Intrathoracic Pressure Regulator During Continuous-Chest-Compression Advanced Cardiac Resuscitation Improves Vital Organ Perfusion Pressures in a Porcine Model of Cardiac Arrest

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Background—A novel device, the intrathoracic pressure regulator (ITPR), combines an inspiratory impedance threshold device (ITD) with a vacuum source for the generation of controlled −10 mm Hg vacuum in the trachea during cardiopulmonary resuscitation (CPR) while allowing positive pressure ventilation. Compared with standard (STD) CPR, ITPR-CPR will enhance venous return, systemic arterial pressure, and vital organ perfusion in both porcine models of ventricular fibrillation and hypovolemic cardiac arrest.

Methods and Results—In protocol 1, 20 pigs (weight, 30 ± 0.5 kg) were randomized to STD-CPR or ITPR-CPR. After 8 minutes of untreated ventricular fibrillation, CPR was performed for 6 minutes at 100 compressions per minute and positive pressure ventilation (100% O2) with a compression-to-ventilation ratio of 15:2. In protocol 2, 6 animals were bled 50% of their blood volume. After 4 minutes of untreated ventricular fibrillation, interventions were performed for 2 minutes with STD-CPR and 2 minutes of ITPR-CPR. This sequence was repeated. In protocol 3, 6 animals after 8 minutes of untreated VF were treated with ITPR-CPR for 15 minutes, and arterial and venous blood gases were collected at baseline and minutes 5, 10, and 15 of CPR. A newer, leak-proof ITPR device was used. Aortic, right atrial, endotracheal pressure, intracranial pressure, and end-tidal CO2 values were measured (mm Hg); common carotid arterial flow also was measured (mL/min). Coronary perfusion pressure (diastolic; aortic minus right atrial pressure) and cerebral perfusion pressure (mean arterial minus mean intracranial pressure) were calculated. Unpaired Student t test and Friedman’s repeated-measures ANOVA of ranks were used in protocols 1 and 3. A 2-tailed Wilcoxon signed-rank test was used for analysis in protocol 2. Fischer’s exact test was used for survival. Significance was set at $P<0.05$. Vital organ perfusion pressures and end-tidal CO2 were significantly improved with ITPR-CPR in both protocols. In protocol 1, 1-hour survival was 100% with ITPR-CPR and 10% with STD-CPR ($P<0.001$). Arterial blood pH was significantly lower and PaCO2 was significantly higher with ITPR-CPR in protocol 1. Arterial oxygen saturation was 100% throughout the study in both protocols. PaCO2 and PaO2 remained stable, but metabolic acidosis progressed, as expected, throughout the 15 minutes of CPR in protocol 3.

Conclusions—Compared with STD-CPR, use of ITPR-CPR improved hemodynamics and short-term survival rates after cardiac arrest. (Circulation. 2005;112:803-811.)

Key Words: cardiopulmonary resuscitation ■ cerebrovascular circulation ■ circulation ■ perfusion ■ resuscitation

The critical importance of controlling intrathoracic pressure during cardiopulmonary resuscitation (CPR) has recently been demonstrated in a number of studies.1–6 New data have demonstrated improvement in vital organ perfusion pressure, blood flow to vital organs, neurological outcomes, and survival in animals and patients with cardiac arrest when performed with devices (ie, inspiratory impedance threshold device [ITD]) that create a greater negative intrathoracic pressure during the decompression phase of CPR compared with conventional CPR.1–6 It has also been recently demonstrated that excessive positive intrathoracic pressure in the form of overzealous ventilation’ or incomplete chest wall...
decompression has a detrimental if not deadly effect during treatment of hypotension and cardiac arrest. Some of these CPR studies have shown that a linear relationship exists between the degree of negative intrathoracic pressure generated during the decompression phase and either coronary perfusion pressure or mean arterial pressure. The generation of negative intrathoracic pressure during conventional manual CPR depends on the intrinsic elastic recoil of the chest wall and the performance of CPR itself. A stiff, noncompliant chest or fractured ribs decrease chest wall elastic properties and recoil. Moreover, it was recently shown that rescuers often fail to allow the chest to fully recoil after each chest compression, which has significant detrimental physiological effects. On the basis of these observations, the benefits of using an ITD during CPR are largely dependent on the elastic properties of the chest; the rescuer’s ability to perform CPR properly, including allowing the chest to fully recoil after each compression; or proper performance of active compression-decompression CPR. To overcome these limitations of current CPR and to use the beneficial effects of negative intrathoracic pressure during CPR, we developed a new device for use by trained rescuers for in- and out-of-hospital cardiac arrest. The new device combines an ITD with a vacuum source and a mechanical valve to maintain an intrathoracic vacuum between −5 and −10 mm Hg but allow intermittent positive pressure ventilation. This novel device, called an intrathoracic pressure regulator (ITPR), is one of several ways to enable the rescuer to mechanically create controlled negative pressure in the airway and subsequently in the intrathoracic space, providing a means to enhance venous blood return to the heart and to improve circulation. At the same time, the ITPR provides a means for intermittent positive pressure ventilation to ensure adequate ventilation and gas exchange.

We hypothesize that using the ITPR during CPR will sustain negative airway pressure between positive pressure ventilations, decrease intrathoracic and right atrial pressure, and increase venous return, systemic arterial pressure, and coronary and cerebral perfusion pressures during ventricular fibrillation (VF) in both normovolemic and hypovolemic cardiac arrest treated with CPR with no detrimental effects on gas exchange and oxygenation. We further hypothesize that the improvement in hemodynamics will translate to higher rates of successful resuscitation and 1-hour survival in a porcine model of nonhypovolemic cardiac arrest. This hypothesis was tested in 2 models of cardiac arrest. The first was a well-established model in pigs in VF. The second was a hypovolemic cardiac arrest model. Clinical outcomes after both causes of cardiac arrest are traditionally poor if immediate treatment is not available.

Methods

The study was approved by the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation at Hennepin County Medical Center. All animals received treatment and care in compliance with the 1996 Guide for the Care and Use of Laboratory Animals by the National Research Council in accordance with the US Department of Agriculture Animal Welfare Act, PHS Policy, and the American Association for Accreditation of Laboratory Animal Care. Anesthesia was used in all surgical interventions to avoid all unnecessary suffering. Experiments were performed by a qualified, experienced team. The study was performed on female farm pigs (weight, 30±0.5 kg).

Three protocols were used in these studies. In protocol 1, 20 female farm pigs, after 8 minutes of untreated cardiac arrest, were randomly assigned to receive either standard (STD) CPR alone or ITPR-CPR for 6 minutes and, if successfully defibrillated, then were observed for 1 hour. In protocol 2, 6 animals were bled an ∼50% of the total blood volume, and VF was then induced. Subsequently, CPR was performed for 4 2-minute intervals in the following order: STD, ITPR, STD, and ITPR. Only hemodynamic parameters were recorded; defibrillation shocks were not used. Finally, in protocol 3, a leak-proof ITPR device was used in this experiment to evaluate the effect of prolonged ITPR-CPR on blood gases and acidosis. Six animals after 8 minutes of untreated cardiac arrest were treated with ITPR-CPR for 15 minutes. Arterial and venous blood gases were sampled at baseline (before induction of VF) and at minutes 5, 10, and 15 of CPR.

Preparatory Phase

All animals received initial sedation with 7 mL (100 mg/mL) of intramuscular ketamine HCl (Ketaject, Fort Dodge Animal Health). While spontaneously breathing but sedated, the pigs were intubated with a 7.0-mm endotracheal tube, and the balloon was appropriately inflated to prevent leakage. Propofol (1 mg/kg) was then administered as a bolus, followed by a propofol infusion of 160 μg · kg⁻¹ · min⁻¹.

During the preparatory phase, animals were ventilated with room air using a volume-control ventilator (Harvard Apparatus Co) with a tidal volume of 12 mL/kg. The rate was adjusted to maintain an arterial CO₂ at 40 mm Hg and PaO₂ of >80 mm Hg (oxygen saturation >95%) based on analysis of arterial blood gases (IL Synthesis, Instrumentation Laboratory).

While the pigs were sedated and mechanically ventilated, a hole was drilled through the skull under aseptic conditions for intracranial pressure recordings. A burr hole was made at the middle of the distance between the left eyebrow and the posterior bony prominence after identification of the posterior bony prominence of the pig’s cranium. A 3.5F continuously recording micromanometer pressure transducer (Micro-Tip Transducer, Millar Instruments, Inc) was inserted 2 cm into the parietal lobe of the animal and secured in place. The pressure transducer was connected to a signal amplifier (model 13-6615-50, Gould Instrument Systems, Inc) and then to a digital recording system (SuperScope II), providing real-time intracranial pressure tracings as previously described. A second hole was drilled in the same way on the right side for a second intracranial pressure transducer (Camino, Intra Life Sciences) used to calibrate the micromanometer pressure transducer.

Subsequently, animals were turned supine, and right external jugular vein and left and right femoral artery cannulations were performed surgically under aseptic conditions. Two micromanometer-tipped catheters (Micro-Tip Transducer, Millar Instruments, Inc) were used for central aortic and right atrial pressure recording from the right femoral and right external jugular, respectively. Left femoral cannulation was used for controlled arterial bleeding for the second protocol. The left common carotid artery was surgically exposed, and a Doppler flow probe (Transonic, 400 series multichannel, Transonic Systems Inc) was placed around it to quantify blood flow.

A surface ECG was recorded continuously. As a surrogate for intrathoracic pressures, endotracheal pressure (ETP) was measured continuously using a micromanometer-tipped catheter positioned 2 cm above the carina inside the distal tip of the endotracheal tube. All data were digitized by a digital recording system (Superscope II v1.295, GW Instruments) and a Power Macintosh G3 computer (Apple Computer, Inc). End-tidal CO₂ (ETCO₂) and tidal volume were measured with a CO₂SMO Plus (Novametrix Medical Systems). Preparation time did not exceed 30 minutes in any of the animals; the average time was 22±3 minutes.

Baseline mean arterial pressure was calculated as (SBP + 2DBP)/3, where SBP and DBP are systolic and diastolic blood pressure, respectively. During CPR, mean arterial pressure was calculated as systolic aortic pressure plus diastolic aortic pressure divided by 2.
because of the 50% duty cycle of CPR. Coronary perfusion pressure was calculated as mean diastolic (decompression) aortic pressure minus mean diastolic (decompression) right atrial pressure. Cerebral perfusion pressure was calculated as mean arterial pressure minus mean intracranial pressure.

ITPR is a novel device (Advanced Circulatory Systems, Inc) that is connected in series with the endotracheal tube. It has 3 ports: 1 connected to the endotracheal tube, 1 connected to a vacuum source, and 1 connected to the ITD with an inspiratory resistance of -10 mm Hg. The ITD can be connected to either a mechanical ventilator or a manual resuscitator bag (eg, AMBU) for manual ventilation (Figure 1). The device has a flow-dependent regulator interconnected with a switch mechanism that allows isolation of the vacuum port during the positive pressure ventilation delivery and isolation of the positive pressure ventilation source during application of the regulated vacuum. Between ventilations, the amount of vacuum generated in the airways is unrelated to the pressure generated by the vacuum source itself because it is regulated by the cracking pressure of the ITD (-10 mm Hg). The ITPR has a dead space of 40 mL.

**Experimental Protocols**

**Protocol 1**

Twenty pigs were randomized prospectively by a computer-generated list to either the control arm (n=10) or the ITPR arm (n=10). VF was induced by intracardiac direct electrical current via a temporary pacing wire (Daig Division, St Jude Medical). At that point, ventilation was discontinued, and ventilator was disconnected from the endotracheal tube. Propofol infusion was decreased to 100 μg·kg⁻¹·min⁻¹. After 8 minutes of untreated cardiac arrest, CPR was initiated with a compression-to-ventilation ratio of 15:2. Ventilations were delivered with a semiautomatic ventilator (Demand Valve model L063–05R, Life Support Products Inc). This pressure-controlled, manually triggered ventilator has a peak airway pressure cutoff set at 40 mm Hg and maximum delivered flow of 100% O₂ at 60 L/min. Breaths were delivered synchronously during the decompression phase over 1 second for 2 consecutive compression-decompression cycles during CPR. Continuous compressions were performed with a pneumatically driven automatic piston device (Pneumatic Compression Controller, AMBU International) as previously described.¹ The compression rate was 100 per minute uninterrupted, with a 50% duty cycle and a depth of 25% of the anterior-posterior diameter of the chest. The chest wall was allowed to recoil passively but completely with this device because the compression piston is actively pulled upward 0.2 cm off the chest after each compression. Aortic pressure, right atrial pressure, intracranial pressure, common carotid blood flow, ETP, ETCO₂, and O₂ saturation were measured continuously and sampled at each minute of CPR. In each animal, 3 measurements were made for each parameter at the end of each minute and then averaged to give the value of that minute. Arterial blood gases were obtained at baseline before cardiac arrest and at minute 5 of CPR. CPR continued for 6 minutes. At the end of 6 minutes of CPR, animals were defibrillated 3 times with a biphasic defibrillator (Zoll M series) starting at 120 J. If VF persisted, epinephrine was administered at a dose of 45 μg/kg IV, and then 3 more shocks (120 to 150 J) were delivered. If VF persisted, all resuscitation efforts were terminated. When resuscitation was successful, animals were again ventilated with a positive-pressure, volume-controlled Harvard ventilator at a rate of 12 breaths per minute with a tidal volume of 12 cm³/kg and were observed for 1 hour. No further interventions were performed after restoration of spontaneous circulation. At the end of the protocol, the animals were euthanized with a bolus of propofol 60 mg IV and then 5 mL IV of 10 mol/L KCl.

Lung autopsy was performed in 6 of the animals from the ITPR-CPR group. Both lungs were macroscopically observed for gross atelectasis and pulmonary hemorrhage and edema. Horizontal 2-cm slices were excised from both lungs, and any abnormalities were recorded. Atelectasis, intra-alveolar hemorrhage, and pulmonary edema were specifically recorded if observed. Microscopic evaluation was not performed.

Statistical analysis was performed with an unpaired *t* test and Friedman’s repeated-measures ANOVA of ranks. Coronary and cerebral perfusion pressures were prospectively selected to be the primary end points. Statistical significance was set at a value of *P*<0.05. For the sample size of 10 animals per group, the power of the study to detect a 15% improvement in coronary and cerebral perfusion pressures was >0.8. Survival was evaluated with 2-way Fischer’s exact test.

**Protocol 2**

Six animals were bled to an estimated 50% of their volume (32.5 mL/kg) at 60 mL/min through the left femoral artery catheter.¹³ Subsequently, VF was induced as described above. After 4 minutes of untreated cardiac arrest, pigs were treated with four 2-minute CPR interventions in the following order: STD-CPR, ITPR-CPR, STD-CPR, and ITPR-CPR without interruption. Compressions and venti-
TABLE 1. Baseline Characteristics of the 2 Groups Before Induction of VF in Protocol 1

<table>
<thead>
<tr>
<th></th>
<th>STD</th>
<th>ITPR</th>
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<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>126±7</td>
<td>126±8</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>16.3±0.5</td>
<td>16.5±16.3</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>91.4±4.6</td>
<td>96±7.8</td>
</tr>
<tr>
<td>CerPP, mm Hg</td>
<td>94±5.3</td>
<td>96.6±8.4</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>82±5</td>
<td>79±6.3</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>3.1±0.4</td>
<td>3±0.4</td>
</tr>
<tr>
<td>CCBF</td>
<td>202.5±51</td>
<td>213±47</td>
</tr>
<tr>
<td>pH</td>
<td>7.4±0.03</td>
<td>7.39±0.02</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>43.2±0.9</td>
<td>43.3±1.5</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>86±3.3</td>
<td>87.8±6.5</td>
</tr>
<tr>
<td>ETCO2</td>
<td>39±2.7</td>
<td>38±3</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; ICP, intracranial pressure; CPP, coronary perfusion pressure; CerPP, cerebral perfusion pressure; HR, heart rate; RAP, right atrial pressure; and CCBF, common carotid blood flow.

Results

Protocol 1: VF in Euvolemic Pigs

Baseline characteristics were similar between the 2 groups in both hemodynamic parameters and arterial blood gases (Table 1).

Mean±SEM ETP between positive pressure breaths was significantly lower with ITPR-CPR compared with STD-CPR throughout the 6 minutes of CPR: −8.1±0.6 versus −0.4±0.5 mm Hg, respectively (P<0.001). Average diastolic right atrial pressure during the 6 minutes of CPR was significantly lower in the ITPR-CPR (2.1±1.5 mm Hg) than in the STD-CPR (5.1±0.8 mm Hg) group (P<0.001). A representative tracing showing ETP with and without ITPR is shown in Figure 2.

Systemic, diastolic aortic, and mean arterial pressures were statistically and significantly higher throughout the 6 minutes of CPR with ITPR by 25% to 30% (P<0.001; Figure 3). Coronary and cerebral perfusion pressures were also statistically significantly increased by an average of 60% to 70% (P<0.001; Figure 3). Common carotid artery blood flow was also increased by an average of 70% during the 6 minutes (P<0.001; Figure 3). There was no difference between groups in mean±SEM intracranial pressure, with values in the STD-CPR group averaging 20.3±1 mm Hg and in the ITPR group averaging 21.7±1.7 mm Hg over 6 minutes (P=0.16). However, during the decompression phase, the intracranial pressure values were lower (13±1 mm Hg) in the ITPR group compared with controls (15.5±0.7 mm Hg; P<0.05).

Figure 2. Protocol 1: 2 real-time tracings (2 different animals) of ETP (mm Hg) during STD-CPR (a) and ITPR-CPR (b). Notice that ETP during ITPR-CPR is maintained constantly <0 mm Hg and is interrupted only during delivery of positive pressure ventilation (PPV). Each square is 500 ms.
Arterial blood gases showed no differences at baseline, but pseudorespiratory alkalosis was observed in the STD-CPR group at minute 5 of CPR. In contrast, a combined metabolic acidosis with mild respiratory acidosis was noted in the ITPR-CPR group. ETCO2 was significantly higher in the ITPR-CPR group. Tidal volumes delivered to the pigs were reduced with ITPR-CPR compared with controls (Table 2).

Finally, all animals (10 of 10) in the ITPR-CPR group survived for 1 hour compared with 10% (1 of 10) in the STD-CPR group. There was an inverse relation between mean ETP and survival (Figure 4). No animal in the ITPR group required epinephrine for return of spontaneous circulation. ITPR-treated pigs required 2.4 shocks for successful defibrillation. In contrast, 9 of 10 animals in the STD-CPR group received 2 sequences of 3 shocks and epinephrine without success. Only 1 animal returned to spontaneous circulation with 1 shock and survived for 1 hour.

Lung autopsies of the 6 animals in the ITPR-CPR group did not show any evidence of macroscopic atelectasis, pulmonary hemorrhage, or pulmonary edema. None of the 20 animals had any clinical evidence of the above-mentioned pathology.

### Protocol 2: VF in Hypovolemic Pigs

Mean ± SEM ETP was decreased with ITPR-CPR each time to 9±2 mm Hg, and it was significantly lower than the STD-CPR value of 0.4±1 mm Hg (P<0.001). In this protocol, generation of negative ETP with the ITPR was immediate and reproducible.

Similar to ETP, right atrial pressure was significantly decreased with the ITPR (Table 3). During hypovolemic cardiac arrest, systemic blood pressures achieved with chest compressions were significantly lower than normovolemic animals, seen by comparing the values in Table 3 with Figure 3. Systolic, diastolic, and mean aortic pressures, cerebral and coronary perfusion pressures, and ETCO2 increased each time that ITPR-CPR was performed (Table 3). Mean intracranial pressure decreased from 14.4±1.2 to 12.8±1.6 mm Hg (P=0.02), further contributing to the increase observed at the cerebral perfusion pressure.

### Protocol 3: Prolonged ITPR-CPR/Blood Gases

In protocol 3, use of a leak-proof ITPR allowed delivery of larger tidal volumes that were no different than in the control group (Table 4). There were no statistically significant differences in Paco2, and Pao2 during 15 minutes of ITPR-CPR. There was a mild progressive metabolic acidosis as can be seen from the mild decrease in pH, bicarbonate, and base excess at minutes 10 and 15 (Table 4). Coronary perfusion pressure was maintained >25 mm Hg for 15 minutes, and ETCO2 was also maintained >20 mm Hg (Table 4). Venous blood gases are also shown in that table. Three of 6 animals returned to spontaneous circulation.

Lung autopsies did not reveal gross atelectasis, pulmonary edema, or pulmonary hemorrhage. One of the 6 animals had 2 broken ribs that caused a left posterior middle lobe contusion.

### Table 2. Protocol 1: Arterial Blood Gases at Minute 5 of CPR

<table>
<thead>
<tr>
<th></th>
<th>STD-CPR</th>
<th>ITPR-CPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.36±0.03*</td>
<td>7.17±0.01*</td>
</tr>
<tr>
<td>Paco2, mm Hg</td>
<td>27.8±2.6*</td>
<td>54±4*</td>
</tr>
<tr>
<td>Pao2, mm Hg</td>
<td>221±42*</td>
<td>158±33*</td>
</tr>
<tr>
<td>Base deficit</td>
<td>9.7±0.7</td>
<td>10±1</td>
</tr>
<tr>
<td>ETCO2, mm Hg</td>
<td>18.2±1.9*</td>
<td>23±1.1*</td>
</tr>
<tr>
<td>Tidal volume, mL</td>
<td>434.7±31*</td>
<td>336±22*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM of arterial blood gases with STD and ITPR-CPR.

*P<0.05.
**TABLE 3. Protocol 2: Hypovolemic CPR**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>STD-CPR, mm Hg</th>
<th>ITPR-CPR, mm Hg</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETP</td>
<td>0.4±0.1</td>
<td>-9±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SArP</td>
<td>33.8±7.6</td>
<td>40±9</td>
<td>0.008</td>
</tr>
<tr>
<td>DArP</td>
<td>8.8±2.3</td>
<td>11.7±2.2</td>
<td>0.05</td>
</tr>
<tr>
<td>MAP</td>
<td>21.3±4</td>
<td>26±5</td>
<td>0.005</td>
</tr>
<tr>
<td>DRAP</td>
<td>-2.7±1.4</td>
<td>-8.2±2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPP</td>
<td>11.5±2.5</td>
<td>20±2.7</td>
<td>0.01</td>
</tr>
<tr>
<td>MICP</td>
<td>14.4±1.2</td>
<td>12.8±1.6</td>
<td>0.02</td>
</tr>
<tr>
<td>CerPP</td>
<td>6.9±3.7</td>
<td>13±3.5</td>
<td>0.002</td>
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<tr>
<td>ETCO2</td>
<td>13.3±0.5</td>
<td>16.3±0.6</td>
<td>0.03</td>
</tr>
</tbody>
</table>

SArP, DArP, and MAP indicate systolic, diastolic, and mean aortic arterial pressures; DRAP, diastolic right atrial pressure; CPP, coronary perfusion pressure; CerPP, cerebral perfusion pressure; and MICP, mean intracranial pressure. Mean±SEM values and probability values (Wilcoxon rank-sum test) of all key hemodynamic parameters with STD and ITPR-CPR in hypovolemic pigs.

Discussion

ITPR is a new device that allows positive pressure ventilation to be delivered as needed during CPR but is otherwise designed to maintain negative intrathoracic pressure. The device transforms the thoracic cavity into an active bellow, causing increases in venous return to the heart and simultaneously adequate gas exchange.

The results of this study demonstrated that using ITPR during CPR provided a new way to generate negative intrathoracic pressures during the decompression phase of CPR, thereby improving hemodynamics, blood flow, vital organ perfusion pressures, and short-term survival rates during CPR. The ITPR generated and sustained the negative ETP, a surrogate of intrathoracic pressure, independently of the intrinsic elastic properties of the chest wall or the quality of CPR performed. Moreover, negative ETP was maintained continuously relative to the rest of the body (except during the delivery of ventilations), thereby providing a vacuum to draw blood back to the heart. The ITPR was also beneficial during CPR for the treatment of hypovolemic cardiac arrest. In this setting, circulation during CPR depends even more critically on venous return to the heart after each chest compression. These results are similar to those obtained with active compression-decompression CPR and an ITD. However, the new device is able to maintain and control negative airway pressure without complete or active chest wall decompression.

During ITPR-CPR, coronary perfusion pressure was significantly increased in both normovolemic and hypovolemic conditions. In the hypovolemic cardiac arrest model, coronary perfusion pressure was maintained >15 mm Hg with ITPR-CPR, which has been shown to be a threshold for successful resuscitation in humans. In the VF cardiac arrest model, coronary perfusion pressure during ITPR-CPR was consistently >25 mm Hg, and 100% 1-hour survival was achieved. On the contrary, after minute 3 of CPR, animals in the STD-CPR group had a coronary perfusion pressure <15 mm Hg, and survival was decreased to 10%.

Arterial blood gases showed pseudorespiratory alkalosis with normal pH values in the STD-CPR group, reflecting decreased blood flow to the pulmonary circulation with a relatively long transit time of the red blood cells through the lungs, thus creating a mismatch between ventilation and perfusion during CPR. The arterial blood gases in this case do not represent the severity of tissue acidosis. In contrast, lower pH values were observed with ITPR-CPR. This likely reflects the true acidic state of the tissues (metabolic acidosis) secondary to 8 minutes of no flow and 5 minutes of CPR. The finding of higher PaCO2 can be explained by the combination of higher pulmonary venous blood flow, better pulmonary perfusion and ventilation matching, and hyperventilation from the delivery of smaller tidal volumes with an ITPR.

We speculate that the higher PaCO2 during low blood flow states may actually be beneficial to the brain blood flow. High PaCO2 is associated with cerebral arteriolar vasodilation. Higher arterial CO2 may also improve tissue oxygen delivery by shifting the O2 oxyhemoglobin dissociation curve to the right and by decreasing systemic and cerebral metabolic demands, resulting in a better coupling between oxygen delivery and demand. Thus, the higher PaCO2 may have contributed to the survival benefit observed in this study in the ITPR group. Taken together, the higher PaCO2, higher cerebral perfusion pressure, and higher common carotid blood flow in the ITPR-CPR group support but do not prove...
that there is an increase in brain blood flow compared with the STD-CPR group.26

Oxygenation was adequate in both STD and ITPR-CPR; 100% saturation was maintained throughout the entire study. The lower tidal volumes delivered in the first 2 protocols were due to a small leak in the prototype ITPR. The vacuum port was not completely sealed during the delivery of ventilation, resulting in loss of tidal volume, as shown in Table 2.

In protocol 2, we investigated the effects of ITPR-CPR during severe hypovolemic cardiac arrest, a common clinical problem.27 Results showed that ITPR-CPR is beneficial in this setting also, when circulatory volume depends heavily on venous return. The most important finding from this protocol was that the ITPR significantly increased coronary and cerebral perfusion pressures by 30% increase (5 mm Hg) in coronary perfusion pressure because of the concomitant increase in PaCO2 that is at least partly responsible for that elevation. In protocol 3, however, larger tidal volumes were delivered, and PaCO2 was kept <40 mm Hg throughout the whole study. Despite lower PaCO2 than in protocol 1, ETCO2 was still significantly higher than in STD-CPR and was maintained >20 mm Hg during the 15 minutes of ITPR-CPR. The arterial blood gases of protocol 3, the higher blood flow observed at the common carotid artery, and the 100% survival in the ITPR-CPR group (protocol 1) support once again but do not prove the speculation that higher pulmonary and systemic blood flows were achieved with ITPR-CPR compared with STD-CPR.

One advantage of using the ITPR during CPR is that it helps to create a significant intrathoracic vacuum between compressions, even if the quality of CPR is poor. More specifically, we recently demonstrated that rescuers often fail to allow the chest to fully recoil after compressing the chest.9 This results in lower coronary and cerebral perfusion pressures because incomplete chest wall recoil results in less of an intrathoracic vacuum after each chest compression.8 We speculate that use of the ITPR will cause an immediate decrease in intrathoracic pressure after each chest compression, regardless of whether the chest wall fully recoils. Thus, chest wall recoil may not be critical to providing adequate vital organ perfusion when the ITPR is used.

In protocol 3, we were able to show that the difference in PacO2 in the first protocol was mainly secondary to the prototype leak and the delivery of smaller tidal volumes, which resulted in a relative hypoventilation and further decreased pH to a significant level. Use of a leak-proof ITPR device during prolonged (15 minutes) CPR allowed

| TABLE 4. Protocol 3: Leak-Proof ITPR (Prolonged ITPR-CPR for 15 Minutes) |
|-----------------------------|-----------------------------|
| Baseline                  | Minutes of CPR              |
| (Before VF)               | 5              | 10             | 15             |
| Mean ETP, mm Hg           | 0.3±0.1         | -9±0.6‡        |                  |
| Tidal volume, mL          | 402±17          | 456±36.2‡      |                  |
| Mean CPP, mm Hg           | 95±5.1          | 26.4±1.7‡      |                  |
| Mean ETCO2, mm Hg         | 37±1.2          | 20.7±0.5‡      |                  |
| Arterial                  |                |                |                  |
| pH                        | 7.4±0.02        | 7.37±0.02†     | 7.25±0.03*       | 7.23±0.04†       |
| PacO2, mm Hg              | 42.2±1.4        | 34.4±1.5       | 34±3.26         | 33.67±2.23       |
| Pao2, mm Hg               | 96±2            | 209±13.6       | 214±12.37       | 198±6.75         |
| HCO3                      | 24.8±0.7        | 18.66±0.4†     | 15.02±1.13      | 14±0.68†         |
| Base deficit              | -0.93±0.8       | 6.62±0.54*     | 12.22±1.1*      | 13.57±1.15       |
| %Sao2                     | 98±1.6          | 100            | 100             |                  |
| Venous                    |                |                |                  |                  |
| pH                        | 7.34±0.01       | 7.20±0.01†     | 7.13±0.02*      | 7.1±0.03†        |
| Pco2, mm Hg               | 48.33±3.56      | 66.40±1.57     | 67.33±2.56      | 68±4.4           |
| Pvo2, mm Hg               | 40±3.86         | 23±1.81*       | 29.17±2.8*      | 29.5±2.38†       |
| vHCO3                     | 27.63±1.1       | 26.24±0.64†    | 22.37±0.56*     | 20.7±0.7†        |
| Base deficit              | -2.8±1.1        | 1.76±0.82†     | 6.77±0.68*      | 9.1±1†           |
| %Svo2                     | 72±4.2          | 27±3.7*        | 35.33±5*        | 33.67±5          |

CPP indicates coronary perfusion pressure. Values are mean±SEM. Shown are the effects of prolonged (15 minutes) ITPR-CPR after 8 minutes of untreated ventricular fibrillation with a newer-version (leak-proof) ITPR device.

*†Statistically significant differences with P<0.05 between cells with the same symbol in the same row.

‡Mean values over 15 minutes.
delivery of larger tidal volumes and showed that $\text{Paco}_2$ and $\text{PaO}_2$ are not negatively affected by the use of this new technology. The finding of progressive metabolic acidosis was expected secondary to the tissue hypoperfusion and lactic acidosis (Table 4). The higher ETCO$_2$ and coronary perfusion pressure were maintained for the whole study, and 3 of 6 animals returned to spontaneous circulation after such a prolonged period of low flow, findings that further support our conclusions.

This study has some limitations. First, we did not directly measure blood flow to the vital organs. However, the increased vital organ perfusion pressures, concurrent increase in the common carotid artery blood flow and ETCO$_2$ levels, and increased survival in the ITPR-CPR group support the hypothesis that greater circulating blood flow was achieved with the new device. Second, we did not examine different levels of negative intrathoracic pressure; the optimum level and duration of the intrathoracic vacuum remain under study. Third, we used propofol, which can cause vasodilation and could have been a confounding factor for interpretation of the results. Fourth, we used a healthy pig model without underlying coronary artery disease or congestive heart failure, which may not mimic the pathophysiology in humans with left ventricular dysfunction. Finally, the prospectively selected outcomes for this ITPR intervention during cardiac arrest were CPR hemodynamics and short-term survival. Longer-term neurologically intact survival studies are needed to assess of the clinical potential of ITPR resuscitation. Postmortem lung autopsies did not reveal macroscopic atelectasis, alveolar hemorrhage, or edema, but microscopic evaluation is needed to definitely address this issue because microatelectasis cannot be excluded with our method.

Conclusions

Use of the ITPR during CPR in pigs improved all hemodynamic parameters, vital organ perfusion pressures, blood flow, and short-term survival without compromising oxygenation and blood gases. Furthermore, ITPR-CPR increased vital organ (coronary and cerebral) perfusion pressures during hypovolemic cardiac arrest. From this first series of studies, the ITPR warrants additional evaluation for treatment of cardiac arrest and other low-flow states.

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Disclosure

Keith G. Lurie is the inventor of the inspiratory impedance threshold device and the intrathoracic pressure regulator used in this study and has founded a company, Advanced Circulatory Systems Inc (ACSI), to develop this technology. David Benditt is a member of the Board of Directors of ACSI. Anja Metzger and Kurt Kruger are employed by ACSI.

References

CLINICAL PERSPECTIVE

The high mortality rate associated with cardiac arrest is due in part to the low blood flow associated with conventional manual cardiopulmonary resuscitation (CPR). To enhance venous return and thus increase vital organ perfusion during CPR, an intrathoracic pressure regulator (ITPR) was developed to generate a constant vacuum of $-10\text{ mm Hg}$ in the thorax during CPR while allowing periodic positive pressure ventilation. This novel lightweight device can be attached to an endotracheal tube or a face mask. It was evaluated in euvolemic and hypovolemic pigs in cardiac arrest. Use of the ITPR resulted in a significant increase in vital organ perfusion pressures in euvolemic and hypovolemic pigs in ventricular fibrillation. Moreover, after 8 minutes of cardiac arrest and 6 minutes of CPR, 1-hour survival rates in the euvolemic pigs were 10% in the control group and 100% in the ITPR group. Oxygenation and elimination of CO$_2$ remained adequate with ITPR treatment. On the basis of this proof-of-concept animal study demonstrating that use of the ITPR during CPR improved hemodynamics and short-term survival rates after cardiac arrest, further animal and clinical evaluation of this new CPR adjunct is warranted.
Intrathoracic Pressure Regulator During Continuous-Chest-Compression Advanced Cardiac Resuscitation Improves Vital Organ Perfusion Pressures in a Porcine Model of Cardiac Arrest

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