause any resistance to exhalation. When the resuscitation bag is squeezed for active ventilation, the one-way valve remains open and does not cause any resistance to gas exchange. In this manner, the ITD functions to lower intrathoracic pressure only during the decompression phase of CPR without compromising patient ventilation. The ITD consists of a valve body, a one-way pressure-sensitive silicone valve, and a safety check valve [5]. When a spontaneous pulse returns, the ITD is removed from the respiratory circuit. The safety check valve serves as a precautionary measure to prevent negative pressure pulmonary edema and potential barotrauma and to enable the patient to breathe if there is a return of spontaneous ventilation and the ITD has not been removed.

Positive data from animal studies and clinical trials, described in detail below, formed the basis for the American Heart Association's Level IIb recommendations for the use of ITDs in the 2010 American Heart Association (AHA) guidelines. Today, the ResQPOD® is sold in the United States

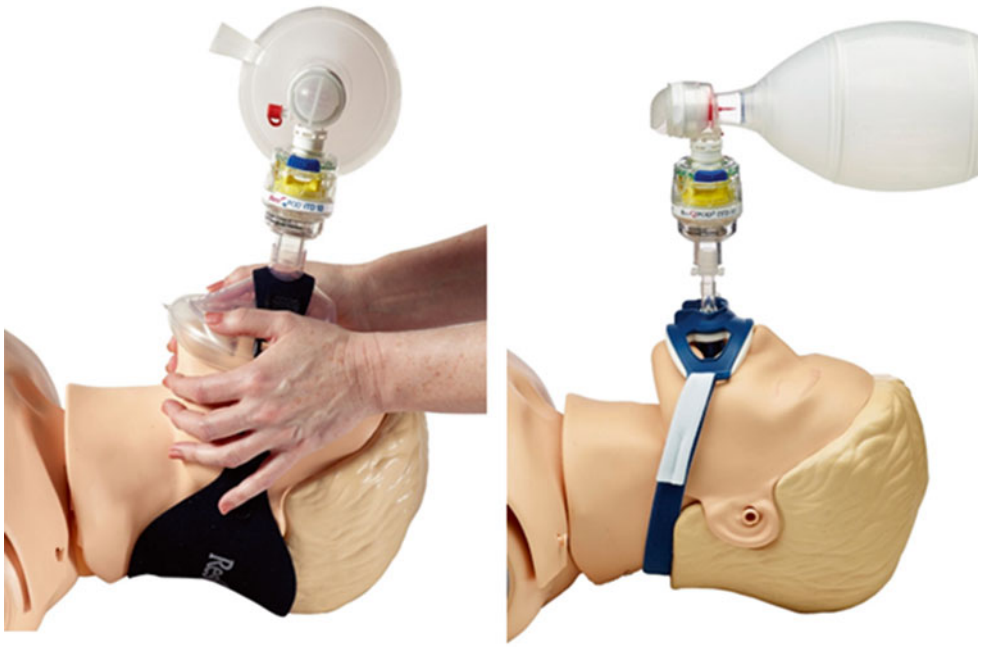


Fig. 38.2 ResQPOD® impedance threshold device on a face mask and endotracheal tube

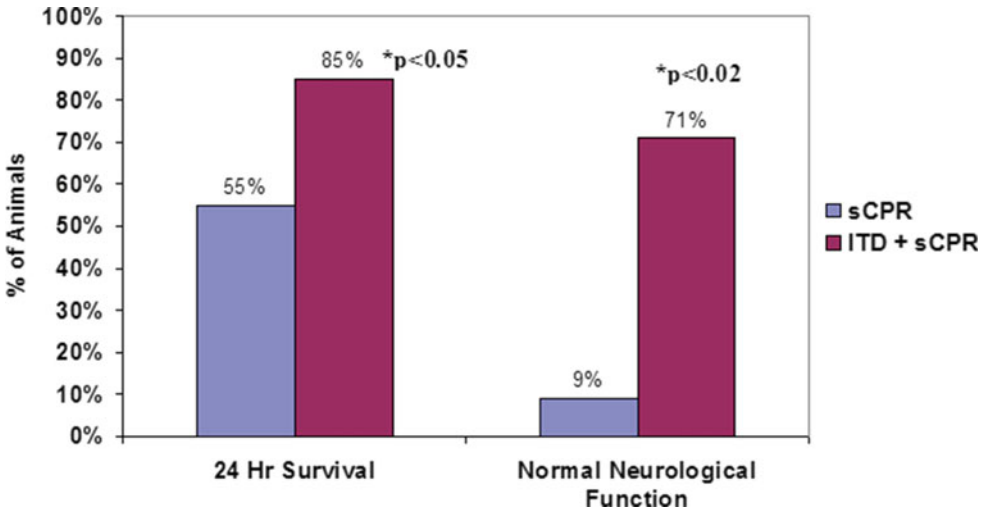


Fig. 38.3 Percentage of animals with 24-h survival and normal neurological function comparing standard CPR (*sCPR*) to impedance threshold device (*ITD*) + standard CPR after cardiac arrest in pigs

as a device that can be used to increase circulation in patients with low blood pressure, including patients in cardiac arrest. Further, Aufderheide et al. reported outcomes from the use of the ITD in seven EMS systems in the United States. They showed that the changes in CPR practice, which now emphasize more compressions and fewer ventilations, complete chest wall recoil, uninterrupted chest compressions during advanced airway management, and the use of the ITD during basic life support (BLS) and advanced life support resulted in a doubling of hospital discharge rates for all patients, regardless of presenting heart rhythm, i.e., from 8 to 16 % [11]. In addition, the neurological outcomes were similar between groups, and patients who had an initial rhythm of ventricular fibrillation had a hospital discharge rate of 28.1 % compared with 17.2 % in the historical control group.

One of the first animal studies performed with the ITD demonstrated that the use of the active ITD increased 24-h survival and preserved neurological function after cardiac arrest in swine [8]. There was a statistically significant increase in both of these key outcome parameters, as shown in Fig. 38.3. The improved neurological function was observed in the overall study group, as well as in the subset of animals that were resuscitated with defibrillation shock therapy and epinephrine. Blood gas data demonstrated that oxygenation was adequate in both groups and no differences were observed between groups on autopsy. The intrathoracic pressures were significantly lower in the ITD group. Subsequent studies have demonstrated that the use of the ITD also lowers intracranial pressures (ICPs) more rapidly than in animals treated with standard CPR alone. It is hypothesized that these observations help to explain the markedly improved neurological outcomes in this porcine survival study [8].

Importantly, the first randomized double-blinded prospective clinical trial showed that the use of the ITD during standard CPR resulted in an increase in systolic blood pressure. However, in that study nearly all of the patients also received excessively high ventilation rates. Follow-up animal studies demonstrated that excessive ventilation (termed *hyperventilation*) during cardiac arrest actually inhibited venous return, compromised hemodynamics, and resulted in increased mortality rates [12, 13]. In addition, frequent incomplete decompression of the chest was also witnessed and recorded in that study. Follow-up studies in animals demonstrated that incomplete chest wall recoil resulted in positive intrathoracic pressures, which in turn decreased venous return and caused markedly poorer cardiac and cerebral blood flows; incomplete decompression is thus a key component in the deficiency of standard CPR [14]. These observations also demonstrate how important the cardiopulmonary cerebral interactions are during CPR.

In the first US double-blinded randomized survival study of the ITD, there was nearly a threefold increase in 1-h and 24-h survival rates in patients with an initial rhythm of PEA when comparing treatment with a sham versus active ITD. Figure 38.4 shows the relative percent survival in all subjects initially presenting with PEA. It is important to emphasize that the results from this study were observed in the setting of real-world CPR, prior to the use of tools to help control ventilation frequency or the adequacy of compression rates, depths, and complete chest wall decompressions. Figure 38.5 shows the percent survival in all subjects presenting with various types of cardiac rhythms.

The benefits of the ITD in patients with PEA can be better understood by examining the hemodynamic tracings of one of the substudy group patients, as shown in Fig. 38.6. When CPR was discontinued, there was a persistent regular electrical activity, but the aortic pressures were inadequate to generate a palpable pulse. This example of PEA demonstrates that although there were small rises in the arterial pressure with each cardiac contraction, this was insufficient to cause a palpable pulse or effective vital organ blood flows. Importantly, without effective vital

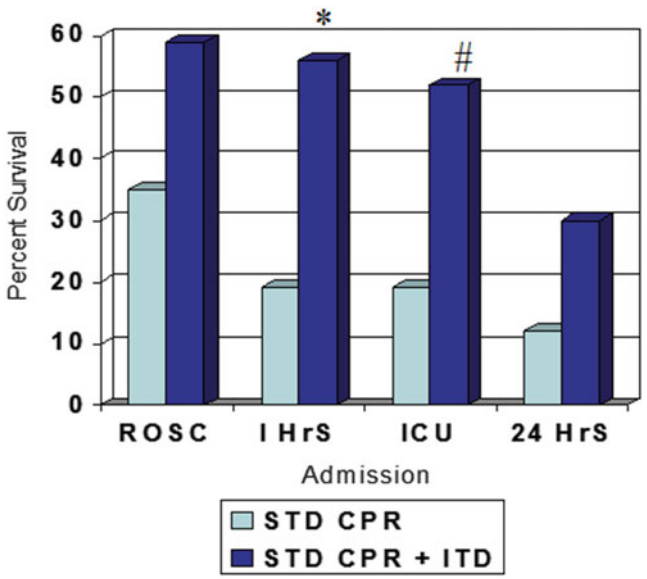


Fig. 38.4 Outcomes for all subjects initially presenting with pulseless electrical activity. *$p=0.01$, #$p=0.02$. *ROSC* return of spontaneous circulation, *1 HrS* 1-hour survival; *ICU* ICU admission rate, *24 HrS* 24-hour survival

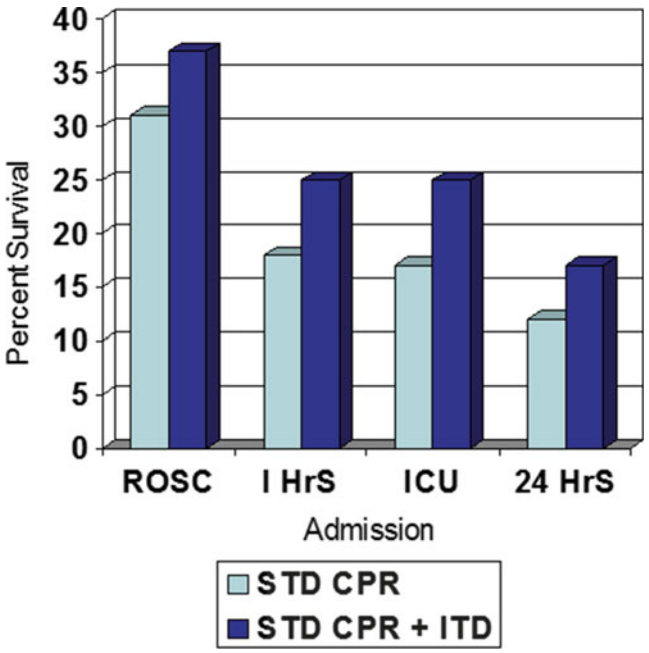
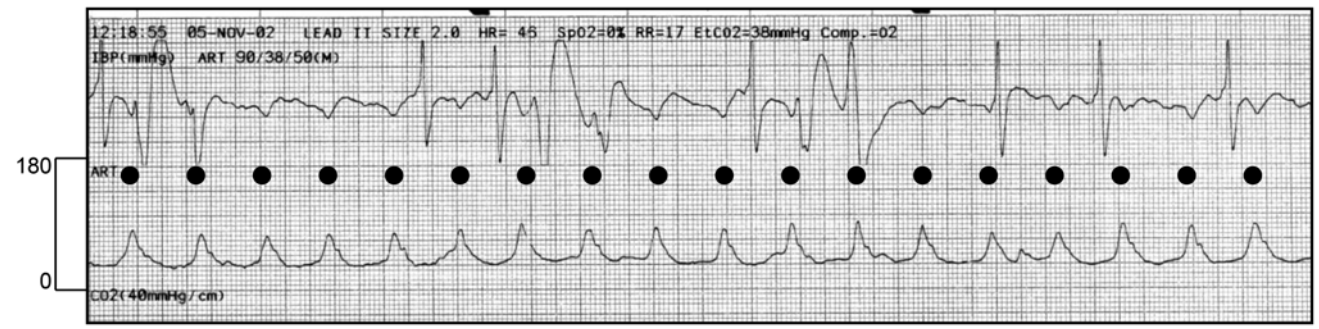
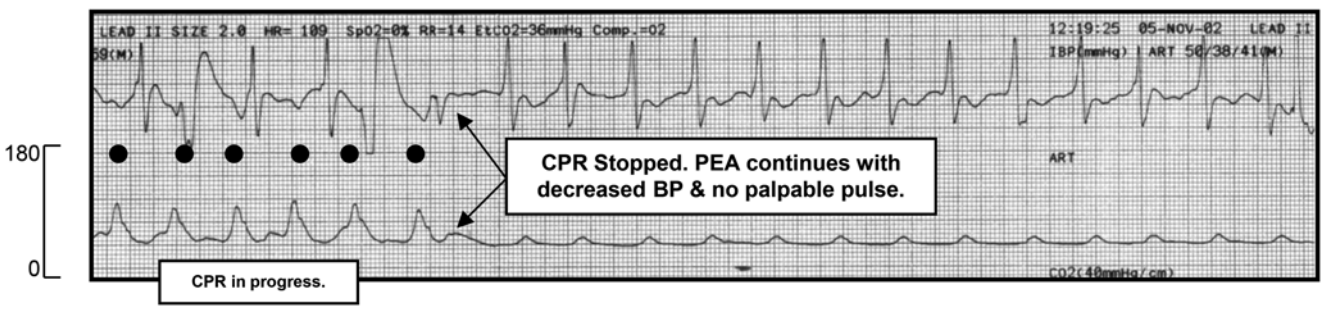


Fig. 38.5 Outcomes for all subjects presenting in all rhythms. *ROSC* return of spontaneous circulation, *1 HrS* 1-hour survival, *ICU* ICU admission rate, *24 HrS* 24-hour survival



Top Tracing: Arterial pressures during CPR with initial rhythm of PEA. In both tracings, top channel is the ECG; bottom channel shows invasive arterial pressures; black dots denote chest compressions. ECG deflections are seen with each compression. In this example, BP is 90/38 mmHg during CPR.



Bottom Tracing: Example of what happens to arterial pressures when CPR is stopped in PEA. In this example, BP is 95/40 during CPR, then decreases to 50/38 when CPR is discontinued.

Fig. 38.6 Hemodynamic tracing of a patient with pulseless electrical activity (*PEA*). *BP* blood pressure, *CPR* cardiopulmonary resuscitation

organ perfusion, return of spontaneous circulation (ROSC) is not possible. We speculate that the known increase in circulation and blood pressures associated with the use of the ITD, in both animals and humans, is enough to increase the aortic systolic and diastolic pressures to a sufficient level to allow for effective vital organ perfusion. It should be noted that the number of patients in VF treated with the ITD in that study was too low to definitively determine if the ITD would benefit this patient subgroup. Nonetheless, hospital discharge rates were 6 % in the control group and 14 % with the active ITD in that study.

One of the most important findings from the first clinical study when the ITD was used with standard CPR was that the overall quality of administered CPR was very poor. Based on the hemodynamic substudy data collected in this clinical trial, hyperventilation was recorded in 100 % of cases, and incomplete chest wall recoil was recorded in approximately 50 % of cases. These critical findings demonstrated the challenges of performing standard CPR with a pair of human hands alone, and this resulted in a change in the initial design of the ITD; a timing light was added that flashes at 10 times per minute to provide the rescuer with guidance on when to ventilate the patient and how to assure that compressions are performed 100 times per minute (compress 10 times per light flash). In the future, the use of the ITD will be even more effective once improved standard CPR is practiced and performed uniformly.

It is also important to emphasize that one of the very exciting recent advances in CPR research has been the rediscovered benefit of therapeutic hypothermia after successful resuscitation. Several studies have demonstrated a 50 % increase in long-term survival rate and improved neurological function in survivors of cardiac arrest with VF who received therapeutic hypothermia in the hospital shortly after resuscitation [15–17]. Therefore, when hypothermia is applied to patients resuscitated after PEA, there should be a similar increase in long-term survival rate with good neurological function. Fortunately, a growing number of patients are now routinely treated with therapeutic hypothermia after successful resuscitation.

38.4 Effects of Incomplete Chest Wall Recoil and Hyperventilation on the Quality of Standard CPR

The AHA recognized the inefficiencies of standard CPR in 2000, 2005, and 2010 when they issued new guidelines for performing CPR. The latest guideline reinforces the importance of the chest decompression phase in teaching CPR: *Rescuers should allow complete recoil of the chest after each compression, to allow the heart to fill completely before the next compression* [18].

As mentioned previously, Aufderheide et al. observed rescuers frequently leaning on the chest during the decompression phase, thereby maintaining some residual and continuous pressure on the chest wall during the decompression phase of CPR. This prevented complete chest wall recoil. More specifically, airway pressures were consistently measured as positive during the decompression phase (>0 mmHg) in 6/13 (46 %) of consecutive adults. This was caused by incomplete chest wall recoil alone or combined with prolonged, positive ventilations. With standard CPR and incomplete chest wall recoil, insufficient intrathoracic vacuum pressures are achieved. In contradistinction, when active compression and decompression are performed in conjunction with the use of an ITD, a significant intrathoracic vacuum results.

In 2005, Yannopoulos et al. conducted an animal study to address the question of the physiological impact of incomplete chest wall recoil [14]. Nine pigs in VF for 6 min were treated with an automated CPR device with compressions at 100/min, a compression depth of 25 % of the anteroposterior diameter, and a compression to ventilation ratio of 15:2. After complete (100 %) chest wall decompression for 3 min during standard CPR, the decompression depth was reduced to 75 % of complete decompression for one minute of CPR and then restored for another one min of CPR to 100 % decompression. CPP was calculated as the diastolic aortic—right atrial (RA) pressure. Cerebral perfusion pressure (CePP) was calculated by measuring the area between the aortic pressure curves and the ICP curves. Figure 38.7 sum-

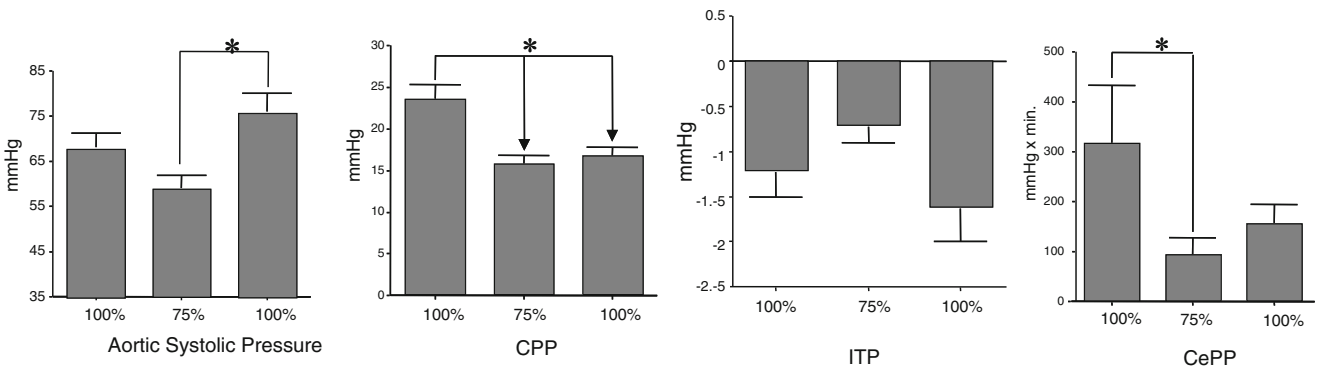


Fig. 38.7 Aortic pressures, coronary perfusion pressure (*CPP*), intrathoracic pressure (*ITP*), and cerebral perfusion pressure (*CePP*) decreases when complete decompression is not allowed (75 %). *$p < 0.05$

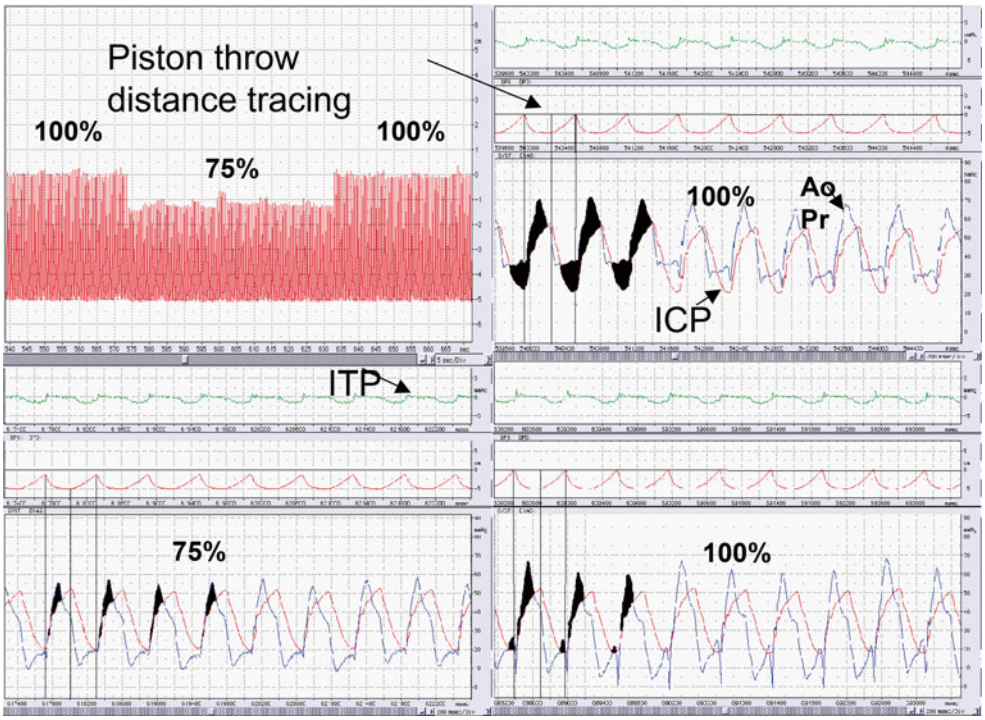


Fig. 38.8 Effect of incomplete chest wall recoil on reducing cerebral perfusion (see text for details). *AoPR* aortic pressure, *ICP* intracranial pressure, *ITP* intrathoracic pressure, *blue* tracings = aortic pressure, *pink* tracings = intracranial pressures

marizes the results of this study including the differences in aortic systolic pressure, CPP, intratracheal pressure (ITP), and CePP. With 100 %–75 %–100 % chest wall recoil, the CPP was 24.2 ± 2.0, 15.0 ± 1.2, and 15.6 ± 1.3 mmHg ($p < 0.05$); CePP was 320 ± 120, 95 ± 15, and 150 ± 30 mmHg min ($p < 0.05$); diastolic aortic pressure was 26.8 ± 2.8, 18.9 ± 2.3, and 18.2 ± 2.1 mmHg ($p < 0.05$); ICP during decompression was 18.1 ± 2.8, 21.6 ± 2.3, and 17.4 ± 2.6 mmHg ($p < 0.05$); RA diastolic pressure was 2.7 ± 1.9, 3.9 ± 1.9, and 2.7 ± 1.6 mmHg ($p < 0.05$); and mean arterial pressure (MAP) was 41.4 ± 2.8, 32.5 ± 2.2, and 36.6 ± 1.9 mmHg ($p < 0.05$). The CPP and CePP never fully recovered after treatment with the 75 % incomplete chest wall decompression. It is striking that a small reduction of chest wall recoil (1 cm), which is a common occurrence during the performance of CPR, resulted in such a marked reduction in cerebral and CPPs.

The effect of incomplete chest wall recoil on reducing cerebral perfusion can be seen graphically in Figs. 38.8 and 38.9 [14]. Figure 38.8a represents, condensed in time, the sequential 100 % chest recoil, 75 % chest wall recoil, and return to 100 % chest wall recoil. Tracings of ITP, aortic pressure (AoPr), and ICP with 200 ms per division are indicated with arrows. Piston throw (in cm) is also shown to sequentially demonstrate the complete (100 %) chest wall recoil (38.8b), 75 % chest wall recoil (38.8c), and return to complete chest wall recoil (38.8d). The positive area between the AoPr and ICP tracing represents cerebral perfusion (marked as black). Note how the area decreases, especially during decompression with incomplete chest wall recoil (75 %) and that it partially recovers when full recoil was restored. Figure 38.9 shows the effect of positive pressure ventilation on CePP. The first tracing shows the aortic and ICP waveforms with full chest wall recoil after a ventilation cycle, while the second tracing shows the aortic and ICP waveforms with incomplete chest wall recoil after a ventilation cycle. Positive pressure gradient (Ao-ICP) is colored black. Note the marked difference in total area during each compression-decompression cycle with and without a positive pressure breath. The bar graphic shows the mean 4-beat area of all animals during and after a ventilation cycle. The mean ± SEM values during 100 and 75 % decompression have been graphed. During positive pressure ventilation, ICP rises and the positive gradient disappears. There was effectively no blood flow to the brain (Fig. 38.9, second panel). This study demonstrated that incomplete decompression has significant deleterious effects on both CPP and CePP. The residual positive intrathoracic pressure during the decompression phase associated with incomplete chest wall recoil decreased forward blood flow, impeded venous return, increased ICP, and undermined the efficiency of CPR. These recent animal studies underscore the fundamental hemodynamic importance of complete chest wall decompression during CPR. Whether rescuers can be retrained to allow for complete chest wall decompression during standard CPR remains an important issue.

A change in CPR technique to allow for the palm of the compressing hand to lift off the chest at the end of decompression may be important to assure full chest wall recoil during standard CPR. Accordingly, Aufderheide et al.

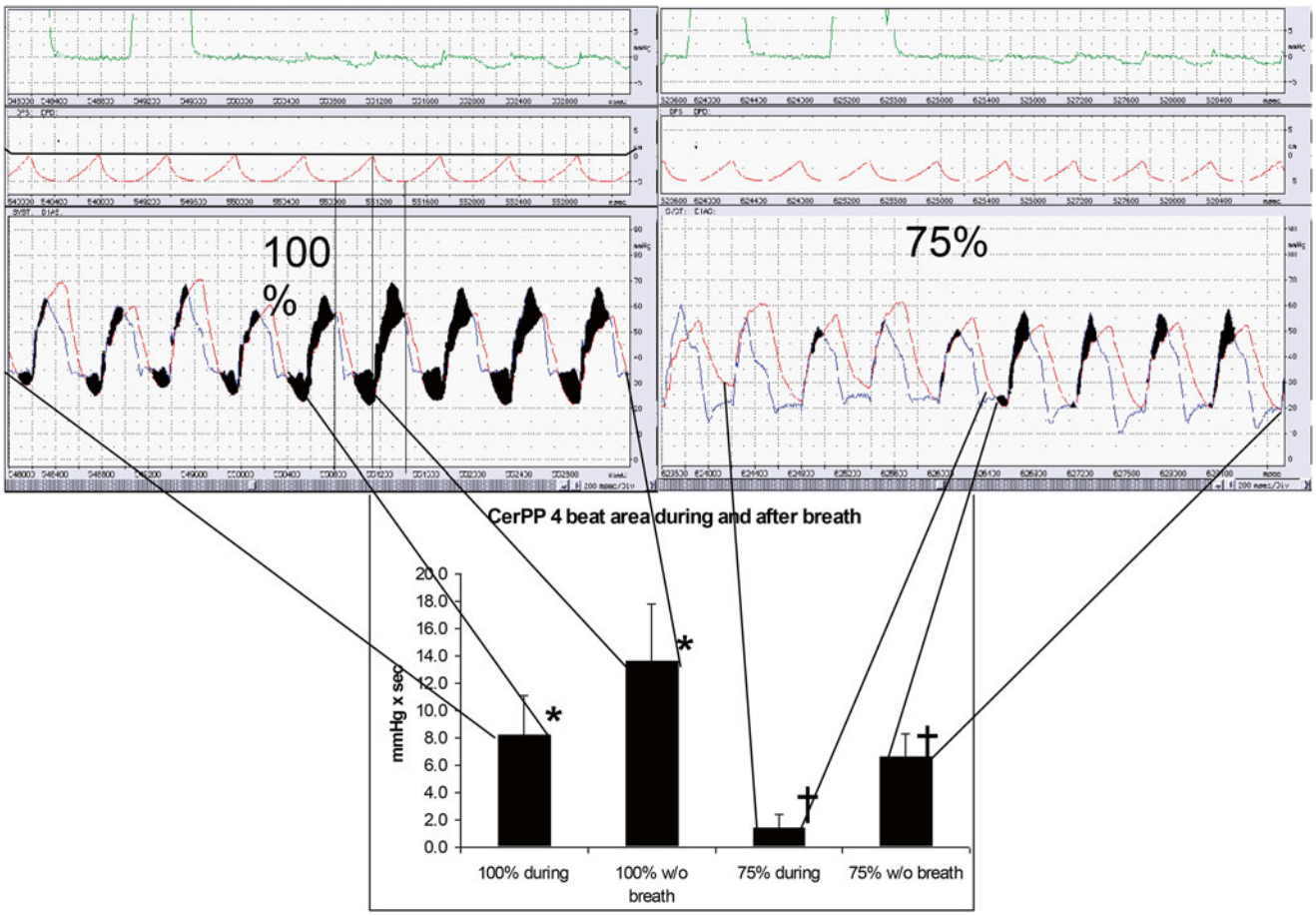


Fig. 38.9 Effect of incomplete chest wall recoil on reducing cerebral perfusion (see text for details). *CerPP* cerebral perfusion pressure

implemented a randomized prospective clinical trial using an independent group of 30 actively practicing and certified EMS providers, not aware of the ongoing trial, in a controlled setting using a recording CPR manikin. The purpose of the study was to evaluate three alternative CPR techniques to determine if they would improve complete chest wall recoil compared with standard CPR while maintaining adequate compression depth and proper hand position placement. The three alternative CPR techniques were: (1) two-finger fulcrum technique (lifting the heel of the hand slightly but completely off the chest during the decompression phase of CPR while using the thumb and little finger as a fulcrum), (2) five-finger fulcrum technique (lifting the heel of the hand slightly but completely off the chest during the decompression phase of CPR, using all five fingers as a fulcrum), and (3) hands-off technique (lifting the heel and all fingers of the hand slightly but completely off the chest during the decompression phase of CPR).

In this study, during standard CPR using the traditionally taught hand position (standard hand position), complete chest wall decompression was recorded in only 16.3 % of all compression-decompression cycles, adequate depth of compression in 48.5 %, and acceptable hand placement in 85.0% of compression-decompression cycles. When compared with standard CPR, the hands-off technique achieved the highest rate of complete chest wall recoil (95.0 % versus 16.3 %, $P<0.0001$) and was 129 times more likely to provide complete chest wall recoil (OR: 129.0; CI: 43.4–382.0) [19]. There were no significant differences in the accuracy of hand placement, depth of compression, or reported increase in fatigue or discomfort with its use compared with the standard hand position. The hands-off technique was easily learned and applied by participating EMTs, because it uses the same hand configuration as is currently recommended by the AHA.

38.5 Optimizing Outcomes with Standard CPR and the Impedance Threshold Device

Aufderheide and colleagues have recently analyzed and applied the combined lessons learned from the initial clinical trials of the ITD and standard CPR. They analyzed data from seven EMS systems that serve a population of more than 3 million patients and reported that, when CPR is performed

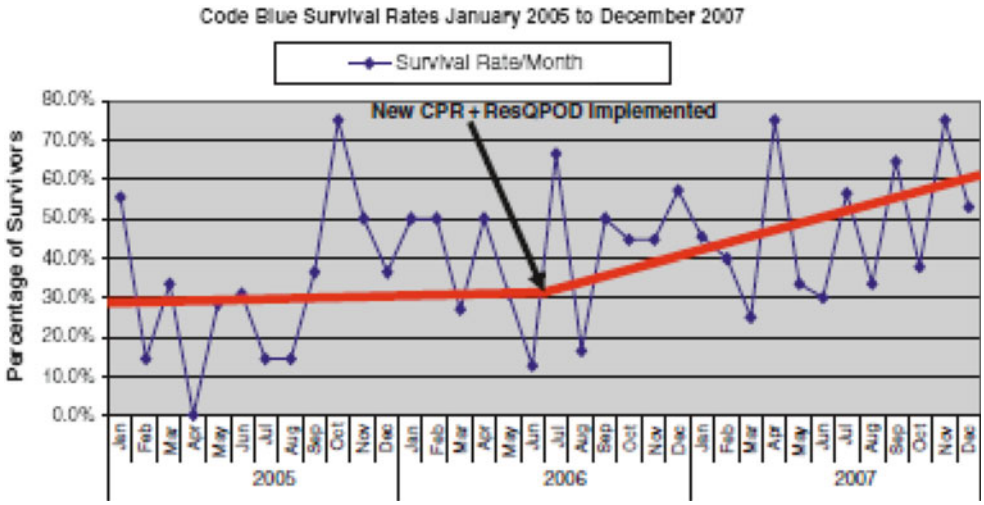


Fig. 38.10 Code blue survival rates in St. Cloud, Minnesota (January 2005 to December 2007). *CPR* cardiopulmonary resuscitation

correctly with the ITD and the mistakes described above are reduced or eliminated by rigorous training and correct ITD used, survival rates increased from 7.9 to 15.7 % for all patients who presented with cardiac arrest; survival rates for those with an initial rhythm of VF increased from 17 to 28 % [11]. Therapeutic hypothermia was not yet in use in these EMS systems and their associated hospitals when these data were obtained. Similar benefits from performing CPR according to the AHA 2005 and 2010 guidelines and the use of the ITD have also been reported for patients in in-hospital cardiac arrest. For example, Thigpen reported that hospital discharge rates in one large Mississippi hospital increased from 17 to 28 % with the administration of this new resuscitation approach [20, 21]. Similar data from St. Cloud Hospital in Minnesota are shown in Fig. 38.10; data from before the change in practice in July 2006 were compared to data after implementation of the new CPR techniques and the ITD. Importantly, the survival rates after an in-hospital cardiac arrest nearly doubled.

A study by Lick et al. investigated the effects of stricter adherence to the AHA guidelines for CPR which included the recommended use of the ITD. The *Take Heart America* initiative was started in an attempt to increase survival from cardiac arrest by focusing on the implementation of the 2005 and 2010 AHA guidelines. It is centered not on a single treatment but rather on a bundle of care approach including community-wide initiatives, including: (1) increased cardiac arrest awareness, (2) increased bystander CPR rates, (3) promoting the use of automated external defibrillator, and (4) the administration of immediate high-quality CPR with the use of the ITD throughout the duration of the code. Further, additional in-hospital treatments such as therapeutic hypothermia, revascularization, and implantable cardiac defibrillators were also emphasized. Survival and outcomes data for patients receiving the bundled interventions were compared to control data prior to implementation of the initiative. Importantly, survival to hospital discharge increased significantly from 8.5 to 19.0 %. These differences were especially striking in the subset of patients who had VF as the initial arrest rhythm; their numbers increased from 17.0 % versus 41.0 % [22]. These results show that when focus is applied to the AHA guidelines including recommended use of the ITD, cardiac arrest survival rates can be greatly improved. In summary, with greater attention to enhancing circulation, based on the newly discovered mechanisms underlying circulation during CPR, significant progress has been made by simply using a pair of hands and the ITD.

It should be noted that a large multicenter study conducted by the Resuscitation Outcomes Consortium (ROC) group looked at outcomes from cardiac arrest using an active ITD versus a sham ITD. The results, originally published in 2011, reported no statistical differences in survival with good neurological function in the active group and the sham group [23]. Additional analyses revealed that the chest compression rates varied widely throughout the study, ranging from 50 compressions/minute to 240 compressions/minute [24]. When the subset of patients received compressions at a rate of 100 ± 10 compressions/minute, the active device showed a marked benefit on survival with good neurological function compared to the sham device. There was also a significant benefit identified for subjects who suffered VF arrests. This second look at the ROC data shows that when CPR is performed correctly, per AHA guidelines, the ITD can increase the rate of survival to hospital discharge with improved neurological function.

Another analysis of the ROC data was independently performed by Yannopoulos et al. [25]. In addition to investigating compression rates as a surrogate for quality CPR, they also included only subjects receiving CPR at a depth of 4–6 cm (AHA recommends depth of 2 in or 5 cm) and a compression fraction (% of time performing chest compressions in a given minute) of >50 %. When these filters were

applied, 7.2 % of subjects receiving CPR with the active ITD survived to hospital discharge with good neurological function, while the rate was only 4.1 % for subjects receiving CPR with the sham ITD ($p = 0.006$). This represents a 43 % increase in survival rate with good neurological function with the active ITD, over the sham ITD. Again, when quality CPR is delivered according to guidelines, the use of an ITD provides benefits to patients.

38.6 Active Compression-Decompression CPR

It has been shown that despite training, it is difficult to perform standard manual CPR correctly, e.g., allowing for the chest to fully recoil following each compression. These problems result in significantly less blood flow back to the heart and reemphasize that perhaps another device is needed to correct this widespread problem. Correction of this basic flaw (incomplete chest wall recoil) through the use of a technique that ensures full chest wall recoil and user guidance has the potential to significantly improve the chance for survival after cardiac arrest. One such technique is ACD-CPR which is performed with an ACD-CPR device.

More specifically, ACD-CPR increases the naturally occurring negative intrathoracic pressure by physically lifting the chest wall and helping it to return to its resting decompressed position. During standard CPR, the chest wall's natural elasticity will partially recoil from compression. Several factors can contribute to less than optimal recoil: (1) patient age, (2) brittle or broken ribs, (3) a separated or broken sternum, (4) a barrel-shaped chest, (5) the presence of chest concavity, and/or (6) the tendency for rescue personnel to lean on the chest and thus cause incomplete chest wall recoil during performance of CPR. The use of an ACD-CPR helps ensure that the chest re-expands to generate the negative intrathoracic pressure needed to allow passive filling of the heart.

For example, ACD-CPR can be performed with a hand-held suction device (ResQPUMP®, Advanced Circulatory Systems) fixed on the anterior chest wall. During the compression phase, the chest is compressed, and blood is forced out of the heart to perfuse the vital organs, as with standard CPR. Next, when the chest is actively pulling up with the device, a vacuum is created within the thorax, drawing more blood back into the heart. This technique improves hemodynamics [26, 27] and, in some studies, long-term survival rates with patients in cardiac arrest, as compared with patients receiving standard CPR alone [28, 29]. The ACD-CPR device is currently being used in many countries throughout the world including France and Israel, as well as parts of China, Japan, and Germany (Fig. 38.11). ACD-CPR in combination with the ITD, known as the ResQCPR™ System, received regulatory clearance in May of 2015 from the Food and Drug Administration (FDA) with an indication for use as a CPR adjunct to improve the likelihood of survival in adult patients with non-traumatic cardiac arrest.

It should also be noted that ACD-CPR + ITD has been evaluated in multiple animal and clinical trials and is currently recommended in the AHA guidelines as an alternative to standard CPR. Importantly, the device combination has been shown to quadruple blood flow to both the heart and brain, compared with manual standard CPR alone.

Fig. 38.11 ResQPUMP®, the US version of the active compression-decompression cardiopulmonary resuscitation device. The force gauge and metronome are used to guide the rescuer in the proper performance

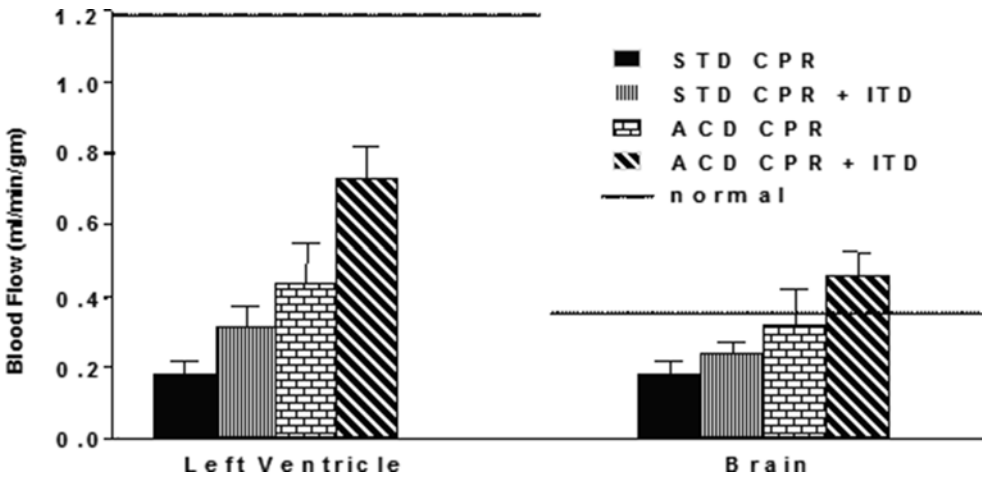


Fig. 38.12 Blood flow in a porcine model. The cumulative effect of ACD-CPR and ITD devices [9]. Solid horizontal line represents normal baseline values. *STD* standard, *ACD* active compression-decompression, *CPR* cardiopulmonary resuscitation, *ITD* impedance threshold device

This device combination also significantly increases blood pressures and survival rates [29–31].

Lurie et al. specifically studied the effects of ACD-CPR and an ITD on blood flow; the results are summarized in Fig. 38.12. Preclinical animal studies demonstrated that left ventricle and cerebral blood flows were markedly improved with ACD-CPR + ITD [10, 32]. In these studies, CPPs were >20 mmHg, the minimum CPP thresholds needed to optimize the chance for survival in both humans and in a porcine model of cardiac arrest [33, 34]. The device combination also optimized perfusion within the brain, which was found to be even greater than baseline levels after a prolonged arrest, when comparing standard CPR to the combination of ACD-CPR + ITD [10]. The investigators believe that one of the reasons that the clinical trials with ACD-CPR + ITD have been successful is secondary to the marked increases in cerebral perfusion that can be achieved with this new approach. These findings have been reproduced by several other investigators using both pediatric and adult pigs in cardiac arrest [4, 35]. Improved forward blood flow and vital organ perfusion with use of ACD-CPR + ITD also enhances drug efficacy during CPR [36]. For example, it was shown that the effects of exogenous vasopressin were significantly enhanced with ACD-CPR + ITD for hypothermic pigs, as reflected by higher coronary and CePPs and improved cerebral metabolic profiles.

In general, the use of the combination of ACD-CPR and the ITD can be considered to be synergistic. To date, four randomized clinical trials have been performed to evaluate the relative effectiveness and safety of the ACD-CPR + ITD in humans [30, 31, 37, 38]. The first blinded randomized clinical trial focused on resultant hemodynamics in patients with out-of-hospital cardiac arrest [37]. Eleven patients were treated with an active (functional) ITD and 10 with a sham (placebo) ITD. In that study, end-tidal carbon dioxide ($ETCO_2$) levels rose more rapidly and reached higher levels with the active ITD; systolic and diastolic blood pressures were nearly normal in the active ITD group (109/57 mmHg) versus the sham ITD group (89/35 mmHg, $P < 0.01$). In addition, ROSC occurred more rapidly in the active ITD group compared with the sham ITD group. Based upon these data, the use of ACD-CPR + ITD was recommended as an alternative to standard CPR in the 2000 AHA guidelines [39].

Another study demonstrated that the ITD augments negative intrathoracic pressure when applied to a face mask [38]. This is important because it indicates that inspiratory impedance can be added during BLS airway management (by first responders and perhaps even lay rescuers prior to intubation). Patients with out-of-hospital cardiac arrest were randomized prior to endotracheal intubation to either a sham or active ITD, and intrathoracic pressure tracings were recorded. Addition of the active ITD to the face mask resulted in an immediate decrease in intrathoracic pressures during ACD-CPR. Each time the active ITD was used, there were significant reductions in the decompression phase intrathoracic pressures. These studies demonstrated, for the first time, the degree of negative intrathoracic pressures achieved with ACD-CPR + ITD in humans. The average maximum negative intrathoracic pressure was −7.3 mmHg with the active ITD on an endotracheal tube versus only −1.3 mmHg with the sham ITD. A second important finding was that it took up to 5 compression-decompression cycles to achieve the maximum negative intrathoracic pressures, as respiratory gases are expelled from the chest and prevented from reentry. This mechanism plays a key role in the function of the ITD. Each time an active, positive pressure, ventilation was delivered, the decompression phase intrathoracic vacuum was lost and required regeneration. Thus, the less frequently the ventilation rate was employed, the greater the blood flow back to the heart. A recent study using standard CPR with the ITD in pigs confirmed this important observation [12]. This has become an important theme for all types of CPR; ventilations interrupt CPP and should be reduced to the minimum required to maintain oxygenation and transpulmonary circulation.

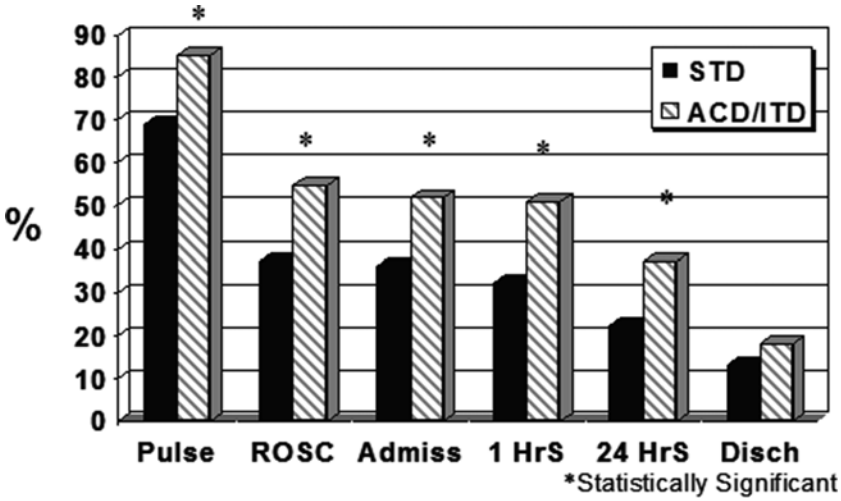


Fig. 38.13 Outcomes associated with comparison of standard cardiopulmonary resuscitation (STD) and ACD-CPR + ITD ($n = 210$) in Mainz, Germany. *1HrS* 1-hour survival, *24HrS* 24-hour survival, *ACD* active compression-decompression, *Admis* hospital admission, *CPR* cardiopulmonary resuscitation, *Disch* hospital discharge, *ITD* impedance threshold device, *ROSC* return of spontaneous circulation

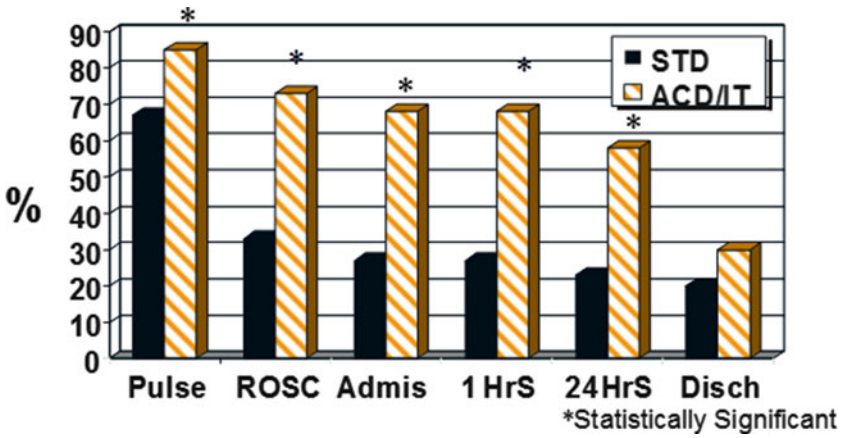


Fig. 38.14 Outcomes in patients randomized with either standard CPR (STD) or ACD-CPR + ITD with witnessed ventricular fibrillation in Mainz, Germany ($n = 70$). *1HrS* 1-hour survival, *24HrS* 24-hour survival, *ACD* active compression-decompression, *Admis* hospital admission, *CPR* cardiopulmonary resuscitation, *Disch* hospital discharge, *ITD* impedance threshold device, *ROSC* return of spontaneous circulation

It is generally accepted that ACD-CPR with an ITD improves short-term survival rates after cardiac arrest. A recent prospective controlled trial was performed in Mainz, Germany [37]; patients with out-of-hospital arrest of presumed cardiac etiology were sequentially randomized to ACD-CPR + ITD or standard CPR (control subjects) by the advanced life support team after intubation. Patients with an identified initial heart rhythm of VF (42 % of the total), who could not be resuscitated by BLS early defibrillation, were enrolled in this clinical trial, as well as patients with an initial rhythm of asystole or PEA. The primary endpoint was 1-h survival after a witnessed arrest. With ACD-CPR + ITD ($n = 103$), ROSC, 1-h and 24-h survival rates were 55 %, 51 %, and 37 % versus 37 %, 32 %, and 22 % for standard CPR alone ($n = 107$; $p = 0.016$, 0.006, and 0.033), respectively (shown in Fig. 38.13).

One-hour and twenty-four-hour survival rates in patients with a witnessed arrest were dramatically higher after ACD = CPR + ITD—68 and 55 %, respectively, versus 27 and 23 % with standard CPR ($p = 0.002$ and 0.009) (shown in Fig. 38.14).

Hospital discharge rates were 18 % after ACD-CPR + ITD versus 13 % in control subjects ($P = 0.41$). Overall neurological function trended higher with ACD-CPR + ITD versus control subjects ($P = 0.07$).

Importantly, patients randomized >10 min after the call for help to the ACD + ITD CPR group had a greater than three times higher 1-h survival rate (44 %) than control subjects (14 %) ($P = 0.002$). These time-related benefits were observed regardless of presenting rhythm. It should be noted that neurological outcomes in the survivors with delays to treatment with ACD-CPR + ITD were similar to those who were treated with ACD-CPR + ITD more rapidly.

Another prospective blinded study performed in France also demonstrated significantly increased 24-h survival rates with use of ACD-CPR + ITD [31]. In one arm of this study, 200 patients were treated by advanced life support personnel with ACD-CPR and an active ITD, and another 200 patients were randomized to the control group and received treatment with ACD-CPR and a sham ITD. As in other studies from France, most of the patients had an initial rhythm of asystole [28, 29]. The group treated with ACD-CPR and an active

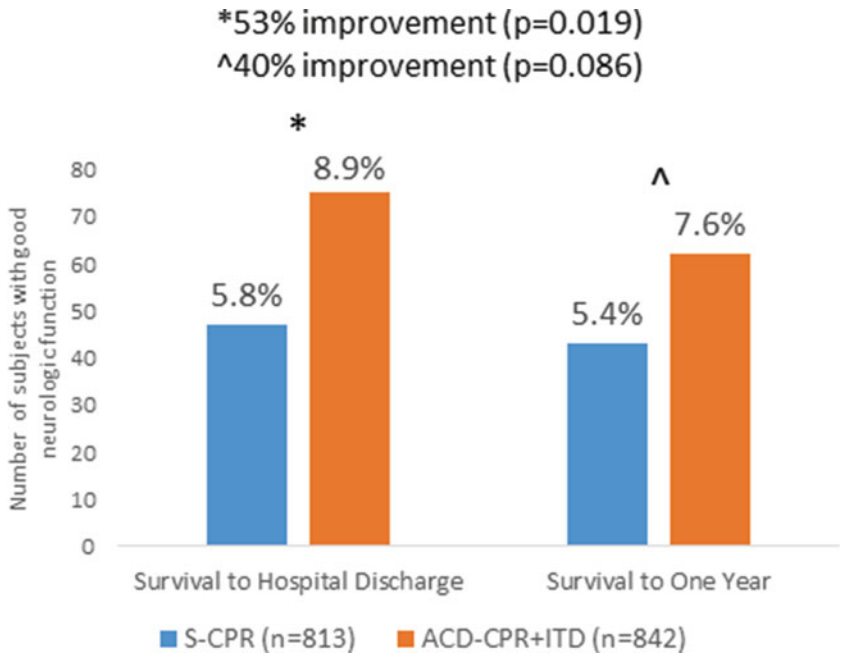


Fig. 38.15 Percentage survival to hospital discharge with favorable neurological outcome in patients randomized to either standard CPR (S-CPR) or ACD-CPR + ITD ($n = 1653$). *ACD-CPR* active compression-decompression cardiopulmonary resuscitation, *ITD* impedance threshold device

ITD had 24-h survival rates of 32 % compared with 24-h survival rates of 22 % in the control population ($P < 0.05$). Because of long EMS response times, survival rates in both groups were very low, but differences in neurological function in the survivors trended in favor of the ACD-CPR + ITD group. Only 1/8 (12 %) of survivors treated with the sham device had normal cerebral function at the time of hospital discharge, versus 6/10 (60 %) in the functional ITD group ($p < 0.07$).

Perhaps the most definitive proof of the effect of ACD-CPR + ITD on long-term survival was demonstrated in a large prospective, randomized clinical trial funded by the National Institutes of Health [40]. This out-of-hospital study compared ACD-CPR plus an ITD to manual standard CPR in adult, nontraumatic cardiac arrest patients. A total of 2470 subjects were randomized and received CPR with one of the two CPR methods, with 1653 subjects meeting final inclusion criteria: 813 in the control group (standard CPR) and 840 in the intervention (ACD-CPR + ITD) group. First, the results of the study demonstrated that the use of these devices was safe. The overall rate of major adverse events, including chest fractures, was not significantly different between groups, although there were more reports of pulmonary edema in the intervention group; this was coexistent with increased survival in this group. Neurological function was similar between groups at 90 days and one year after cardiac arrest. There were no increases in the number of patients with severe neurological impairments in the intervention group.

This study also demonstrated the efficacy of these employed devices. ACD-CPR with the augmentation of negative intrathoracic pressure using an ITD improved long-term survival (to hospital discharge) with favorable neurological function by 53 % ($p = 0.019$), and the survival benefits persisted to a 1-year time point following cardiac arrest, as shown in Fig. 38.15. In the patient population which typically resulted in poor neurological function at hospital discharge, the use of ACD-CPR with an ITD and therapeutic hypothermia resulted in a sixfold improvement in neurological function by 90 days, compared to standard CPR with therapeutic hypothermia [41]. In patients with out-of-hospital cardiac arrest from a variety of nontraumatic etiologies, ACD-CPR with an ITD resulted in a 38.5 % increase in survival to hospital discharge, with favorable neurological function ($p = 0.027$) and a 35.4 % increase in survival at 1 year with favorable neurological function (not significant), compared to patients receiving S-CPR [42]. In the absence of treatment with therapeutic hypothermia after cardiac arrest, survival rates with favorable neurological function at hospital discharge and 90 days after cardiac arrest were nearly twice as high with ACD-CPR plus an ITD compared to standard CPR, indicating that the combination therapy is neuroprotective, independent of in-hospital therapeutic hypothermia.

38.7 Treatment of Life-Threatening Hypotension with the ITD in Spontaneously Breathing Patients

Shock can be defined as life-threatening hypotension and results in inadequate tissue perfusion. Hypovolemia caused by uncontrolled hemorrhage in trauma is the most common form or cause of shock and is referred to as *hemorrhagic*

shock. Death following severe blood loss commonly develops secondary to profound hypotension and vital organ ischemia. In other words, in the absence of a critical central blood volume, both stroke volume and cardiac output are decreased and hypotension ensues.

Intravenous fluids and vasopressor agents have traditionally been the mainstay of therapy for patients with marked hypotension. Commonly, intravenous fluids and blood replacement, together with intravenous therapies such as epinephrine and other vasopressors, have been effective as short-term therapies, i.e., providing a bridge to more definitive repair of the primary injury. Yet, their use is also associated with significant clinical shortcomings such as the following: (1) they require intravenous or intraosseous access; (2) nonblood volume expanders can decrease the effectiveness of normal thrombus formation (by dilution of critical clotting factors); and (3) their use can ultimately reduce the oxygen carrying capacity of the blood. In addition, massive intravenous fluid replacement can in turn cause both pulmonary and peripheral edema (in some cases, cerebral edema), as well as hypothermia. Furthermore, vasopressors can also cause ischemia, especially to the gut. Vasopressors and fluids have been associated with "popping the clot" in the patient with significant blood loss secondary to sudden increases in blood pressure to normal or above normal values. Moreover, vasopressors like epinephrine can cause supraventricular or ventricular tachycardias, which can lead to a further compromise of the patient's already tenuous hemodynamic status. It should be noted that even the sinus tachycardia that is normally observed after epinephrine therapy can be detrimental in the setting of shock, as it results in a decreased amount of time for cardiac filling after each ventricular systole. This is an important issue since blood flow back to the heart is markedly decreased because of the low central venous pressures. In other words in this setting, one needs more time (and thus a slower heart rate) for effective refilling of the heart after each contraction.

As such, there is strong evidence that one of the primary mechanisms that contribute to reduced cardiac filling, decreased stroke volumes, and ultimately shock following an acute hemorrhage is the reduction in the circulating blood volume and a subsequent reduction in cardiac filling pressures (i.e., lower central venous pressures or cardiac preloads). Therefore, countermeasures designed to increase venous return and decrease cardiac filling without causing hemodilution and without "popping the clot" may be an effective therapy for the acute treatment of massive blood loss. It is important to recognize that the primary goal of any therapy used for the treatment of hemorrhagic shock is the restoration of sufficient vital organ perfusion to prevent death, even if the primary cause of the blood loss has not yet been established or repaired. Such therapies should act primarily to increase stroke volumes rather than to increase peripheral resistance, as the latter may cause more harm than good. Ideally, a new therapy designed to improve vital organ perfusion in the setting of hemorrhagic shock should act primarily to optimize stroke volumes, improve vital organ blood flow by a mechanism that is independent of increasing peripheral vascular resistance, and help to stabilize a permissive hypotensive state that provides adequate cerebral perfusion.

Fig. 38.16 ResQGARD® impedance threshold device on a face mask

Building upon the needs described above, two new technologies have been developed by Advanced Circulatory Systems to treat clinically significant hypotension. One is termed the ITD for spontaneously breathing patients (ResQGARD® ITD), and the other is called the intrathoracic pressure regulator (ITPR, CirQlator®). The ResQGARD, shown in Fig. 38.16, is designed for the spontaneously breathing patient and can be considered as a natural extension of a normal physiological process, i.e., the transformation of the normal respiratory muscle function from a primary gas exchange function to the dual functions of gas exchange and augmentation of venous return, as well as enhancement of cardiac stroke volume. The ITPR was designed for the mechanically ventilated patient where it actively provides a low level of negative pressure during the expiratory phase of ventilation, thereby increasing venous return and improving cardiac output, stroke volume, and blood pressure. To avoid confusion, the differences between the ITDs and the ITPR device are summarized in Fig. 38.17.

ResQGARD ITD	Intended Use: Used in spontaneously breathing patients to assist in enhancing circulation. Device can be used on a facemask.	
ResQPOD ITD	Intended Use: Used in non-spontaneously breathing patients in cardiac arrest where CPR is being performed to assist in enhancing circulation. Device can be used on a facemask or an endotracheal tube.	
ITPR	Intended Use: Used in non-spontaneously breathing patients who are hypotensive and intubated, including those in cardiac arrest undergoing CPR. Device is directly attached to an endotracheal tube or other airway adjunct.	

Fig. 38.17 Differences between an impedance threshold device (*ITD*) for spontaneously breathing patients and for those in cardiac arrest and the intrathoracic pressure regulator (*ITPR*)

The ITD works by lowering intrathoracic pressure in the thorax with each inspiration, thereby enhancing venous blood flow back to the heart and lowering ICPs. These mechanisms serve to enhance both cardiac output and blood pressure. There is also experimental data suggesting that the use of the ITD will reduce the amount of vasopressors needed, since it increases overall cardiac outputs and circulation [36]. In this manner, the ITD provides an indirect drug-enhancing effect, enabling the rescuers to use less of a vasopressor drug, and perhaps less fluid resuscitation, to obtain the same or greater hemodynamic effectiveness.

The spontaneously breathing version of the ITD is a small disposable plastic airflow regulator that can be attached to a face mask, mouthpiece, or tracheal tube. The device has a spring-loaded diaphragm that requires a certain threshold (*cracking pressure*) to be achieved before it opens to allow airflow, thus functioning like a partial Mueller maneuver (inhaling against a closed glottis) to augment negative intrathoracic pressure with each inspiration [9]. In this manner, the device harnesses the patient's own respiratory pump to enhance circulation. In 1947, Cournand was the first to show that *increases* in mean airway pressure result in decreased systemic venous return, decreased pulmonary blood flow, and a fall in cardiac output. Lower negative intrathoracic pressure during spontaneous inspiration, however, represents a natural mechanism for enhancing venous return and cardiac filling. Several natural physiological reflexes, such as gasping and the Mueller maneuver, augment negative intrathoracic pressure and increase cardiac output. Several authors have shown that artificially induced negative pressure ventilation can be used to increase cardiac output [43, 44]. The ITD has been evaluated in animals and humans for the treatment of: (1) cardiac arrest, (2) hemorrhagic and heat shock, and (3) orthostatic hypotension and (4) for enhancing blood donation.

In 2004, Lurie et al. demonstrated that spontaneous breathing through the ITD during hemorrhagic and heat shock in a porcine animal model resulted in an immediate sustained rise in systolic blood pressure in both conditions [45]. As shown in Fig. 38.18, addition of the ITD (set to open at a cracking pressure of −12 cmH_2O) after an acute hemorrhage resulted in immediate rises in systolic blood pressure that was sustained for 30 min. Upon removal of the ITD, the blood pressure decreased back to values identical with the controls. These studies showed a 30 % increase in cardiac output when the ITD was utilized for the pigs in shock. Subsequent studies showed that the use of the ITD in spontaneously breathing pigs after severe hemorrhage resulted in increased cardiac output, blood pressure, cardiac chamber dimensions, transvalvular blood flow, and survival rates [46]. These studies demonstrate how the ITD augments cardiac output, improves hemodynamics, and increases survival in spontaneously breathing pigs under conditions of hypovolemic hypotension [47].

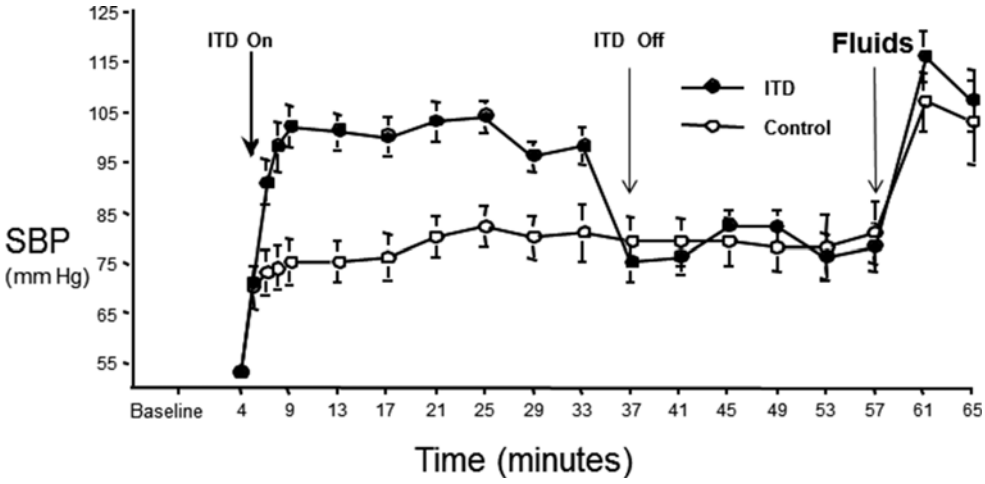


Fig. 38.18 Changes in systolic blood pressure (*SBP*) with and without impedance threshold device (*ITD*) breathing following controlled hemorrhage and shock in spontaneously breathing pigs

More recently, Metzger et al. studied the use of the ITD in a porcine hemorrhagic model to determine if the negative intrathoracic pressure therapy provided by the device could improve systolic blood pressure but still allow permissive hypotension, thereby avoiding "popping the clot" [48]. They compared the use of the ITD to the current standard of care, i.e., infusing normal saline to treat a 55 % hemorrhage. Maximum systolic blood pressure during 15 min of treatment was significantly higher in the normal saline group compared to the ITD and control groups, but at a level of 131 ± 7.6 mmHg, it was well above the threshold believed for the risk clot dislodging in animals (94 ± 3 mmHg). Conversely, pigs treated with the ITD had significant improvements in systolic blood pressure throughout the 30-min course of treatment compared to controls, but the levels were much more moderate and well within the levels of permissive hypotension. Another benefit to the ITD was that blood pressures were considered adequate for organ perfusion, but importantly the ICPs were not elevated. This allowed for improved perfusion to the brain, while increased ICP resulting from normal saline infusion would likely impede cerebral blood flow. These results show that the ITD can be effective in treating hypotension secondary to trauma or hemorrhage without the negative effects associated with excessive systolic blood pressure.

The ITD with a cracking pressure of −6 cmH_2O was first studied in normal volunteers by Convertino et al. at NASA, in studies related to post-flight orthostatic hypotension [49]. Inspiration through the ITD increased cardiac output by about 1.5 L/min in supine subjects and was well tolerated. The ITD increased stroke volume and was shown to maintain blood pressure in normal volunteers subjected to acute orthostatic stresses and later in patients with symptomatic orthostatic hypotension. The use of the ITD in normal volunteers resulted in: (1) an immediate increase in cardiac stroke volume, (2) increases in both systolic blood pressure and heart rate, and (3) improved cardiac output as shown in Fig. 38.19 [50]. It was also observed that total peripheral resistance was reduced by the ITD.

Also highly relevant is how the ITD affects the work of breathing. To assess the work of breathing associated with the use of the ITD, the power of breathing was measured in collaboration with NASA scientists in 9 female and 9 male subjects breathing through a face mask at two separate ITD conditions: (1) −6 cmH_2O and (2) control (0 cmH_2O). The results from this study demonstrated that breathing through the ITD was well tolerated by all subjects. For the sham and active ITD groups, respectively, peak inspiratory pressures were −1.13 ± 0.63 cmH_2O and −9.92 ± 6.2 cmH_2O ($p < 0.0001$); tidal volumes were 958 ± 396 mL and 986 ± 389 mL (not significant); and inspiratory times were 189 ± 81 ms and 296 ± 109 ms ($p = 0.002$). For the sham and active ITD groups, respectively, imposed work of breathing (WOBi) was 0.064 ± 0.04 J/L and 0.871 ± 0.117 J/L ($p < 0.0001$); power of breathing (POBi) was 0.88 ± 0.63 J/min and 7.56 ± 3.55 J/min ($p < 0.0001$); peak inspiratory pressures were −1.13 ± 0.63 cmH_2O and −9.92 ± 6.2 cmH_2O ($p < 0.0001$); tidal volumes were 958 ± 396 mL and 986 ± 389 mL (not significant); and inspiratory times were 189 ± 81 ms and 296 ± 109 ms ($p = 0.002$). Interestingly, there were no significant observable differences between men and women in terms of work of breathing [51].

To put these data into perspective, one must understand the power of breathing for a normal individual, where power is work per unit time ($W = W \times f$, where f is respiratory frequency). The maximal power output for normal young adults is 613 cal/min (range: 500–860) [52]. Thus, the amount of power output required during quiet breathing or the use of the ITD seems rather minimal, amounting to less than 1.0 % of maximum. Vigorous exercise requiring minute volume of 60–80 L requires ~80 J/min of power. The −6 cmH_2O ITD requires about 1–2 cal/min of respiratory power. For the ITD to be functional, the energy required for its operation should not exceed the energy available in the patient population in

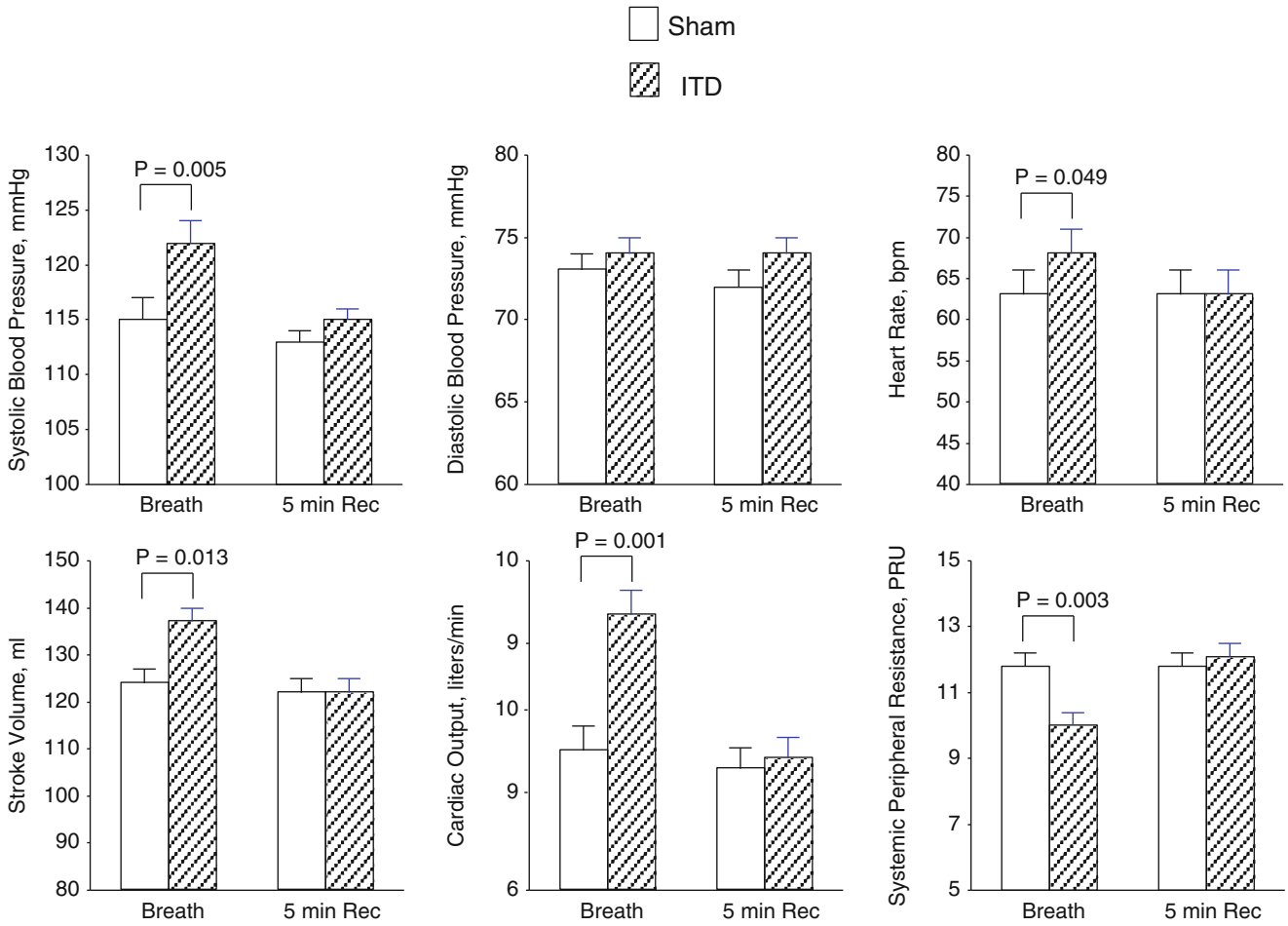


Fig. 38.19 Hemodynamic results. Systolic and diastolic blood pressures, heart rate, stroke volume, cardiac output, and total peripheral vascular resistance during (breath) and after (5-min recovery) spontaneous breathing on the impedance threshold device (*ITD*) at 0 cmH_2O resistance (sham control, *open bars*) and −6 cmH_2O resistance (*solid bars*) ($n = 20$)

which it is expected to be applied, for example, ill and injured patients with hypotension. It is known that ill patients who require mechanical ventilator support use about 1–2 cal/min for self-triggered ventilation and are generally able to sustain this level of effort for long periods (hours to days) [52]. Therefore, we expect that most patients will be able to tolerate the use of the ITD without excessive fatigue, given that it requires only a fraction of the respiratory power needed for a similarly ill group of patients to self-trigger a mechanical ventilator. Based on these measurements, we conclude that the vast majority of conscious but hypotensive patients will be able to inspire through the ITD with a resistance of −7 cmH_2O and should therefore benefit hemodynamically from the device.

Most recently, the ITD was studied by Convertino et al. at the US Army Institute of Surgical Research, using a lower body negative pressure chamber (LBNP) to lower central blood volume and thus induce a state of severe hypotension [53]. A photo of the LBNP chamber is shown in Fig. 38.20. The application of negative pressure to the lower body (below the iliac crest) results in a redistribution of blood away from the upper body (head and heart) to the lower extremities and abdomen. Thus, this model provides a unique method of investigating interventions such as the ITD under conditions of controlled, experimentally induced hypovolemic hypotension. Absolute equivalence between the magnitude of negative pressure applied and the magnitude of actual blood loss has recently been evaluated in a baboon model which demonstrated the absolute equivalence between the simulated bleed and the actual blood loss [54]. On the basis of the magnitude of central hypovolemia induced, Convertino et al. provide data to support that 10–20 mmHg negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss ranging from 400 to 550 mL, 20 to 40 mmHg negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss ranging from 550 to 1000 mL, and greater than 40 mmHg negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss approximating 1000 mL or more

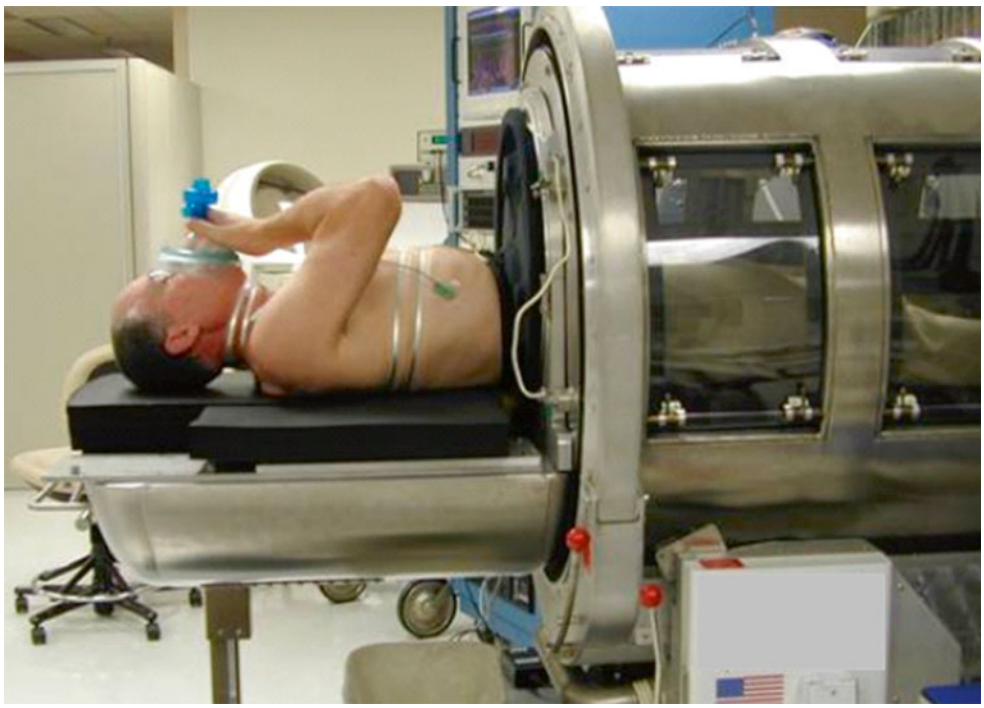


Fig. 38.20 Lower body negative pressure chamber used to simulate severe hypotension

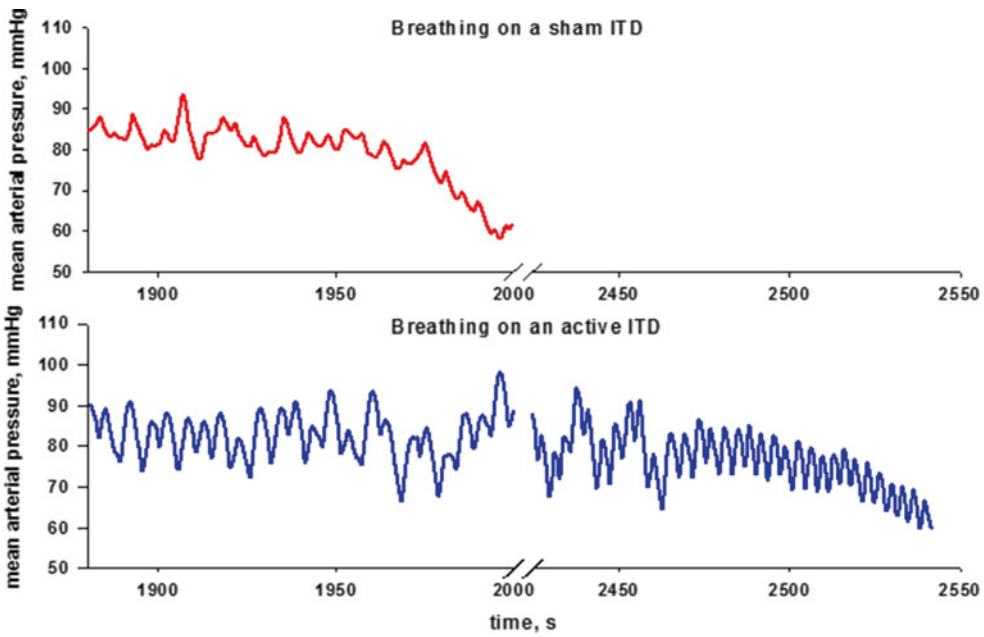


Fig. 38.21 Representative tracings of beat-to-beat mean arterial blood pressure obtained from the same subject while breathing on a sham impedance threshold device (ITD; *top panel*) and active ITD (*bottom panel*) during the final two minutes of lower body negative pressure chamber exposure prior to cardiovascular collapse

[53]. Nine healthy normotensive volunteers completed two counterbalanced protocols with (active) and without (sham) an ITD set to open at −6 cmH_2O pressure. Continuous non-invasive measures of systolic (SBP), diastolic (DBP), and mean (MAP) arterial blood pressures were obtained during a LBNP protocol consisting of a 5-min rest period (baseline) followed by 5 min of chamber decompression at −15, −30, −45, and −60 mmHg, as well as additional increments of −10 mmHg every 5 min until the onset of cardiovascular collapse. Overall, SBP (79 ± 5 mmHg), DBP (57 ± 3 mmHg), and MAP (65 ± 4 mmHg) at the time of cardiovascular collapse were lower ($P < 0.02$) when subjects breathed through the sham ITD than when they breathed through the active ITD at the same time points of LBNP (102 ± 3, 77 ± 3, 87 ± 3 mmHg, respectively). Elevated blood pressures were associated with a 23 % increase ($P = 0.02$) in LBNP tolerance using an active ITD (1639 ± 220 mmHg-min) compared with a sham ITD (1328 ± 144 mmHg-min). A representative tracing of data obtained in these studies is shown in Fig. 38.21.

These results are the first to demonstrate, in humans, that the time to cardiovascular collapse associated with progressive reduction in central blood volume and subsequent

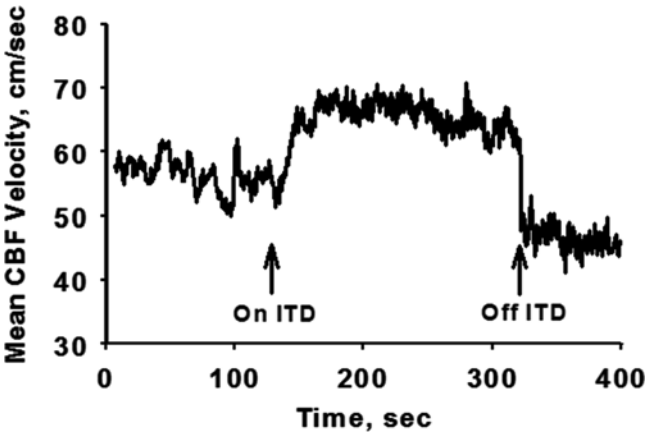


Fig. 38.22 Typical continuous recording of mean cerebral blood flow (*CBF*) velocity in a subject before, during (On ITD), and at the cessation (Off ITD) of spontaneous breathing on the impedance threshold device (*ITD*)

development of severe hypotension can be significantly improved by inspiratory resistance induced by spontaneous breathing through an ITD. The results from the present experiment demonstrated an average elevation in SBP of 23 mmHg when estimated central blood volume was reduced by more than 2 L [53].

Importantly, the use of an ITD also has striking effects on cerebral artery blood flow. With each inspiration through the ITD, ICPs are lowered, and simultaneously cardiac output is increased. Measurement of middle cerebral intracranial Doppler demonstrated that the use of the ITD increased middle cerebral artery blood flow in spontaneously breathing adult humans, as shown in Fig. 38.22 [55].

Our group recently performed another clinical trial which evaluated the use of the ITD to treat non-life-threatening hypotension (SBP<95 mmHg) in the emergency room setting. In this randomized double-blind clinical trial, patients received the current standard of care for hypotension, which consists of controlling the bleeding, reversing other potential causes of low blood pressure such as correcting hyperthermia, and administering fluids, oxygen, and/or blood products as appropriate. The use of the ITD did not interfere with standard therapy. Once it was determined that the subjects met enrollment criteria based upon the inclusion and exclusion criteria and informed consent was obtained, subjects were randomized to either a sham ITD or an active (functional) ITD; the sham and active ITDs appeared identical. The devices were kept in an opaque package, preventing anyone involved with the study from knowing whether any given device was a sham or active ITD based upon visual inspection. Baseline blood pressure, heart rate, respiratory rate, oxygen saturation, and clinical findings including quality of the pulse and quality of respirations were recorded immediately. The ITD was then placed, and hemodynamic parameters were assessed every 2 min, for a minimum of 6 min and up to 10 min. Standard therapies, including intravenous fluids, were administered as deemed clinically necessary, regardless of the effect of the ITD. The active device was found to be significantly more effective than the sham. Specifically, the mean rise in SBP for the active ITD group was 13.2 ± 7.8 mmHg ($n = 16$) versus 5.9 ± 5.5 mmHg for the sham ITD group ($n = 19$) ($p = 0.003$). Mean fluids given during the study were 92 ± 170 ml for the active ITD group and 192 ± 200 ml for the sham ITD group ($p = 0.13$). In a subgroup of patients that received no fluids during device use, the maximum rise in SBP (mean ± STD) was 12.8 ± 7.8 mmHg for the active ITD group and 5.6 ± 5.0 mmHg for the sham ITD group ($p = 0.04$). MAP was also statistically higher in the active ITD group (9.2 ± 7.8 versus 4.8 ± 3.3, $p = 0.03$) [56].

More recently, a study conducted by Wampler et al. looked at the use of the ITD in patients with hypotension, which was defined as a SBP less than 90 mmHg [57]. The primary endpoint was MAP before application of the ITD versus MAP after 2–4 min of ITD use. They found that average systolic and diastolic blood pressures and MAPs all increased by a statistically significant amount with ITD use in all patients (78 ± 13 mmHg versus 97 ± 19 mmHg, 51 ± 13 mmHg versus 63 ± 15 mmHg, and 60 ± 10 mmHg versus 70 ± 15 mmHg, respectively). Additionally, systolic and diastolic pressures were increased for the subset of patients who elicited hypotension due to trauma. These findings support the use of the ITD as a safe and tolerable means to treat hypotension from traumatic and nontraumatic causes.

It is now the general consensus that the ITD harnesses the patient's own thoracic pump to enhance circulation and offers a noninvasive means to treat some of these patients. However, the spontaneous breathing version of the ITD requires that patients be able to breathe on their own, and most patients in severe shock are usually intubated and require assisted ventilation. To fill this gap, the ITPR was developed. This technology was developed based on the concept of lowering intrathoracic pressures to enhance circulation for patients with life-threatening hypotension that are dependent upon assisted ventilation.

38.8 ITPR Therapy: A Potential Novel Treatment of Severe Hypotension in Severely Ill Patients

To date, the ITPR described below has been tested in animals and in limited clinical studies. It combines a way to generate a controlled intrathoracic vacuum with a method to provide controlled positive pressure ventilation. It can be used for the treatment of cardiac arrest, multiple forms of shock to buy time until more definitive therapy is available, or cerebral

injuries. The device can be used with a handheld resuscitator bag or it can be attached to a mechanical ventilator or anesthesia machine. While multiple designs are possible to embody this concept, the main function of the ITPR is to create a preset continuous and controlled expiratory phase negative intrathoracic pressure that is interrupted only when positive pressure ventilation is needed to maintain oxygenation and provide gas exchange. Today, the ITPR has been cleared for sale by the FDA with the approved indication of a device to "temporarily decrease intrathoracic pressure to increase blood circulation."

It was recognized from the start of device development that it would be important to develop a modification of the ITD for the use with nonbreathing and more critically ill hypotensive patients; this resulted in the concept of the ITPR. The ITPR employs an external vacuum source to lower intrathoracic pressures and thus enhance venous blood flow back to the heart in nonbreathing hypotensive patients. This refinement is based on the breakthrough in our clinical understanding of the basic physiological principles of blood flow in hypotensive states. By transforming the chest into an active bellows during CPR, the combination of a relatively low level expiratory phase intrathoracic vacuum and intermittent positive pressure ventilation results in a significant augmentation of venous blood flow to the right heart, thereby increasing both stroke volume and cardiac output.

Contemporaneously, the decrease in intrathoracic pressure results in decreases in ICP and thus provides an additional mechanism whereby the ITPR increases CePP; this is illustrated in Fig. 38.23. When the ITPR is turned on, the intrathoracic pressure between positive pressure breaths is lowered immediately, as is the ICP. Based on these findings, the ITPR may also ultimately have the potential for treatment of brain injury.

To date, the potential beneficial effects of the ITPR have been studied in pigs in VF during CPR. In this setting, the ITPR was used to lower intrathoracic pressure and thus enhance venous return to the heart and increase overall efficacy [58]. Vital organ perfusion pressures and end-tidal carbon dioxide levels were significantly improved with ITPR-CPR, and animal survival was 100 % (10/10) with ITPR-CPR versus 10 % (1/10) with standard CPR alone. The use of ITPR-CPR improved hemodynamics, vital organ perfusion pressure, and carotid blood flow in animals eliciting both VF and hypovolemic cardiac arrest. Figure 38.24 demonstrates the significant hemodynamic differences observed when using the ITPR during standard CPR in this animal model of cardiac arrest.

The physiological goals of the ITPR are to lower intrathoracic pressure during the expiratory phases of ventilation and provide positive pressure ventilation in patients requiring assisted ventilation. The first preclinical studies evaluating the effects of the ITPR on vital organ perfusion pressure were performed in both normovolemic and hypovolemic swine [59, 60]. Six anesthetized animals received 5-min interventions with endotracheal pressure (ETP) set to 0, −5, 0, −10, 0, −10, 0, −5, 0 mmHg during euvolemia and then after a fixed hemorrhage of 50 % of their total blood volumes. Hemodynamic parameters were continuously measured, and blood gases were obtained at the end of the first four 5-min intervals. Under both euvolemic and hypovolemic conditions, right atrial pressure and ICP decreased proportionally to the intrathoracic pressure, with the more marked changes observed with hypovolemic conditions. By contrast, the increases in MAP, coronary perfusion pressure, and CePPs

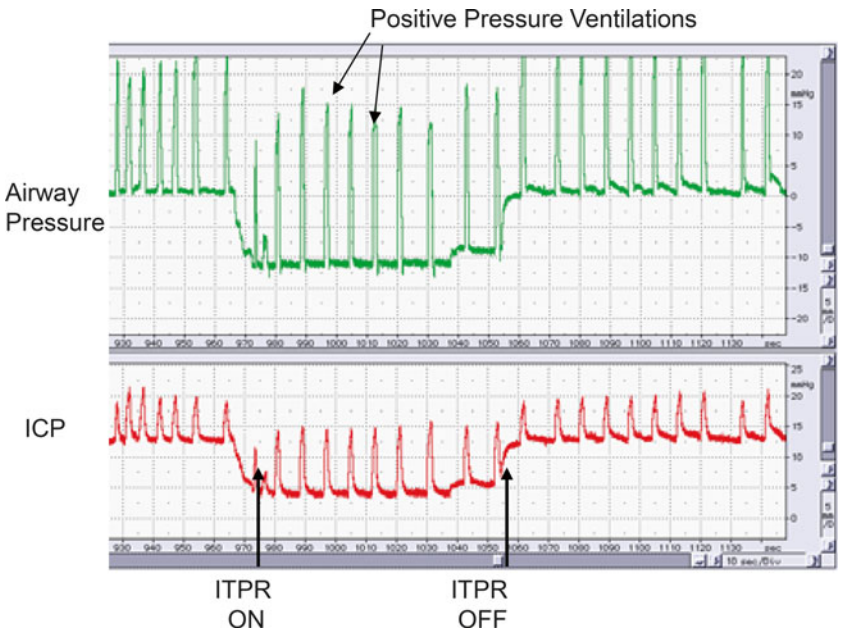


Fig. 38.23 Changes in airway pressure and intracranial pressure (*ICP*) when the intrathoracic pressure regulator (*ITPR*) is turned on and then off again

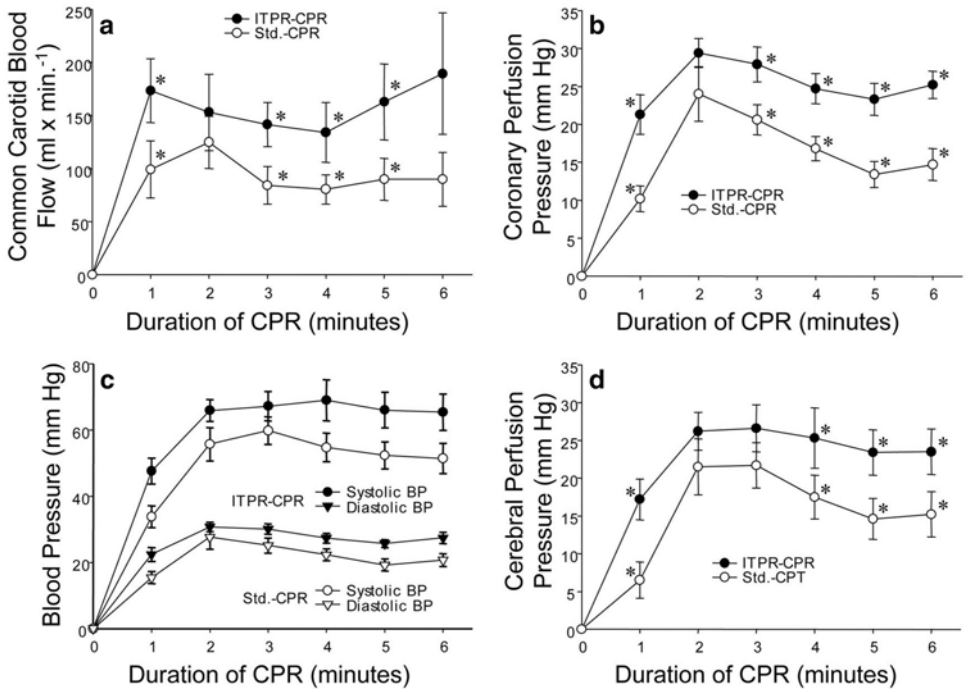


Fig. 38.24 Effect of intrathoracic pressure regulator (*ITPR*) CPR on carotid blood flow, coronary perfusion pressure, blood pressure, and cerebral perfusion pressure compared to standard CPR (*Std-CPR*). *BP* blood pressure, *CPR* cardiopulmonary resuscitation

Table 38.1 Basic hemodynamic parameters with endotracheal pressure set at 0, −5, and −10 mmHg with the ITPR for blood volumes after 0 and 50 % blood loss

Blood loss (%)	ETP	0	−5	−10
0	MAP	89.9 ± 4.5	104.3 ± 7.3*	108.5 ± 6.1*
	RAP	1.8 ± 0.4	−0.8 ± 0.6*	−4.8 ± 0.4†,*
	CPP	80 ± 3.9	94.2 ± 6.4*	103.3 ± 5.3*,†
	CerPP	74 ± 4.8	90.3 ± 7.4*	95.1 ± 6*
	ICP	15.6 ± 0.6	14 ± 0.7	13.5 ± 0.6*
50	MAP	28.8 ± 4.3	39.8 ± 5.9*	47.3 ± 7.3*,†
	RAP	−2 ± 0.9	−5.7 ± 0.6*	−9.3 ± 0.3*,†
	CPP	25.8 ± 5	38.5 ± 3.7*	48.3 ± 3.8*,†
	CerPP	18.1 ± 4.4	32.9 ± 5.8*	43.1 ± 7.2*,†
	ICP	10.7 ± 1.3	6.8 ± 1.4*	4.2 ± 1*,†

ETP endotracheal pressure, *MAP* mean arterial pressure, *RAP* right atrial pressure, *CPP* coronary perfusion pressure, *CerPP* cerebral perfusion pressure, *ICP* intracranial pressure

*Statistically significant difference ($0.05 > p > 0.001$) when compared to the values with ETP of 0 mmHg

†Statistically significant difference between values with −5 and −10 mmHg of ETP ($p < 0.05$)

were inversely proportional to the negative intrathoracic pressure both in the normovolemic pigs and after induced hemorrhage. These data are consistent with findings in spontaneously breathing adult and pediatric swine models of shock and the use of the ITD [45, 46]. The major hemodynamic parameters for 0, −5, −10 mmHg of ETP are shown in Table 38.1. Based on the data available to date, we believe that the generation of intrathoracic pressures greater than −15 mmHg may be excessive and not beneficial with long-term use.

Our initial studies demonstrated that the ITPR could reproducibly decrease ETP, intrathoracic pressure (as seen by the decreases in right atrial pressure), and ICP. The ITPR provided hemodynamic improvements with no acid-base changes during normovolemia. We have applied the ITPR in euvolemic anesthetized pigs for up to 6 h, with an intrathoracic vacuum set to −9 mmHg, without obvious adverse effects on gas exchange or the overall metabolic state of these animals. The long-term benefits of the ITPR after hemorrhage are considered to be much more dependent upon the degree of hypotension. During 50 % hypovolemia, there was more acidosis associated with the generation of negative ETP, as reflected by a lower pH and higher $PaCO_2$. However,

despite the lower pH values, which may be secondary to greater clearance of lactate, ITPR use increased blood pressure, pulse pressure, vital organ perfusion pressure, and $ETCO_2$ levels suggesting there was improved balance between the increase in circulation and the potential for induced metabolic acidosis with ITPR use. Oxygenation saturations remained at 100 % with ITPR use.

To date, the 510k cleared IPR device (CirQlator®) has been used by emergency medical personnel in Toledo, Ohio, during CPR administration [61]. In these cases, end-tidal CO_2 ($ETCO_2$) was assessed as an indirect surrogate for circulation. $ETCO_2$ values in 11 patients were compared pre- and during IPR therapy and then compared to 74 patients that were not treated with IPR therapy, but that were treated with an ITD. $ETCO_2$ levels increased from 21 ± 1 mmHg immediately prior to IPR application to an average of 32 ± 5 mmHg and a maximum of 45 ± 5 mmHg during IPR treatment ($p < 0.0001$). Note that $ETCO_2$ levels did not change significantly in the group not receiving active IPR therapy. More importantly, ROSC rates were 46 % in the standard CPR plus ITD group (34/74) and 74 % in the IPR-treated group (8/11) ($p < 0.001$). Huffmyer et al. reported that in 20 patients about to undergo coronary artery bypass graft surgery, thermodilution cardiac output increased significantly with the application of the ITPR (4.9 versus 5.5 L/min, $p = 0.017$); similarly, cardiac output measured by transesophageal echocardiography was 5.1 versus 5.7 L/min, respectively ($p = 0.001$). There were also significant increases in pulmonary artery systolic blood pressure (35 mmHg versus 38 mmHg, $p < 0.001$) and mean pulmonary artery pressure (24 mmHg versus 26 mmHg, $p = 0.008$) with this therapy [62].

Additional clinical experiences with the IPR device have further demonstrated the potential of this technology to treat brain insult. For example, Kiehna et al. recently reported the first use of the ITPR (10-min applications) in 10 patients with compromised cerebral perfusion, highlighting increases in CePP and decreases in ICP with use of this new technology [63].

To date, studies on the potential benefits of longer-term application of negative intrathoracic pressure have been initiated in a preliminary manner. For example, in pilot studies on spontaneously breathing swine, in collaboration with researchers at the US Army Institute of Surgical Research, we applied the ITD to spontaneously breathing animals in severe hemorrhagic shock, an uncontrolled model of severe blood loss [47, 64]. These splenectomized swine were subjected to a 60 % blood loss, followed by a 4 mm hole created in their abdominal aortas. Remarkably, the use of the ITD in pilot studies stabilized these animals for about 60 min after the hemorrhage and injury occurred. However, after 75 min, we observed the development of a significant metabolic acidosis, as reflected by a progressive negative base excess. At that point, the swine were hemodynamically stable, but shortly thereafter they became extremely agitated, hypotensive, and then died [47]. These pilot studies provided us with some fundamental insights related to the limitations of using the ITD, and by analogy the ITPR by itself, in the setting of severe blood loss. While these devices can be used to "buy time," ultimately some fluid resuscitation and correction of the underlying causes of the blood loss are essential. Although some fluids are ultimately needed, we hypothesize that the use of the ITD and ITPR can function by actually being fluid sparing and will extend the window of opportunity to provide lifesaving care in the setting of severe blood loss.

The ITPR was designed to provide a noninvasive means to increase MAP in the setting of cardiac arrest and significant hypotension in apneic patients. The effects are rapid and can be turned on or off by the flip of a switch, unlike more long-lasting and sometimes harmful effects of fluid and drug administration. This switch-like effect is shown in Fig. 38.23. In another study (shown in Fig. 38.25), the intrathoracic pressures were varied between 0, −5, and −10 mmHg; with each change, there were rapidly adjustments in key hemodynamic variables and ICPs. Based upon the combined effects of the ITPR shown in multiple preclinical studies, we believe

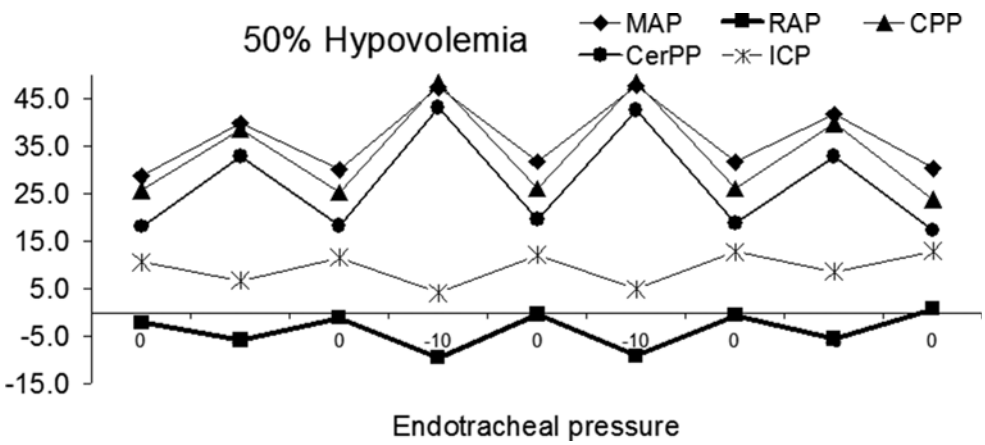


Fig. 38.25 Sequential changes in mean arterial pressure (*MAP*), coronary perfusion pressure (*CPP*), cerebral perfusion pressure (*CerPP*), right atrial pressure (*RAP*), and intracranial pressure (*ICP*) for sequential changes of endotracheal pressure (a surrogate for intrathoracic pressure) of 0, −5, 0, −10, 0, −10, 0, −5, 0 mmHg during 50 % hypovolemia. Differences between the values of all parameters are statistically significant with $p < 0.05$

that that ITPR has the potential to become a *first-line therapy* for all patients in cardiac arrest, as well as provide benefits for many individuals eliciting hypotension from a wide variety of causes. Importantly, the device can be applied quickly, often before intravenous access and intraosseous access, or fluids may be available, and it safely and quickly increases systemic, coronary, and CePPs. Based upon our experience in noncardiac preclinical arrest models, the use of the ITPR may be of significant benefit after traditional therapies have been provided, in that the ITPR application may reduce: (1) the amount of fluid volume needed for resuscitation from multiple etiologies, (2) secondary brain injury, and/or (3) the amount of vasopressors needed to maintain "permissive hypotension." The clinical use of ITPR may thereby become a commonplace therapy in both operating rooms and intensive care units, to help maintain vital organ perfusion. To date, the ITPR has been used in patients with acute hypotension intraoperatively; it has been well tolerated and resulted in significant increases in MAP, pulse pressure, and systolic blood pressure in the absence of fluid administration or vasopressor therapy [65].

Studies to date have also shown that the application of ITPR therapy in cardiac arrest cases results in marked improvements in hemodynamics in both human and animal models. Application of the device in hypovolemic pigs was shown to enhance circulation, stroke volume, MAP, CPP, and CePP and decrease ICP. Studies in a porcine model of peritonitis (septic shock) have indicated an augmentation in cardiac index and MAP while simultaneously lowering pulmonary artery pressure during ITPR use [66, 67]. Yet, it should be noted that the longer-term potential consequences of the ITPR remain unknown. One known limitation is that, in order for this technology to be of clinical benefit, the thorax must be intact; otherwise, it is not possible to generate expiratory phase negative intrathoracic pressure with the ITPR. Furthermore, it is not possible to lower the expiratory phase intrathoracic pressure and use positive end expiratory pressure concurrently, unless the ITPR is used as a pulsed therapy (currently under evaluation). Thus, the benefit of circulatory enhancement with the ITPR must be balanced clinically with the need to concurrently maintain at least minimally adequate ventilator support. Animal studies to date have suggested the ITPR can provide both circulatory and ventilatory support for up to 24 h in duration, without negative pulmonary consequences.

38.9 Summary

Clinicians and researchers continue to investigate methods for enhancing standard CPR techniques and design various novel devices to treat sudden cardiac arrest and shock. The limitations of standard CPR are discussed, as well as methods to improve this technique to enhance the delivery of oxygenated blood to the heart and brain. A recent advance in CPR research has been the rediscovered benefit of therapeutic hypothermia after successful resuscitation, a therapy that has shown increased long-term survival rates and improved neurological function. Further, we described some novel noninvasive technologies that can be used to increase the patient's chance for survival, such as IPR therapy to improve perfusion in profound states of shock, impedance threshold devices, and ACD-CRP treatment.

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