Intrathoracic Pressure Regulation for the Treatment of Hypotension

I. Cinel, A. Metzger, and R.P. Dellinger

Introduction

Intrathoracic pressure regulation therapy is based upon the physiological principles of the inspiratory impedance threshold device which was developed to increase the return of venous blood back to the heart for treatment of a number of different clinical conditions associated with clinically significant hypotension, including cardiac arrest [1–9]. Intrathoracic pressure regulation therapy works by modulating pressures inside the thorax to augment circulation in states of low blood pressure. This technology was first used in the setting of cardiopulmonary resuscitation (CPR). In the non-spontaneously breathing patient, by harnessing the chest wall recoil with a device that prevents air from entering the lungs each time the chest re-expands after a chest compression, an impedance threshold device (ResQPOD®, Advanced Circulatory Systems, Minneapolis, MN) lowers intrathoracic pressures, enhancing blood return to the heart while lowering intracranial pressures (drop in internal jugular vein pressure). In spontaneously breathing patients, inspiration through a differently configured impedance threshold device (ResQGard®) lowers intrathoracic pressures and similarly enhances cardiac preload and lowers intracranial pressures. Both mechanisms contribute to increases in cerebral perfusion during CPR and in spontaneously breathing patients. Based upon collaborative research with the National Aeronautics and Space Administration (NASA) and the United States Army Institute for Surgical Research, the impedance threshold device has recently been recommended in spontaneously breathing patients for treatment of hypotension due to multiple potential causes, including blood loss, intradialytic hypotension, perioperative hypotension, orthostatic hypotension, and hypotension associated with labor and delivery [10–16]. The technology was evaluated by NASA, as some astronauts develop severe orthostatic hypotension after space flight. It is now used as part of the care for astronauts after prolonged space flights. In this chapter, the potential use of intrathoracic pressure regulation for the treatment of hypotension will be discussed, including preliminary preclinical data on use of this approach to treat hypotension in pigs secondary to *Escherichia coli* peritonitis.

Active Intrathoracic Pressure Regulation Therapy for Apneic Hypotension Patients

The active intrathoracic pressure regulation device for non-breathing patients is called the CirQlator®. Whereas the ResQPOD requires complete chest wall recoil during CPR in order to generate negative intrathoracic pressures, the CirQlator
requires an external regulated vacuum source to actively increase negative intrathoracic pressure in apneic patients. The CirQlator is used to treat hypotensive patients requiring positive pressure ventilation to maintain adequate respiration and generates an intrathoracic vacuum during the expiratory phase of ventilation to enhance venous blood flow back to the heart and to simultaneously lower intracranial pressures. The CirQlator was approved by the United States Food and Drug Administration (FDA) in 2007 and is illustrated in Figure 1. The device works in a biphasic manner: First, a positive pressure ventilation breath from a manual resuscitator or ventilator is delivered and then the device rapidly draws respiratory gases out of the thorax until a predetermined vacuum develops inside the thorax. The currently available device generates a vacuum of –12 cmH₂O in between positive pressure breaths. The positive and negative intrathoracic pressures are instantaneously transmitted throughout the intrathoracic cavity and the physiological effects of the resultant pressure changes impact cardiovascular hemodynamics.

While this novel approach has recently been applied to patients in cardiac arrest and to those with hypotension secondary to low intravascular volume who are able to breathe spontaneously, the sickest patients in shock are usually not able to breathe independently. This is particularly true for patients who have suffered significant traumatic injury, and those with septic shock. The CirQlator was developed specifically to improve blood pressure for any non-breathing patient with significant hypotension secondary to a decrease in cardiac preload or central blood volume. In cardiac arrest, it provides a more continuous and controlled negative intrathoracic vacuum between positive pressure ventilations, potentially improving circulation to the heart and brain. In non-cardiac arrest applications, it actively lowers intrathoracic pressure continuously when a positive pressure ventilation is not being delivered, thereby enhancing the gradient for venous blood flow back to the heart while lowering intracranial pressure. Combined, these mechanisms offer potential to exploit normal physiological processes to enhance circulation in hypotensive non-breathing patients.

**Intrathoracic Pressure Regulation Therapy in Cardiac Arrest with CPR**

Since its discovery, there have been more than fifteen published studies using the impedance threshold device in animal models of cardiac arrest from multiple animal
laboratories and seven published clinical randomized prospective studies with the impedance threshold device in patients in cardiac arrest [1–7, 17–25]. These studies have demonstrated that use of the impedance threshold device with either conventional manual CPR alone or active compression-decompression (ACD) CPR resulted in increased blood pressure, increased circulation of drug therapies, and increased survival rates. With conventional manual CPR, double blinded randomized clinical trials with the impedance threshold device showed that systolic blood pressures were twice as high when the active impedance threshold device was used (85 mmHg compared to 44 mmHg in sham-treated controls, p < 0.001) and short-term survival rates were also doubled in patients who presented with an initial rhythm of either ventricular fibrillation (VF) or pulseless electrical activity [17, 19]. As a result of the multiple, published, clinical outcomes-based trials involving nearly 1000 patients, the impedance threshold device was given a level 2a recommendation in the 2005 American Heart Association Guidelines for CPR [26]. Aufderheide et al. showed that treatment using the combination of the impedance threshold device and application of the new CPR Guidelines, compared to historical controls, doubled survival to hospital discharge rates for patients with an out-of-hospital cardiac arrest, regardless of the initial presenting rhythm [27].

Intrathoracic Pressure Regulation Therapy and CPR

The effects of intrathoracic pressure regulation therapy using the CirQlator have been studied in pigs in VF during CPR. In this setting, an early prototype of the CirQlator was used to lower intrathoracic pressures. This change in intrathoracic pressure resulted in: 1) Enhancement of venous return to the heart to refill the heart with blood after each compression; 2) an increase in cardiac output with each compression; and 3) lowering of intracranial pressure linked directly to the lowering of intrathoracic pressure, which reduces the resistance for blood flow from the brain. The newly discovered benefit of lowering intracranial pressures by lowering intrathoracic pressures during CPR and other states of low blood pressure is one of the more unique aspects of this new technology as it provides potential to enhance cerebral circulation and increase CPR efficacy [28].

In a porcine model of cardiac arrest, after 8 minutes of untreated cardiac arrest, CPR was performed on 20 pigs for 6 minutes at 100 compressions/min with positive pressure ventilation (100 % O₂) and a compression:ventilation ratio of 15:2 [28]. In a second protocol, 6 animals were bled 50 % of their blood volume. After 4 minutes of untreated VF, interventions were performed for 2 minutes with standard-CPR (Std-CPR) and 2 minutes with intrathoracic pressure regulator-CPR (ITPR-CPR). Vital organ perfusion pressures and end tidal carbon dioxide (ETCO₂) were significantly improved with ITPR-CPR in both protocols. Survival rates were 100 % (10/10) with ITPR-CPR versus 10 % (1/10) with Std-CPR. Oxygen saturation was 100 % throughout the study in both protocols. Compared to Std-CPR, use of ITPR-CPR improved hemodynamics, vital organ perfusion pressures, and carotid blood flow in both VF and hypovolemic cardiac arrest. Figure 2 demonstrates the significant hemodynamic differences seen when using the intrathoracic pressure regulation device during standard CPR in the animal model of cardiac arrest.
Intrathoracic Pressure Regulation Therapy and Survival Outcomes in Hemorrhagic Shock

To test the hypothesis that intrathoracic pressure regulation therapy using the CirQLator would demonstrate significantly increased mean arterial pressures and 24-hour survival rates when compared with no intervention in a fixed bleed model of controlled and severe hemorrhagic shock, a prospective trial randomizing two groups of pigs after a fixed bleed to receive: 1) no resuscitation, or 2) resuscitation with the intrathoracic pressure regulation device was conducted [29].

After an acute 55% blood loss and 5 minutes of stabilization, 18 pigs with an average weight of 28 ± 1.2 kg were prospectively randomized to either a CirQLator intervention group, with the device set to maintain intrathoracic pressures of -8 mmHg in between positive pressure ventilations, or a control group treated only with positive pressure ventilation (plus 3 cmH₂O positive end-expiratory pressure [PEEP]). After 90 minutes, surviving animals received intravenous fluid resuscitation and were followed for 24-hours to evaluate survival and neurological outcomes. There were no differences in the average blood loss in each group. After 55% blood loss, the application of a negative airway pressure of -8 mmHg resulted in a significant increase in mean arterial pressure for the entire 90 minutes of treatment as compared with the control group (Fig. 3). Mean arterial blood pressure returned to normal after blood re-infusion at 90 minutes. Arterial blood gases showed progres-
Fig. 3. Following controlled blood loss (55%), the intrathoracic pressure regulator (ITPR), set at -8 mmHg, resulted in a significant decrease in endotracheal pressure (ETP) and a significant increase in mean arterial blood pressure (MAP), compared to controls [29]. BL: pre-bleed baseline; *p < 0.05 between groups. The numbers in parentheses are the animals alive at the end of 90 minutes.

These results supported prolonged application of the intrathoracic pressure regulation device with intermittent positive pressure ventilation during hypovolemic hypotension as a route to increased blood pressure and improved survival rates compared with untreated controls. The data support the use of the intrathoracic pressure regulation-CirQLator to increase survival rates by enhancing perfusion pressures and preventing the development of severe metabolic acidosis in the setting of severe hypotension [29].
Intrathoracic Pressure Regulation Therapy and Sepsis

Treatment of sepsis is a critically time-sensitive emergency; patients stand the best chance for survival when effective therapeutic interventions are delivered as early as possible [31, 32]. Cellular injury and organ injury have been shown to occur rapidly, as a direct consequence of both the inflammatory response and hypoperfusion in sepsis [33, 34]. Rapid stabilization of the patient’s hemodynamic status, including volume expansion and administration of combined vasopressors/inotropes titrated to selected physiological endpoints of resuscitation, is critically important to limit further cell death and to optimize the chances for organ function restoration [35, 36]. To further improve survival, there is a need for novel therapeutic interventions which target the critical initial resuscitation phase in sepsis.

A series of pilot studies were performed in order to examine the effects of the CirQlator on cardiac output and stroke volume in porcine peritonitis and septic shock. The goal of these pilot studies was to determine whether pulsed intrathoracic pressure regulation device therapy could alter progressive hypotension in a well accepted, well characterized, reproducible animal model. Seven pigs were subjected to the previously published peritonitis protocol [37, 38] and treated with the CirQlator starting 30 minutes after \textit{E. coli} clot implantation (\(5 \times 10^9\) cfu/kg \textit{E. coli O111:B4}). In untreated animals, this produces cardiovascular collapse within 6 hours in > 60% of all animals [37, 38]. Each animal was then followed for six hours and the intrathoracic pressure regulation device therapy was cycled 30 min on and then 30 min off [39]. Two control animals were not treated with the intrathoracic pressure regulation device to confirm the basic time course of the hemodynamic changes of this model. These control pigs responded in a similar fashion to the numerous other control pigs that have been previously recorded using the same pig model.

Application of the intrathoracic pressure regulation device (28 times in 7 animals) in the absence of fluid resuscitation consistently caused a marked increase in cardiac index, stroke volume and mean arterial pressure, consistent with the mechanism of action of the intrathoracic pressure regulation device to increase venous return and cardiac preload (Cinel et al., unpublished data). These changes occurred in the absence of fluid resuscitation, within 2–5 minutes. Importantly, in these pigs, normal saline infusion was restricted to 1 ml/kg/hour to replace insensible losses. There was no statistical change in heart rate and oxygen saturation stayed above 90% during the entire treatment course. Pulmonary artery pressures decreased. The data from this preclinical study are supportive that intrathoracic pressure regulation device therapy will provide a significant hemodynamic benefit in the early treatment phase of sepsis.

Some might argue that current fluid resuscitation measures are acceptable during the early resuscitative phase of septic shock and that an alternate therapy is not needed. However, we hypothesize that intrathoracic pressure regulation therapy provides a number of advantages, especially when considered as a complementary therapy to the current standards of care. These include: 1) the intrathoracic pressure regulation device can be used when fluids are not available or in complement with a reduced amount of fluids and the device can be simply added in line to an endotracheal tube as long as the patient is intubated; 2) the current pig data suggest that the circulation can be increased faster with intrathoracic pressure regulation therapy then with traditional fluid therapy alone and certainly when central venous access is not available; 3) the intrathoracic pressure regulation device may also buy time to insert a central line in a more controlled and less hurried manner; 4) in contrast to
fluids, intrathoracic pressure regulation therapy appears to reduce pulmonary artery capillary pressures, at least when administered in pulse doses of 30 minutes each; 5) intrathoracic pressure regulation therapy may reduce or avoid the need for vasoressor therapy which might have detrimental effects on renal function and cardiac function (ischemia) and rhythms (atrial and ventricular dysrhythmias); 6) finally, even if the intrathoracic pressure regulation device is used in conjunction with fluids or vasoressors, we speculate that less fluid resuscitation therapy would be required for the same hemodynamic benefit and less vasoressor therapy may be required. In many ways, intrathoracic pressure regulation therapy functions like a mechanical drug, except that it provides its therapeutic benefit non-invasively.

**Potential Adverse Consequences and Limitations of Intrathoracic Pressure Regulation Therapy**

While studies to date have shown that application of intrathoracic pressure regulation in cardiac arrest and hypovolemic shock results in a marked improvement in hemodynamics and survival rates, the longer-term potential consequences of intrathoracic pressure regulation therapy remain unknown. One can speculate that with more negative intrathoracic pressures there may be greater flow/perfusion mismatch within the lungs, the potential for shunting, and the potential for pulmonary atelectasis. Another potential limitation is that in order for this technology to be of clinical benefit, the thorax must be intact and the patient needs to be intubated. Otherwise it is not possible to consistently generate expiratory phase negative intrathoracic pressures. While this limitation can be overcome by paralyzing and intubating a patient, some patients may at present not warrant endotracheal intubation but develop significant hypotension. As such, a minor paradigm shift may be necessary once the diagnosis of sepsis has been confirmed by currently recommended clinical criteria.

Another potential limitation is that it is not possible to lower the expiratory phase intrathoracic pressures and concurrently use PEEP, unless the intrathoracic pressure regulation device is used as a pulsed therapy, which is under evaluation. Thus, the benefit of circulatory enhancement with the intrathoracic pressure regulation therapy must be balanced clinically with the need to provide PEEP. Animal studies to date suggest that intrathoracic pressure regulation therapy can provide both circulatory and ventilatory support for up to 6 hours.

**Conclusion**

The significance of this innovative approach rests in its simplicity, the anticipated significant enhancement in blood pressure and circulation, and the ability to harness the body’s natural response mechanism to hypotensive stress to improve circulation and blood pressure. Analogous to optimizing the heart rate on an implantable pacemaker based upon the patient’s underlying medical condition, different patients will respond differently to different levels of negative intrathoracic pressure based upon their overall condition, the amount of central volume, their starting venous pressure, and other co-existing medical conditions. To date, preclinical and clinical data using intrathoracic pressure regulation therapy to treat cardiac arrest and hypotension in spontaneously-breathing patients confirm that this innovative
approach provides an important new therapeutic option for the hypotensive patient population where increased cardiac preload would be beneficial.

References