Perfusion on Demand

How Intrathoracic Pressure Regulation improves blood flow in shock & cardiac arrest

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• introduction •

By Craig Manifold, DO

This JEMS supplement on Intrathoracic Pressure Regulation (IPR) presents current perspectives and data from EMS medical directors and researchers on this non-invasive therapy that improves circulation in cardiac arrest and shock states from a variety of etiologies. Changes in intrathoracic pressure, subtle and invisible to prehospital providers, dramatically affect coronary and cerebral blood flow.

IPR therapy was discovered in 1987 when Keith Lurie, MD, treated a patient resuscitated twice by using a toilet plunger for CPR and survived neurologically intact. This led to the development of the CardioPump, a device that performs active compression-decompression CPR (ACD-CPR). However, studies of ACD-CPR saw mixed results. Subsequent research demonstrated an open airway during CPR eliminated negative pressure created during CPR and that negative intrathoracic pressure dramatically increased when the airway was temporarily blocked during chest wall recoil, improving cardiac preload and coronary artery perfusion. This finding led to the development of the impedance threshold device (ITD) to limit the influx of air during chest wall recoil to enhance intrathoracic vacuum and perfusion during CPR. Clinical studies have shown increased survival when an ITD is used with an ACD-CPR device and a bundled approach to cardiac arrest. This supplement highlights EMS agencies using a systems-based approach (including the ITD) reporting survival rates above national averages.

The therapeutic concept to enhance perfusion by increasing negative intrathoracic pressure, termed intrathoracic pressure regulation (IPR), drew the interest of NASA and the U.S. military as a treatment for patients suffering from hypotension and shock. The ITD 7 (ResQGARD ITD) was developed to enhance circulation in spontaneously breathing hypotensive patients non-invasively. Use of the ResQGARD has been shown in studies to increase blood pressure by up to 30%. In this supplement, systems using the ITD 7 will share their experiences and data.

Current research and experience with IPR supports its use to enhance perfusion; the more we learn, the more the potential for IPR therapy grows. We’ll explore exciting new areas where IPR therapy is showing an impact.

Our goal is to provide you with an understanding of IPR Therapy and its future potential in this supplement so that you can be more effective in implementing it in the field.
Helping the Body Help Itself

How Intrathoracic Pressure Regulation Therapy improves perfusion

By Victor A. Convertino, PhD
Hypotensive patients, like those experiencing shock or, in extreme cases, cardiac arrest, require enhanced blood flow to provide sufficient oxygen to vital organs. Poor perfusion results in poor survival and compromised neurological function. One way to improve outcomes is to regulate negative intrathoracic (chest) pressure by using intrathoracic pressure regulation (IPR)—an innovative therapy that leverages the body’s own physiology.

IPR enhances blood circulation, improves cardiac output and lowers intracranial pressure (ICP) noninvasively to provide better perfusion to the brain. In this article, we’ll explore in detail the physiology behind IPR and its use with hypotensive and cardiac arrest patients.

**Physiology & Basic Scientific Evidence**

The human body is continually regulating circulation of blood by using positive and negative pressures inside the thoracic cavity. This regulation acts like a bellows. During inhalation, the diaphragm moves down and the chest wall moves out, which creates a negative pressure (or vacuum) that draws air into the lungs and blood into the chest, and slightly lowers ICP. During exhalation, the diaphragm moves up and the chest wall moves in. This creates a positive pressure that forces air out of the lungs, diminishes blood return to the chest and slightly raises ICP.

In addition to moving air, intrathoracic pressure affects blood flow. It is well understood that respiration and circulation are inextricably linked. As far back as 1967, an inverse relationship between intrathoracic pressure and blood flow was observed. Moreno et al showed that as intrathoracic pressure decreases, blood flow back to the heart increases. Results from experiments conducted using an animal hemorrhage model support the concept that reduced intrathoracic pressure results in a lowering of right atrial pressure, which in turn pulls more venous blood back into the thorax and increases arterial pressure and cerebral perfusion. This hydraulic effect is shown in Figure 1.

In a healthy person, the body’s normal compensatory response regulates intrathoracic pressure to influence blood pressure. Under stress, such as during exercise, a person breathes harder, faster and deeper. These enhanced pressures in the thoracic cavity help to improve circulation. However, sometimes the body is unable to adequately compensate. For example, in a shock patient, the heart rate increases in an effort to maintain sufficient blood flow, and intrathoracic pressure is modulated in an effort to increase perfusion. If the cause of the shock is not corrected, eventually the patient will decompensate and blood pressure will fall. This results in insufficient perfusion to protect the brain and other vital organs.

**How IPR Therapy Works**

IPR can help patients who are no longer able to compensate for reduced blood flow. Figure 2 (see p. 4) summarizes how this works. IPR enhances the negative pressure in the chest, pulling more blood back to the heart (i.e., increasing preload), which results in increased cardiac output. And

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**Impact of IPR on blood pressures**

![No IPR vs With IPR graph]

**Figure 1:** Results from experiments conducted using an animal hemorrhage model support the concept that reduced intrathoracic pressure results in a lowering of right atrial pressure, which in turn pulls more venous blood back into the thorax and increases arterial pressure and cerebral perfusion.
because pressures in the chest are also transmitted to the brain, IPR also lowers ICP, which decreases resistance to forward blood flow and makes it easier to get blood to the brain. The net result is improved perfusion to the brain and other vital organs.

Another way to think about IPR Therapy is to contrast it to continuous positive airway pressure (CPAP). IPR works in the opposite manner as CPAP, which instead generates positive intrathoracic pressure by forcing air into the lungs. Used to treat patients with pulmonary edema, CPAP employs positive pressure to drive unwanted fluid out of the lungs. CPAP’s positive pressure ventilation therefore has an opposing effect on the cardiovascular system as compared to IPR: CPAP decreases cardiac output and blood pressure, while IPR Therapy increases these physiological parameters. (See Figure 3, p. 5.)

IPR Therapy is currently delivered through impedance threshold devices (ITDs) which have mechanisms to enhance the negative pressure in the chest. This greater vacuum draws more blood into the chest and also lowers intracranial pressure, resulting in more perfusion to the brain and vital organs.  

The primary function of an ITD is to improve circulation by enhancing negative intrathoracic pressure. Data from clinical and preclinical studies support the notion that ITDs enhance negative intrathoracic pressure in both cardiac arrest and hypotensive patients.

- During active compression decompression CPR (ACD-CPR), an ITD lowered intrathoracic pressures from -1 mmHg (sham ITD) to -5 to -7 mmHg (active ITD) in out-of-hospital cardiac arrest patients in a randomized, double-blinded, prospective clinical trial.  
- In a study conducted using humans subjected to a simulated hemorrhage of 30%, peak negative intrathoracic pressure was negligible with a sham ITD, but decreased to -12 cmH₂O when an active ITD was applied.  

Data on the use of ITDs to deliver IPR is extensive. More than 50 animal and human studies have been conducted on the use of ITDs in both conventional and ACD-CPR, and more than 30 animal and human studies have been published on the use of an ITD in improving hemodynamics during shock from a variety of etiologies.
How an ITD Works in Hypotensive Patients

The ITD works in spontaneously breathing patients with low blood pressure by creating a slight amount of therapeutic resistance during inhalation. (See Figure 4.) This resistance enhances negative intrathoracic pressure, which in turn improves perfusion to the brain and other vital organs. An ITD is simple to use and can be applied by all levels of rescuers. With or without intravascular fluids, studies have shown that use of the ITD increases systolic and diastolic blood pressures by up to 30%.6

However, an ITD has advantages over fluids in that it is non-invasive, it does not dilute clotting factors, and it does not cause spikes in blood pressure that may be associated with “popping the clot,” thus complementing a permissive hypotensive approach to blood pressure management.8,9 Supplemental oxygen may also be administered through the device.

Clinical and experimental studies on use of the IPR in hypotension have shown many benefits:

• In a pre-clinical study, use of an ITD increased cardiac output by nearly 25% during a reduction of >50% in central blood volume.10

• The ITD improved systolic blood pressure (SBP) by 25% to 30% during prehospital treatment of hypotensive patients.7,11

• Use of an ITD allowed for permissive hypotension in a recent clinical study.11

• Application of IPR Therapy results in improved oxygen delivery to the brain, which is frequently associated with an improved feeling of well-being in severely hypotensive patients during prehospital care.2,12

Use of an ITD has also been shown to extend the window of treatment for shock patients. In a laboratory experiment designed to simulate continuous progressive hemorrhage in humans, use of an ITD increased the time to cardiovascular collapse (decompensatory shock) by an average of 44%.6

In two studies conducted at independent sites, use of an ITD was shown to be effective in elevating blood pressure in hypotensive patients (78/50 mmHg) during prehospital care, while still maintaining permissive hypotension (100/65 mmHg).21 After application of the ITD, a 47% increase in pulse pressure and improved feelings of well-being were reported in >85% of the patients, which is consistent with mechanisms of increased stroke volume and cerebral perfusion. We will explore the use of an ITD in hypotension in another article in this supplement.

Comparison of positive and negative pressure therapies

<table>
<thead>
<tr>
<th>Intrathoracic Pressure</th>
<th>Positive (i.e., CPAP)</th>
<th>Negative (i.e., IPR)</th>
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<tr>
<td>• 5 to 25 cmH₂O</td>
<td>• -7 to -10 cmH₂O</td>
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<tr>
<td>• Therapy for pulmonary edema</td>
<td>• Risk of pulmonary edema if negative intrathoracic pressure is excessive</td>
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Figure 3: We use positive pressure therapies (e.g., CPAP) to push fluids and air out, while negative pressure (e.g., IPR) can be used to draw fluids and air back to the chest.

Figure 4: IPR is delivered by the ITD 7 for spontaneously breathing hypotensive patients.
Studies on the use of IPR during CPR have shown increased blood flow to the heart and brain. Evidence has also shown that when an ITD is used in conjunction with ACD-CPR, which optimizes chest wall recoil, blood flow is even further enhanced. 

Key findings from clinical trials showed:

- IPR increased systolic blood pressure (SBP) compared to standard CPR (an 85% increase in SBP after 14 minutes of IPR use) in a small, prospective, double-blind study in out-of-hospital cardiac arrest patients randomized to IPR versus a sham control. 
- Near-normal blood pressures were obtained when an ITD was used in conjunction with an ACD-CPR device in human subjects. 

In addition, several pre-clinical trials have shown (note that pre-clinical results may not be indicative of clinical results):

- IPR significantly increases cardiac output compared to standard CPR. In a basic science study of nine pigs, cardiac output increased by 57% using IPR as compared to standard CPR.
- A pre-clinical study showed IPR increased global brain blood flow by 27% compared to standard CPR.
• Mean carotid blood flow increased by 37% using IPR as compared to standard CPR in a pre-clinical study. 17

Multiple studies using ITDs have demonstrated improved outcomes from cardiac arrest. One study showed that ACD-CPR with an ITD improved 24-hour survival by 45% compared to ACD-CPR alone. 19

An even larger prospective, randomized, controlled study showed that long-term survival improved by 49% in adult patients with non-traumatic cardiac arrest who received the combination of an ITD with ACD-CPR vs. standard CPR. 20

**Conclusion**

Intrathoracic pressure regulation (IPR) helps the body help itself in cardiac arrest and shock, and is uniquely designed to improve cerebral perfusion. Animal and human studies have shown that IPR enhances vital organ circulation and outcomes in both hypotensive and cardiac arrest patients. 

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**References**


More than 1,000 people suffer out-of-hospital cardiac arrest every day in the United States. After more than 50 years, survival remains dismal in most communities, with less than 8% of people, on average, surviving neurologically intact to hospital discharge. While the use of active compression-decompression cardiopulmonary resuscitation (ACD-CPR) has shown mixed results in improving outcomes, the combination of ACD-CPR with an impedance threshold device (ITD) has been shown to improve overall survival to one year by 49% in adults with non-traumatic cardiac arrest of cardiac etiology. We'll discuss how the device combination works and review the data supporting its use in resuscitation.

Physiology of CPR
Understanding the physiology of CPR helps us understand how the ResQCMR System works. There are two theories on the mechanism of CPR. The first is the Cardiac Pump Theory. This theory states that when the chest is depressed (compression) the heart is compressed between the sternum and spine, which squeezes the blood out of the heart and into the systemic vasculature. Blood naturally goes back into the heart and the process starts all over again with the next compression. People are most familiar with this theory because it’s been established for quite some time.

The second, newer theory is the Thoracic Pump Theory. This theory states that with each compression of the chest, a resultant positive pressure is created in the chest. This positive pressure aids in blood flow to the heart, allowing for better cardiac performance. The combination of these two mechanisms may explain the improved outcomes observed with ACD-CPR and ITD use.

By R.J. Frascone, MD, FACEP
pressure is transmitted to the blood inside the heart, and that blood then moves from the relative higher pressure inside the heart to the relative lower pressure of the systemic vasculature. Because compression of the chest increases the pressure to all the structures inside the chest, including the lungs, air in the lungs is expelled. Following chest compression, the chest passively recoils. (See Figure 1.)

The Thoracic Pump Theory states that this recoiling of the chest, or decompression, creates a small but very important vacuum (negative pressure), which sucks blood back into the heart, thereby providing preload. This negative pressure also lowers intracranial pressure (ICP) by promoting venous and cerebral spinal fluid drainage from the brain. The lowered ICP results in less resistance to blood flow in the brain, which promotes cerebral perfusion. This alternating positive and negative pressure (modulation of intrathoracic pressure) helps circulate blood until the heart can be restarted.

Unfortunately, studies have shown that even when performed correctly, conventional CPR delivers less than 25% of normal blood flow to the heart and brain. Understanding the reasons for this can help us improve the effectiveness of CPR.

Research has helped us to better understand potential issues with CPR. First, an inherent inefficiency of CPR contributes to suboptimal blood flow. When the chest wall recoils, air is drawn in through an open airway, eliminating the vacuum responsible for creating preload. The heart stops filling as soon as the vacuum is neutralized.

Second, poor CPR quality can impact outcomes. Chest compression quality (rate and depth) have been shown to directly impact survival. Also, preload is dependent upon passive recoil during the chest decompression phase. If the chest doesn’t recoil completely, the vacuum doesn’t develop and preload is compromised. Inadequate chest wall recoil can be caused by broken ribs, poor chest wall compliance in old age or the weight of fatigued rescuers on a patient’s chest.

The use of ACD-CPR with an ITD during CPR can address both of these inefficiencies.

**Active Compression-Decompression CPR**

Active compression-decompression CPR (ACD-CPR) was first described by Rudolf Eisenmenger in 1903 when he published an article on a device called the Biomotor, which applied suction and pressure on the abdomen and lower chest to promote breathing and circulation. Interest in the Thoracic Pump Theory was rekindled in 1990 when Keith Lurie, MD, and colleagues published the case of a man whose family members resuscitated him by performing CPR with a household toilet plunger. This led to the development of an ACD-CPR device called the CardioPump outside the U.S. (See Figure 2, p. 10.)

This ACD-CPR device is a handheld device with a suction cup that’s placed on the chest during CPR. As with manual CPR, it’s used to compress the chest to a depth of 2 inches, but instead of relying on the chest wall to recoil passively, rescuers pull up on the handle to provide active decompression of the chest. This ensures that the chest wall recoils to at least neutral, and even beyond neutral, thereby enhancing the vacuum and improving the amount of blood that’s returned to the heart. The handle contains a force gauge to guide compression and lifting forces, and a metronome to guide compression rate.

Early studies showed that in addition to doing a good job compressing and lifting the chest, ACD-CPR also moved more air in and out of the chest during CPR; in fact, tidal volumes are two to four times that of conventional CPR. This was initially seen as a way to both compress and decompress the chest, as well as potentially providing an alternative to having to perform mouth-to-mouth ventilation.

It wasn’t until years later that researchers realized that the movement of air into the chest while pulling up effectively eliminated the vacuum created by chest decompression and, therefore negated the vacuum we were trying so hard to promote. Early studies comparing...
ACD-CPR alone to conventional standard CPR showed mixed results, with little effect on the enhancement of the intrathoracic vacuum and no significant effect on long-term survival.7 Researchers realized they needed to find a way to move more blood, not more air.

**ACD-CPR with an ITD**

While studying the ACD-CPR device, researchers discovered that if air was impeded from moving into the chest during the decompression phase, the resultant vacuum was much larger and was sustained for a much longer period of time. This finding led to the development of the impedance threshold device (ResQPOD ITD), a check valve that’s placed between the facemask or advanced airway device, and the ventilation bag or ventilator. It selectively prevents air from being drawn into the chest during the decompression phase of CPR. The ITD does not restrict air movement during exhalation and ventilation, but checks during decompression. Preventing air from being drawn down the trachea and into the chest during decompression markedly improves the filling of the heart (preload) and, thus, markedly improves cardiac output during the next

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**Case Study from the ResQTrial**

Professor Steve Dunn was working out at his gym in Oshkosh, Wis., when he began experiencing chest pain. He attempted to drive himself to the hospital but went into cardiac arrest and crashed his vehicle in the hospital’s parking lot. EMS crews arrived on scene and began performing CPR using an ACD-CPR device and ITD according to study protocol.

‘To the medics’ surprise, Dr. Dunn became conscious during CPR and asked them to stop. When they complied, Dunn lost consciousness. Once again they began ACD-CPR with the ITD, and once again Dunn regained consciousness.

Dunn ultimately survived with no neurologic deficits and, thankfully, no memory of the event. Signs of improved levels of consciousness (e.g., gasping, gagging, eye and limb movement) were reported during the ResQTrial and are indicative of how well the brain was being perfused.
compression phase. Further, this increase in negative pressure also significantly lowers ICP, and also promotes significant increase in coronary circulation (which occurs during the decompression phase).

The combination of the ITD with ACD-CPR has shown significant improvements in both hemodynamics and ultimate survival in cardiac arrest.8 The two devices work synergistically to enhance the intrathoracic vacuum during the decompression phase. (See Figure 3.) Again, this has three effects:

1. Markedly lowers ICP, which lowers the resistance to forward blood flow, thus improving cerebral perfusion pressure.9
2. Increases preload, which leads to increased cardiac output on the subsequent compression.
3. Improves coronary circulation.

A carefully conducted, large study showed that all of these improvements in circulation result in an increased likelihood of survival in patients with non-traumatic cardiac arrest. In addition to human outcome trials, animal studies have shown that vital organ blood flow with the combination of ACD-CPR and the ITD is significantly better than when either device is used individually, and can result in normal blood flow to the brain.10–12 (See Figure 4.)

In human trials, Plaisance et al demonstrated that negative intrathoracic pressure could be significantly enhanced with both a facemask and an endotracheal tube during ACD-CPR with an ITD.13 Other human CPR trials have shown that the device combination:

- Provided near-normal systolic and diastolic blood pressures.14,15 (See Figure 5, p. 12)
- Improved 24-hour survival in witnessed arrest by 78% compared to standard CPR.16
- Improved 24-hour survival by 45% compared to ACD-CPR alone.17

The largest randomized, controlled trial of ACD-CPR with an ITD to date, called the ResQ-Trial, showed that improved long-term survival can be a reality.8 This multicenter study compared conventional standard CPR to ACD-CPR with an ITD in more than 1,600 patients who had suffered a cardiac arrest of presumed cardiac
etiology. Interestingly, rates of prehospital return of spontaneous circulation and survival to hospital admission were statistically similar; however, survival was 26% higher at hospital discharge, and 49% higher at one year in the group that received the device combination, despite receiving similar hospital care. In the larger cohort of patients who arrested from all non-traumatic causes, survival was 33% better in the group who received ACD-CPR with an ITD at one year.\textsuperscript{18} The neurological outcome in these patients appeared to be no worse than the control (standard CPR). The intervention group did experience a higher rate of pulmonary edema, but all other complication rates between groups were similar. Interestingly, the presence of pulmonary edema was actually associated with a more than two-fold increase in survival to hospital discharge with good neurologic function.\textsuperscript{19} Thus, the ResQTrial clearly showed that ResQCPR is as safe as standard CPR across the board.

Although the four-year trial was prospective and randomized, there were a couple key limitations. First, it wasn’t possible to blind rescuers to the CPR method, though follow-up after resuscitation and out to one year was blinded. Secondly, the quality of CPR wasn’t measured in either group, though the device group had the availability of visual and audible metronomes to guide compression and ventilation rates.

In addition to overall survival, neurologically intact survival was measured during the ResQTrial. Although some of this data is presented below, conclusions and inferences regarding neurologic outcomes cannot be drawn from the ResQTrial due to interpretability issues related to the neurologic component of the data.

Neurologically intact survival was 52% higher at hospital discharge for patients with presumed cardiac etiology who received ACD-CPR + ITD compared to patients who received standard CPR. Similar improvements were measured in the larger cohort of patients who arrested from all non-traumatic causes, both at hospital discharge and one year, as shown in Figure 6.

The trial showed that ACD-CPR with an ITD exhibited cardio- and neuro-protective qualities when used with or without therapeutic hypothermia. When using therapeutic hypothermia and ACD-CPR with an ITD, there was a

![Systolic and diastolic blood pressure in humans](Image)

**Figure 5:** Results from a human study show that near normal blood pressures were achieved with ACD-CPR + ITD.

![Survival in the ResQTrial](Image)

**Figure 6** shows results from the ResQTrial. Adult patients with cardiac etiology who received ACD-CPR + ITD had a 49% better chance of survival to one year than those who received standard CPR. Adult patients with non-traumatic cardiac arrest showed a 38% increase in survival to one year when they received ACD-CPR + ITD vs. standard CPR.
six-fold improvement (11.1% to 69.2%) in the percentage of patients who improved from poor neurologic status at hospital discharge to favorable neurologic status at 90 days, compared to those patients who received standard CPR with therapeutic hypothermia. Conversely, for those patients who didn’t receive therapeutic hypothermia, use of the device combination was independently associated with a nearly two-fold increase in the number of survivors with favorable neurological function at the time of hospital discharge and 90 days after the cardiac arrest.

**Conclusion**

While the FDA has not yet approved the ResQCPR System (ResQPUMP ACD-CPR device and ResQPOD ITD) for use in the United States, we hope that the device combination will soon be made available. Use of ACD-CPR with an ITD has been shown to have no increased risk, while at the same time resulting in a marked increase in survival over standard CPR in adult patients with non-traumatic cardiac arrest. With the potential of improved one-year survival of 49% in non-traumatic arrests of cardiac etiology, widespread adoption of the device combination could result in thousands more lives saved each year in the U.S. alone.

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How will IPR Therapy impact the way we treat patients in the future?

By Ray Fowler, MD, FACEP, DABEMS
As discussed in other articles in this supplement, Intrathoracic Pressure Regulation (IPR) is a novel therapy that leverages our natural physiology to increase perfusion in hypotensive patients and shows promise for improving outcomes for multiple etiologies. In this summary, I’ll briefly review how IPR works, results with current delivery methods and then discuss the future applications of this exciting therapy.

How IPR Works

The heart and lungs work together to create negative intrathoracic pressure (a vacuum), which aids in filling the heart. When we inhale, the diaphragm moves downward and the intercostal muscles cause the rib cage to expand, making the thoracic cavity larger.

The enlargement of the chest makes the pressure within the chest more negative, drawing air in and pulling some blood back to the heart, filling it to create cardiac output on the next contraction. This negative pressure also helps to lower intracranial pressure (ICP), making it easier to get blood flow to the brain.

Maintenance of negative filling pressure is essential to maintaining cardiac output. Recall that:

\[
\text{Blood Pressure} = \text{Cardiac Output} \times \text{Peripheral Vascular Resistance}
\]

The heart only pumps out the blood that it can pull back through the negative pressure on the right side of the heart; thus, cardiac output is maintained by negative filling pressure. Anything that decreases the negative filling pressure reduces blood return to the heart (preload), lowers cardiac output, and may result in hypotension and shock. Conversely, anything that enhances the negative filling pressure increases preload and cardiac output and lowers ICP, offering a potential treatment for cardiac arrest and shock.

IPR does just that. By enhancing negative intrathoracic pressure, IPR has been shown in multiple studies to increase preload, lower ICP and increase blood flow to the brain. The potential of this therapy is significant, and early results look promising.

Current IPR Delivery Mechanisms & Results

Currently, IPR is delivered through impedance threshold devices (ITDs), which improve circulation in patients in cardiac arrest or shock. Studies from EMS agencies in Toledo, Ohio, and San Antonio, Texas, have shown that, when used in hypotensive patients, the ITD is well tolerated and can also increase blood pressure by up to 30%, while still allowing for permissive hypotension in traumatically injured

Overall performance score category comparing SNPeCPR to standard CPR

![Overall performance score category comparing SNPeCPR to standard CPR](image)

Figure 1 shows results from a pre-clinical study in a porcine model by Schultz et al comparing outcomes in animals receiving standard CPR vs. subjects receiving SNPeCPR or “Snappy CPR”, which includes ACD-CPR with an ITD (eCPR) and sodium nitroprusside (SNP), a vasodilator.
patients. Contrary to fluids, the device appears to enhance blood flow, not just pressure.\(^1\)\(^2\)

Dozens of animal and clinical studies have been conducted on the ITD in CPR showing enhanced blood flow to the heart and brain.\(^3\)

In addition, studies have shown that when ACD-CPR is performed in combination with an ITD, it further enhances negative intrathoracic pressure, resulting in near-normal blood flow circulation to the heart and brain.\(^4\)\(^5\) The combination of ACD-CPR with an ITD was compared to conventional standard CPR alone in the ResQTrial, a National Institutes of Health-funded, multi-center, randomized, controlled trial, the results of which were published in 2011 in *The Lancet*.\(^7\)

Overall survival to one year with standard CPR was near the national average of 5.9%; but with the ACD-CPR/ITD combination, survival improved 49% to 8.8% in adult patients with non-traumatic arrest of cardiac etiology. This data supports the concept that enhancing negative intrathoracic pressure improves perfusion and survival.

**The Foundation for Innovative Approaches to Treating Cardiac Arrest**

Enhanced blood flow improves perfusion and provides a more effective way to circulate drugs and deliver therapeutic hypothermia. Thus, the ACD-CPR/ITD combination opens the door to new ways to improve outcomes, even in patients with prolonged downtimes or resuscitation efforts. Let’s take a look at a few of those approaches.

**Sodium nitroprusside, aka “Snappy” CPR:** Shultz and colleagues have studied the use of sodium nitroprusside (SNP) during enhanced CPR (eCPR) in a porcine model.\(^6\) SNP is a potent vasodilator that could be detrimental if given when circulation is poor, but when used with eCPR (ACD-CPR/ITD), this device/drug combination (SNPeCPR, or “Snappy CPR”) dramatically improves circulation and short-term outcomes.

Studies have shown that in porcine models with extended downtimes (15 minutes of untreated v fib), animals receiving SNPeCPR had significantly improved 24-hour survival, better neurologic function and less post-resuscitation left ventricular dysfunction compared to animals receiving standard CPR.\(^8\) (See Figure 1, p. 15.)

**“Stutter” CPR:** A newly identified concern in the treatment of cardiac arrest is that the sudden influx of blood from CPR, following minutes without flow, can lead to reperfusion injury. Reperfusion is a recognized issue following organ transplantation; as a result, blood is gradually reintroduced to the new organ, allowing it time to get acclimated to a state of better perfusion. Reperfusion may also be a problem in cardiac arrests, particularly those with longer downtimes.

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**24-hour cerebral performance category score**

![24-hour cerebral performance category score](image)

Note: * ¶ § Mean statistically significant difference compared to standard CPR, SNPeCPR and SNPeCPR + adenosine respectively.

**Figure 2** illustrates survival from a pre-clinical study in a porcine model by Yannopoulos et al comparing 4 CPR methods:\(^10\) 1) standard CPR (S-CPR); 2) ACD-CPR + ITD + sodium nitroprusside (SNPeCPR); 3) SNPeCPR + adenosine; and 4) Controlled pauses (CP) with SNPeCPR (CP-SNPeCPR) + adenosine, to assess outcomes.
To assess whether cardiac arrest victims would benefit from a more gradual reintroduction of blood flow, Yannopoulos and colleagues used SNPeCPR (ACD-CPR/ITD and SNP) with intentional 20-second pauses during the first few minutes of CPR in pigs. Results showed a significant decrease in reperfusion injury and a significant increase in functional neurologic recovery compared to standard CPR.  

This “stutter” CPR approach is in stark contrast to the long-held tenet that all interruptions in CPR are harmful. It may be that in specific cases, controlled pauses at strategic times could actually be immensely helpful.

**Adenosine:** Other fascinating research is being conducted to determine whether uncommon resuscitation drugs and anesthetic gases may provide cardio- and neuro-protection during and after cardiac arrest. One such animal study looked at the impact of adenosine, a drug known...
to improve coronary blood flow but typically only used in EMS for the treatment of arrhyth-
mias. The study compared outcomes in four
groups of animals receiving treatment following
15 minutes of v fib:
1. Standard CPR
2. SNPcCPR
3. SNPcCPR + adenosine
4. SNPcCPR + adenosine with controlled
pauses (“stutter” CPR)
The results were striking, as you can see in
Figure 2 (p. 16).10

“Head-up” CPR: Patients in cardiac arrest
sometimes need to be tipped head-up or feet-
up to be transported down stairs or in eleva-
tors. Investigators studying the impact of body
position on cerebral circulation during car-
diac arrest hypothesized that when a patient is
treated in a head-up position, blood will need
to flow against gravity and cerebral perfusion
will be compromised.

One of the most exciting findings is that the
use of the ITD with automated CPR (LUCAS 2
from Physio-Control) actually enhances venous
return, cardiac output and cerebral perfusion
during “head-up” CPR. Debaty and colleagues
compared coronary and cerebral perfusion
pressures in animals receiving CPR with a
LUCAS 2 chest compression device and ITD in
three positions: 30 degrees head down, supine,
and 30 degrees head up. They found cerebral
perfusion pressure was nearly doubled when
the upper body was elevated to 30 degrees com-
pared to when the body was supine (0 degrees)
during CPR.11 (See Figure 3, p. 17.)

Use of the ITD appears to work synergisti-
cally with gravity to improve hemodynamics.
During chest compression, use of an ITD with
automated CPR appears to improve cardiac
output in conjunction with the 30-degree eleva-
tion. Automated chest decompression, gravity
and use of the ITD help to lower ICP, result-
ing in reduced resistance to forward blood
flow and better blood flow to the heart and
brain.11 (See Figure 4.) Although more research
is required to better understand the synergies
of the devices with gravity, initial results show
“head up” CPR could become a simple BLS
technique to improve neurologic outcomes
from cardiac arrest.

The bottom line: Early research is clearly
challenging long-standing beliefs about the
treatment of cardiac arrest. We’ll need to keep
our “heads up” and stay tuned to upcoming
clinical trials of these device, drug and gravity
combinations.

Future Technologies & Applications
So what’s next for IPR? We know the efficacy of
an ITD is dependent upon the quality of CPR or
the way a patient breathes through it. In addi-
tion, its therapeutic effect is only present dur-
ing inhalation or chest compressions. Studies
of a device that actively delivers ongoing IPR

Figure 4: In a study by Debaty et al, the 30 degree head up angle showed significant improvements in both
coronary (CPP) and cerebral perfusion pressures (CePP).11

Relationship between body position and CPP and CePP
therapy, even if the patient is not breathing or undergoing chest compressions, are ongoing and results again look compelling.

A device still in studies, an intrathoracic pressure regulator (CirQLATOR from Advanced Circulatory), combines a continuous vacuum source and a pressure regulator with a means to provide intermittent positive pressure ventilation, resulting in a device that creates a controlled, ongoing therapeutic vacuum in between ventilations. In a clinical study of this device in cardiac arrest patients in Toledo, Ohio, patients who received the CirQLATOR exhibited significantly higher end tidal carbon dioxide levels than patients with the ITD alone.12 This technology may also be applicable to hypotensive patients who are not spontaneously breathing.

Another area of development for IPR: head injuries. Studies have shown IPR not only enhances circulation, it lowers ICP and increases cerebral perfusion pressure.13 The ability to do this noninvasively has naturally attracted the attention of neurologists interested in using the therapy in patients with head injuries or other cerebral insult. Solutions available today to lower ICP are invasive and have associated risks. In the future, it’s possible IPR therapy could be applied not only in the critical care setting, but also at the point of injury with the ResQGARD or CirQLATOR. A study to assess the impact of IPR with the CirQLATOR device on patients in the ICU with brain injury is currently underway.

**Summary**

Scientific advances are bringing new revelations to the management of critical conditions such as cardiac arrest and shock. Harnessing the mechanics of IPR and understanding their effect is resulting in improvements in cardiac resuscitation and therapy for hypotension in both hemorrhage and non-trauma shock states. Perfusion is improving. Our understanding of the relationship of IPR and cerebral perfusion is also expanding. Therapies that can improve forward flow and perfusion of vital organs are being utilized by BLS personnel. Noninvasive bridging tools that capture the benefit of IPR hold further potential to improve hemodynamics.

In the years to come, these and other insights gained through careful research will allow medical providers the world over to find new opportunities to save thousands of lives that would otherwise have been lost.

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**References**


Hypotension is a common clinical problem that has plagued individuals suffering from reduced central blood volume, such as hemorrhage due to trauma, cardiovascular failure, infection, dehydration and anaphylaxis. Although each process affects the cardiovascular system somewhat differently, untreated hypotension from any cause can quickly result in irreversible shock.

In the trauma patient, shock resulting from low-circulating blood volume often results in poor outcomes. Fluid administration has traditionally been the therapy of choice for the hypotensive patient, but crystalloid infusion is not necessarily benign.1,2

Difficult vascular access, hemodilution, acidosis (which results in decreased oxygen-carrying capacity) and loss of clotting factors continue to be problematic in the poorly perfused patient.3 Optimizing cardiac output and ultimately tissue perfusion in this patient population can provide a critical bridge during transport to definitive care.

**Inspiratory Resistance**

As discussed previously in this supplement, Intrathoracic Pressure Regulation (IPR) reduces intrathoracic pressure (the opposite of CPAP) during the inspiratory phase of ventilation in spontaneously breathing patients by creating inspiratory resistance.

This vacuum-generating effect in the thorax acts directly on the great vessels in the chest, and has been shown to enhance blood return from the capillary beds into the great vessels via the same vacuum mechanism with each breath.4

Clinical and experimental evidence supports enhancing the intrathoracic vacuum with the intent to:

1. Improve hypotension secondary to severe blood loss, hemorrhagic shock and hypovolemia;
2. Relieve the adverse clinical effects of orthostatic hypotension and hypotension secondary to vasovagal syncope, dehydration and renal dialysis;
3. Provide a treatment for right heart failure after myocardial infarction; and
4. Reduce intracranial pressure (ICP) for the treatment of secondary brain damage after head trauma and improve cerebral blood flow.\textsuperscript{5,6,7}

Today, IPR Therapy is delivered through impedance threshold devices (ITDs). One ITD, the ResQGARD ITD 7, is a single-use valve that can be attached to a facemask or small mouthpiece to treat spontaneously breathing patients.

Clinical Studies on the ITD

The Institute for Surgical Research has developed an elegant mechanism to simulate hemorrhage in healthy adults. Using a machine that can produce lower body negative pressure (LBNP), the central blood volume can be displaced into the lower extremities. (See Figure 1.) This displacement leaves the upper body in a simulated, yet physiologically precise, hypovolemic state. LBNP has been shown to be an effective model of the stages of shock.

Using this model, Convertino et al have been able to predict when a patient will begin to experience progressive reductions in central blood volume leading to hemodynamic decompensation; i.e., a precipitous decrease in systolic blood pressure < 90 mmHg concurrent with the onset of pre-syncopal symptoms such as bradycardia, gray-out (loss of color vision), tunnel vision, sweating, nausea or dizziness.\textsuperscript{8}

Interestingly, with repeated exposures to LBNP, the healthy volunteer would cycle through the stages of decompensation consistently until placement of the ITD. An ITD contributed to the delay in symptoms of syncope, as compared to those with a sham ITD device in patients subjected to progressive simulated hemorrhage.\textsuperscript{9}

One of the first clinical studies of the ITD came from the Hennepin County (Minn.) Medical Center Department of Emergency Medicine.\textsuperscript{10} This was a double-blinded, randomized, controlled trial using either a real or sham ITD device on patients who presented to the ED hypotensive, or developed hypotension during the ED visit.

Figure 1: A lower body negative pressure chamber is used to simulate hemorrhage in healthy adults.
Spontaneously breathing adults with hypotension and a normal mental status were enrolled. Patients were excluded if they had evidence of a myocardial infarction, stroke, dilated cardiomyopathy, CHF, pulmonary hypertension, shortness of breath, face or chest trauma, pneumothorax, atrial fibrillation with rapid ventricular response, or if the patient was pregnant.

The treating physician placed either a real or sham ITD on the patient for 10 minutes, then monitored vital signs and assessed how well the patient tolerated the device. They enrolled 47 subjects; 23 received a sham device and 24 received an active ITD.

The results of the study demonstrated significantly higher systolic blood pressure increases in the active ITD group (13 mmHg) versus the sham group (6.5 mmHg). It took an average of 6 minutes to obtain the maximal rise in systolic blood pressure. There was no difference in mean arterial pressure or diastolic blood pressure. Also, the vast majority of patients tolerated the device well. (See Figure 2.)

Because this was a research study, the participants had to be alert enough to be able to provide informed consent, so many of the critically ill patients were not eligible to participate. Additionally, the cause of hypotension was highly variable across the study, and it is unknown if the use of the device reduced hospital stays or improved the patients’ final outcome.

A case series of ITD use for treating hypotensive patients in a prehospital EMS setting was recently published in the Journal of Trauma Acute Care Surgery. This report provided information on the use of the ITD in clinical practice by paramedics with Lucas County EMS (Ohio), Cypress Creek EMS (Texas), and Empress EMS (N.Y.). Patients with traumatic and non-traumatic blood loss were included.

To ensure standardization of the prospective data collection method (e.g., vital signs, questions regarding tolerance and mental status) between sites, all participating EMS personnel were trained by the same instructor, and all hemodynamic data were extracted from EMS run reports, including recordings of various physiological parameters before, during and after ITD use.

During the study period, the three EMS agencies used the ITD on 255 patients, including 26 who were hypotensive secondary to non-traumatic blood loss, and 13 patients who were classified as trauma patients. Mean blood pressure, recorded before and after ITD placement, improved from 78/47 to 111/65 mmHg, and was statistically and clinically significant. There were no significant changes in other vital signs. (See Figure 3, p. 22.)

The strengths of this report were that it focused on a patient population that was able to be divided into groups with hypotension due to blood loss, and a group with hypotension from other than blood loss (i.e., sepsis). Both groups had similar initial blood pressures and showed similar increases in blood pressure after application of the ITD.
Patient tolerance

During the course of patient care, the patient’s clinical picture improved. One of the components of treatment included the ITD, but this treatment was not performed in absence of other therapy. Positioning, intravascular fluids, movement and physical stimulus by EMS interaction may have also contributed to improvement of the clinical condition of the patient.

One limitation of this study: No data was collected on injury severity of the trauma patients, or of the patients’ final outcomes. There were no data collected to support the notion that increasing blood pressure of a trauma patient with unknown or uncontrolled hemorrhage could potentially worsen the outcome. Additional studies are ongoing.

The San Antonio Experience

The San Antonio Fire Department Emergency Medical Services, in partnership with the University of Texas Health Science Center at San Antonio Department of Emergency Health Science Center, and the U.S. Army Institute for Surgical Research, conducted a study on the deployment of the ITD in a large urban EMS setting.12

In this study, more than 740 paramedics were trained in the use of the ResQGARD ITD, and patients were enrolled in the study if they were identified by paramedics as having a SBP < 90 mmHg.

Each paramedic in the system received 30–45 minutes of training that included patient inclusion and exclusion criteria, use of the device and human subject protection. This training was reinforced by a video (www.youtube.com/watch?v=kg2e_agYBo) and an 8.5” x 11” laminated visual reminder that was posted inside the ambulance.

Similar to the study described in the previous section, hypotension from all causes was included, as well as exclusion criteria (e.g., pulmonary edema, respiratory distressed or “air starved,” and the inability to maintain an airway).

Primary outcomes were the net change in systolic, diastolic and mean arterial blood pressures. Secondary outcomes sought to identify frequency of ITD use within the EMS system, patient tolerance and patient comfort. The trauma subset was isolated, and primary and secondary outcomes were determined as well. The intended enrollment was 200 patients within 12 months.

Within the first six months of ITD deployment, all 200 approved subjects were enrolled. Thirty-two patients were excluded because of incomplete documentation. Of the 168 patients analyzed, 26 (15%) were trauma patients. Blood pressure changes for this study were similar to those described in the previous EMS study.

A mean initial blood pressure before ITD was 78/51 mmHg, with a pulse of 86 and respiratory rates of 18. After ITD, mean blood pressure values rose to 97/63 mmHg, while the pulse and respiratory rates remained similar at 85 and 18 respectively. This represented a change in systolic blood pressure that was both statistically and clinically significant, but no change in other measured physiological parameters.

Figure 2: The ResQGARD ITD 7 was well tolerated by patients in the San Antonio study.
Specifically, the trauma subset demonstrated an increase in blood pressure from 79/55 to 101/70 mmHg without a statistically significant change in mean heart rate or respiratory rate. (See Figure 3, p. 22.) Eighty-four percent of the patients receiving ITD Therapy reported moderate to easy tolerance of the device.

Strengths of this study included examination of consecutive patients treated with the ITD for hypotension, no observed or reported adverse events, and successful implementation of a permissive hypotensive resuscitation effect. A limitation was that the ITD Therapy was concurrent with other standard therapy so the change in blood pressure cannot be solely attributed to the ITD.

Conclusions
Enhanced negative intrathoracic pressure during spontaneous inspiration has been recognized for more than 50 years as a natural mechanism for enhancing venous return and cardiac filling. Taking advantage of these fundamental relationships between respiratory, cardiovascular and cerebrovascular physiologies, it’s possible to harness natural physiologic processes to create a greater vacuum within the thorax during each spontaneous inspiration, and consequently to enhance venous return and preload to the heart.

ITD application may become a powerful clinical tool to enhance circulation during hypotensive crises secondary to central hypovolemia, particularly in austere environments where resuscitation fluids may not be readily available (e.g., combat medicine) or access to the patient is limited (e.g., patient entrapment).

What makes the ITD attractive is that it’s small and lightweight, can be administered by BLS providers, is reversible and will not result in hemodilution. Even if these effects are temporary, the ITD may provide a sufficient bridge therapy for trauma or medical scenarios until patients can receive advanced or definitive care.

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References
The generally cleared indication for impedance threshold devices available for sale in the United States is for a temporary increase in blood circulation during emergency care, hospital, clinical and home use. Research is ongoing in the United States to evaluate the long-term benefit of ITDs for specific indications. The studies listed here are not intended to imply specific outcomes-based claims not yet cleared by the US FDA.

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In a study of 22 patients undergoing CPR, systolic BP rose 98% (p<0.01) and diastolic blood pressure rose 25% (p=NS). Pirrallo et al. Resuscitation 2005;66:13-20.


Studies available upon request. The generally cleared indication for the ResQPOD ITD available for sale in the United States (US) is for a temporary increase in blood circulation during emergency care, hospital, clinic, and home use. Research is ongoing in the US to evaluate the long-term benefit of the ResQPOD for other specific indications. The studies referenced here are not intended to imply specific outcomes-based claims not yet cleared by the US FDA.

Perfusion on Demand

Pre-clinical studies show that use of the ITD during CPR results in 50% more blood flow to the brain.²

(Note: pre-clinical data may not indicate clinical results.)

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