Use of an Inspiratory Impedance Valve Improves Neurologically Intact Survival in a Porcine Model of Ventricular Fibrillation

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Background—This study evaluated the potential for an inspiratory impedance threshold valve (ITV) to improve 24-hour survival and neurological function in a pig model of cardiac arrest.

Methods and Results—Using a randomized, prospective, and blinded design, we compared the effects of a sham versus active ITV on 24-hour survival and neurological function. After 6 minutes of ventricular fibrillation (VF), followed by 6 minutes of cardiopulmonary resuscitation (CPR) with either a sham or an active valve, anesthetized pigs received 3 sequential 200-J shocks. If VF persisted, they received epinephrine (0.045 mg/kg), 90 seconds of CPR, and 3 more 200-J shocks. A total of 11 of 20 pigs (55%) in the sham versus 17 of 20 (85%) in the active valve group survived for 24 hours ($P<0.05$). Neurological scores were significantly higher with the active valve; the cerebral performance score (1=normal, 5=brain death) was 2.2 ± 0.2 with the sham ITV versus 1.4 ± 0.2 with the active valve ($P<0.05$). A total of 1 of 11 in the sham versus 12 of 17 in the active valve group had completely normal neurological function ($P<0.05$). Peak end-tidal CO_2 (P_{ETCO_2}) values were significantly higher with the active valve (20.4 ± 1.0) than the sham (16.8 ± 1.5) ($P<0.05$). P_{ETCO_2} >18 mm Hg correlated with increased survival ($P<0.05$).

Conclusions—Use of a functional ITV during standard CPR significantly improved 24-hour survival rates and neurological recovery. P_{ETCO_2} and systolic blood pressure were also significantly higher in the active valve group. These data support further evaluation of ITV during standard CPR. **(*Circulation*. 2002;105:124-129.)**

Key Words: cardiac arrest ■ fibrillation ■ cardiopulmonary resuscitation ■ valves ■ survival ■ arrhythmia ■ brain

Survival rates remain poor for most patients who suffer from a cardiac arrest. Studies on the mechanism of blood flow during cardiopulmonary resuscitation (CPR) have recently focused on the importance of the decompression phase of CPR.[1–4] During the decompression phase of standard CPR, a small vacuum is created within the chest relative to the rest of the body every time the chest wall recoils back to its resting position.[5] This draws venous blood back into the right heart. In addition, during the decompression phase of standard CPR, air is drawn into the lungs. We previously described the use of an impedance threshold valve (ITV) to prevent the inflow of respiratory gases during the active chest wall recoil phase, or decompression phase, of standard CPR.[4,5] The ITV is a small (35-mL) disposable plastic valve that is attached to the endotracheal tube or a face mask. It works by allowing the rescuer to freely ventilate the patient but impeding inspiratory airflow during the decompression phase of CPR when the patient is not being actively ventilated. This creates a small vacuum within the chest to further enhance venous return.

We recently demonstrated in a porcine model that use of the ITV resulted in a nearly 2-fold increase in blood flow to the brain and the heart after 6 minutes of ventricular fibrillation and 6 minutes of standard CPR.[6] Although use of the ITV during standard CPR has been reported previously in 2 studies involving >30 animals, to date there have been no definitive data in support of a survival benefit from the use of the ITV with standard CPR.[4,6] Thus, the purpose of this investigation was to test the hypothesis that the ITV would improve neurological function and 24-hour survival in an established animal model of cardiac arrest during performance of standard CPR.

Methods

Preparatory Phase

The study was approved by the Committee of Animal Experimentation at the University of Minnesota. Anesthesia was used in all

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surgical interventions to avoid all unnecessary suffering. This study was performed according to Utstein-style guidelines[7] on 40 female farm pigs weighing 28 to 33 kg. Each animal received 7 mL (100 mg/mL) of ketamine HCl (Ketaset, Fort Dodge Animal Health) IM for initial sedation. Intravenous access with an 18-gauge angiocatheter (Jelco Ethicon, Inc) was rapidly obtained through a lateral ear vein. Propofol anesthesia (PropoFlo, Abbott Laboratories) (2.3 mg/kg) was initially delivered as an intravenous bolus. While the animals were spontaneously breathing but heavily sedated, they were intubated with a 7.0F endotracheal tube (Medline Industries Inc). The animals were then given an additional 30 mg of propofol and were maintained on a propofol infusion of 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until just after induction of ventricular fibrillation.

The animals were positioned in the supine position. Femoral artery cannulation was performed under aseptic conditions, and arterial blood pressures were monitored and recorded as previously described.[2,6] Continuous ECG monitoring was recorded with a lead II ECG. Data were digitized, recorded, and analyzed as previously described.[2,3,6] Intrathoracic pressures were measured with a micromanometer-tipped catheter positioned 2 cm below the tip of the endotracheal tube. End tidal CO_2 ($ETCO_2$) (CO_2 SMO Plus Respiratory Profile Monitor, Novametrix Medical Systems), arterial pressures, and intrathoracic pressures were recorded continuously during both the preparatory phase and the experimental protocol. Animals received 400 mL of normal saline before the induction of ventricular fibrillation. Temperature was recorded with a rectal thermometer and maintained between 37.5°C and 39.5°C with either a fan and a cooling blanket or a Bair Hugger, Temperature Management System (Augustine Medical, model 505), as needed.

Animals were positioned on a rigid cradle for standard CPR with an automated CPR device. A circular compression pad with a diameter of 6.4 cm was attached to a pneumatically driven compression-piston device (CPR Controller, Ambu International) and positioned over the lower third of the sternum.

During the preparatory phase, the animals were ventilated with room air by use of a positive-pressure ventilator (Harvard Apparatus Co, model 607) at an average rate of 16 breaths per minute and a tidal volume of 20 mL/kg. The rate was adjusted on the basis of analysis of arterial blood gases every 30 minutes (IL Synthesis, model 20, Instrumentation Laboratory).

Protocol

Ventricular fibrillation was induced in the anesthetized animals with a 3-second, 60-Hz, 140- to 160-V AC shock applied across the thorax with 2 half-circle stainless steel surgical needles as electrodes. CPR was performed continuously at a rate of 80 compressions per minute, with a compression-decompression duty cycle of 50%. Compressions were performed to a depth of 25% of the anteroposterior diameter of the thorax with a circular compression pad. During the decompression phase, the compression pad was elevated at a rate of 7.5 in/s to allow for the natural recoil of the anterior chest wall. After ventricular fibrillation was induced, the intravenous saline and propofol infusions were immediately discontinued, and the animal was disconnected from the mechanical ventilator. After 6 minutes of untreated cardiac arrest, standard closed-chest CPR was delivered continuously with an automated pneumatic piston device as described above. Thirty seconds before initiation of CPR, either a sham or an active ITV was attached to the endotracheal tube. The ITVs used in this study have been described previously in detail.[5,6] Assignment of each valve was made according to a computer-generated randomization list. Researchers were blinded to the kind of valve used until after the pigs were euthanized 24 hours after resuscitation.

During CPR, ventilation was delivered during the decompression phase. Animals were ventilated during CPR with 100% O_2 with a demand valve resuscitator (Life Support Products, Inc, model L063-05RM) through either a sham (nonfunctional) or active functional ITV (ResQ-Valve, CPRx LLC) at a compression-to-ventilation ratio of 5:1. It was not possible, when looking at the blue impedance valves, to determine whether or not there was a silicone diaphragm within the valve. In addition, the silicone diaphragm venting ports were occluded during the manufacturing of the sham valves, such that they functioned as a hollow conduit for respiratory gas exchange. As such, half of the ITVs were made as sham valves and the other half were active. Figure 1 depicts the function of the ITV during the chest compression and decompression phases of CPR.[2,5,6]

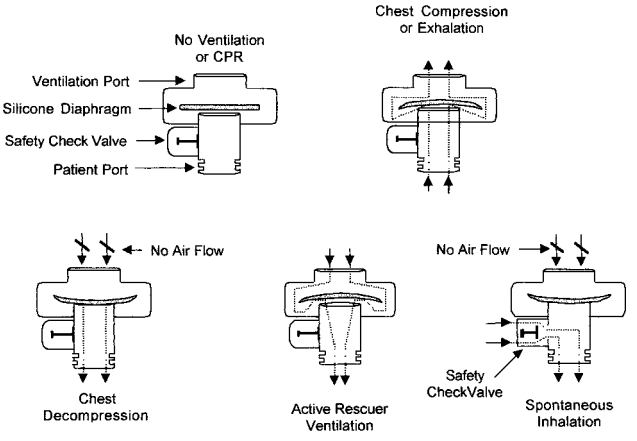

Figure 1. Schematic of respiratory gas flow through ITV.

After 12 minutes of ventricular fibrillation and a total of 6 minutes of CPR, the impedance valve was removed, and each animal was immediately defibrillated with up to 3 sequential 200-J transthoracic monophasic shocks (Lifepak 6, Physio-Control). Animals that were successfully resuscitated were reconnected to the automatic ventilator. Animals that remained in cardiac arrest received a single dose of intravenous epinephrine (0.045 mg/kg) and an additional 90 seconds of CPR with the previously assigned sham or active ITV. Each animal that remained in cardiac arrest then received up to 3 additional sequential 200-J transthoracic shocks. All animals with successful restoration of spontaneous circulation were treated with intravenous fluids. Dopamine, at a concentration of 1.6 mg/mL, was administered to maintain the systolic blood pressure at >70 mm Hg, as needed. Mechanical ventilation with supplemental oxygen (10 L/min) was continued throughout the immediate postresuscitation period. The endotracheal tube was removed once the animal was able to breathe independently, as judged by measurement of peak inspiratory flow rates and maintenance of adequate ventilation as the mechanical ventilation rate was progressively reduced. Each animal was transferred to a heated holding area until it woke up and was able to move around and drink water independently. The survivors were held in an observation area for 24 hours before undergoing further assessment. They then underwent euthanasia and autopsy 24 hours after resuscitation.

Survival rates, complication rates, and neurological status were evaluated 24 hours after resuscitation. Neurological function was evaluated 24 hours after resuscitation by 2 investigators (S.M., T.Z.) who remained blinded to the device that was used. Evidence of pulmonary congestion, as judged by blood gas analysis, was assessed 1 to 3 hours after resuscitation. Pulmonary congestion was also assessed by observing for pink frothy exudate in the endotracheal tube during and after CPR and at autopsy. Neurological function was assessed quantitatively, as described by Bircher, Safar, Vaagenes, and colleagues.[8,9] The Swine Neurologic Deficit Score was used to evaluate level of consciousness, respiratory pattern, cranial nerve function, motor and sensory function, and behavior evaluation, including ability to drink, chew, stand, and walk.[8] The Cerebral Performance Score was also used.[9] It is a neurological assessment based on a 5-point evaluation of the level of consciousness.

Statistical Analysis

Hemodynamic and perfusion parameters were analyzed by ANOVA (a value of $P<0.05$ was considered statistically significant). The χ^2 test was used for survival rate analysis. A priori, the sample size was

TABLE 1. Twenty-Four Hour Survival and Neurological Assessment Score

	Sham Valve (n=20)	Active Valve (n=20)
24-hour survival, n (%)	11 (55)*	17 (85)*
Neurological assessment		
Consciousness	25.0±6.2	10.6±4.4*
Respiratory pattern	10.8±8.5*	0.0±0.0*
Painful stimulus	13.3±4.1	4.7±2.1
Muscle tone	16.7±5.6	5.9±2.7
Standing	5.0±2.6	1.2±1.2
Walking	13.3±3.3	5.3±2.1*
Restraint	30.8±5.3*	12.9±4.8*
Total deficit score	16.4±3.3†	5.8±1.8†

*$P<0.05$.
†$P<0.02$.

calculated on the basis of expected differences in 24-hour survival between groups. All data are expressed as mean±SEM.

Results

Survival Outcomes

The main study end points were 24-hour survival and neurological function. Twenty animals received standard CPR plus a sham valve, and 20 received standard CPR plus an active valve. Twenty-four-hour survival was 55% in the sham valve group and 85% in the active valve group ($P<0.05$).

Neurological function was significantly improved in the 24-hour survivors that received treatment with the active valve. The cerebral performance score, based on a 5-point scoring system (1=normal, 5=brain death),[9] was 2.2±0.2 for animals treated with the sham valve versus 1.4±0.2 for those treated with the active valve ($P<0.002$). With the Swine Neurologic Deficit Score,[8] there were similar statistically significant improvements in the active valve group (Table 1, Figure 2). The neurological deficits in survivors treated with

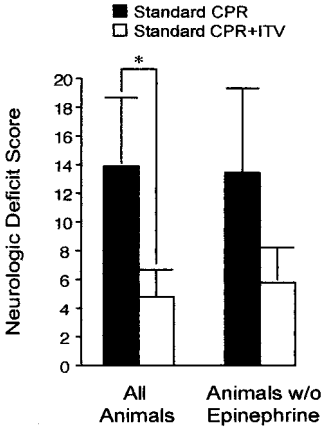

Figure 2. Pittsburgh neurological deficit score for all animals receiving standard CPR with either sham (n=11 of 20 survivors 24 hours after resuscitation) or active (n=17 of 20 survivors 24 hours after resuscitation) valve and subgroup of animals that were resuscitated without (w/o) epinephrine. All values are mean±SEM. *$P<0.03$.

TABLE 2. Twenty-Four Hour Survival and Neurological Assessment Score by Level of Care (BLS or ALS) Received

	Sham Valve (n=20)		Active Valve (n=20)	
	BLS	ALS	BLS	ALS
24-hour survival, n (%)	6 (30)	5 (25)	12 (60)	5 (25)
Neurological assessment				
Consciousness	25.0±9.2	25.0±9.2*	13.9±5.5	0.0±0.0*
Respiratory pattern	5.0±5.0	16.7±16.7*	0.0±0.0*	0.0±0.0
Painful stimulus	15.8±7.8	10.8±3.3*	6.6±2.6	0.0±0.0*
Muscle tone	18.3±8.9	12.5±6.0	6.0±2.8	6.3±6.3
Standing	6.7±4.2	3.3±3.3*	1.5±1.5	0.0±0.0*
Walking	13.3±5.6	13.3±4.2	6.2±2.7	2.5±2.5
Restraint	30.0±8.2	32.0±7.5*	15.4±6.0	5.0±5.0*
Total deficit score	16.3±3.4*	16.3±3.6†	7.0±2.2*	2.0±1.0†

*$P<0.05$.
†$P<0.002$.

the sham valve were striking. The animals often appeared docile and disoriented, frequently walking into the wall of the cage without apparently realizing that it was there. Only 1 of 11 survivors had a completely normal neurological score. By contrast, 12 of 17 survivors treated with the active valve had normal neurological function ($P<0.05$). Improved neurological function was observed in many of the different categories in animals treated with the active valve (Tables 1 and 2).

The initial return of spontaneous circulation (ROSC) rate was 80% in the sham valve group and 95% in the active valve group. For those animals that had ROSC after the first 3 defibrillatory shocks, there was no significant difference in the amount of energy needed between groups. Without epinephrine treatment (ie, with only Basic Life Support [BLS] techniques during the resuscitation), 35% of the pigs in the sham valve group versus 60% in the active valve group could be resuscitated initially (P=NS). Five pigs in the sham valve group and 2 in the active valve group died after being successfully resuscitated, but before 24 hours.

We also analyzed 24-hour survival results in the subset of animals that were resuscitated with DC shock alone, without epinephrine. With BLS followed by defibrillation, 24-hour survival in the sham controls was 30% versus 60% in the active valve group ($P=0.057$). The neurological score in this subgroup also showed a significant improvement in the active valve group (Table 2). Similarly, when advanced life support (ALS) measures were needed and used, use of the ITV also resulted in a statistically significant improvement in the neurological status of the animals 24 hours after resuscitation.

Epinephrine therapy had no observed beneficial impact on neurological function in the sham valve group but did improve the likelihood of successful resuscitation in both the sham and active valve groups. The cerebral performance score was 2.0±0.4 in the sham valve group with BLS alone versus 2.3±0.3 in the sham valve group that received ALS (epinephrine and additional shocks). The total neurological deficit scores were similar as well, with and without epinephrine treatment, in animals treated with the sham valve (Table 2). By contrast, pigs requiring epinephrine in the active valve

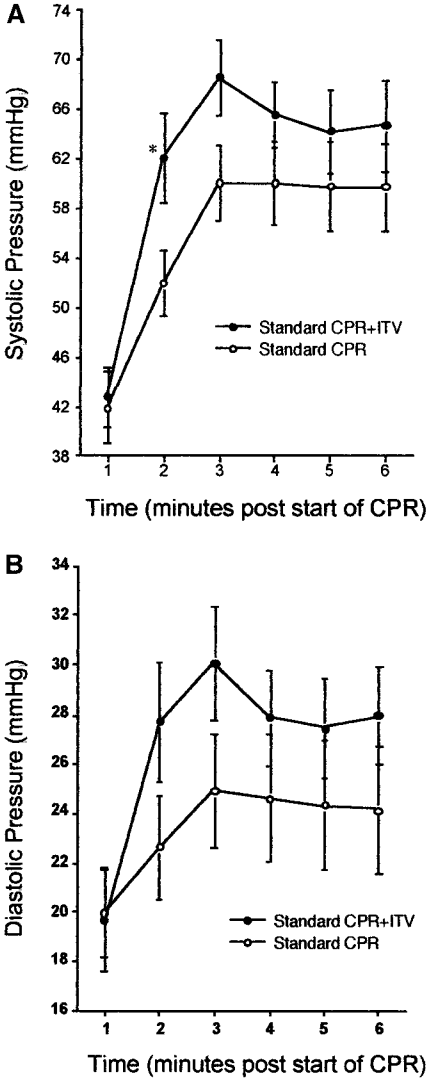

Figure 3. Standard CPR was performed with either a sham or active ITV. Systolic pressures (A) were recorded continuously during 6-minute study period during CPR. Systolic pressures, plotted on *y* axis from 38 to 74 mm Hg, were significantly higher during time points marked with asterisk. Diastolic arterial pressures (B) were also recorded continuously during study period and from 16 to 34 mm Hg. Values are mean±SEM for time period indicated on each graph. *$P \leq 0.05$.

group that lived for 24 hours all had a normal cerebral performance score.

A total of 5 animals in the sham group and 4 in the active valve group required dopamine supportive therapy after resuscitation, secondary to hypotension. The duration of support varied between 1 minute and 30 minutes and was similar between groups.

Hemodynamic Outcomes

Systolic arterial pressures (Figure 3A) as well as peak $ETCO_2$ ($PETCO_2$) (Figure 4) levels were significantly higher in the group treated with the active valve. The systolic and diastolic pressures (Figure 3B) rose more rapidly and remained higher in the active valve group than in controls. With a χ^2 test, there was a significantly greater chance for 24-hour survival when

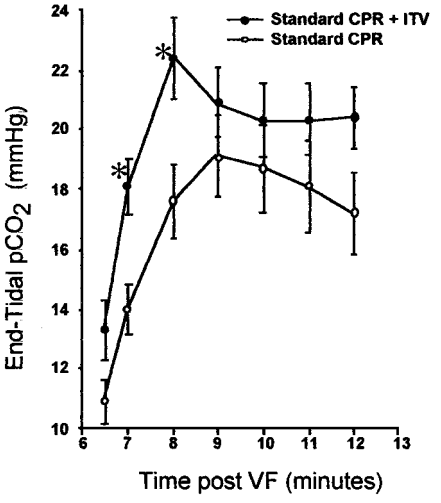

Figure 4. End-tidal CO_2 values were measured over 6-minute study period. All values plotted from 10 to 24 mm Hg are expressed as mean±SEM. Standard CPR was performed with either a sham or active ITV. VF indicates ventricular fibrillation. *$P \leq 0.05$.

the diastolic blood pressure was >21 mm Hg (80%) compared with animals with a diastolic blood pressure of ≤21 mm Hg (40%) ($P<0.05$).

$PETCO_2$ levels were significantly higher among survivors than among the animals that died. There was a significantly greater chance for 24-hour survival in animals with a maximum $PETCO_2$ level of ≥19 mm Hg (79%) than in animals with a peak $PETCO_2$ value of <18 mm Hg (45%) ($P<0.05$).

Changes in intrathoracic pressure were also monitored continuously during the performance of CPR. As shown in Figure 5, intrathoracic pressures were consistently lower in the active valve group. There was a significantly greater chance for 24-hour survival when intrathoracic pressure was ≥1.5 mm Hg (80%) than in animals with thoracic pressure of ≤1.5 mm Hg (40%) ($P<0.05$).

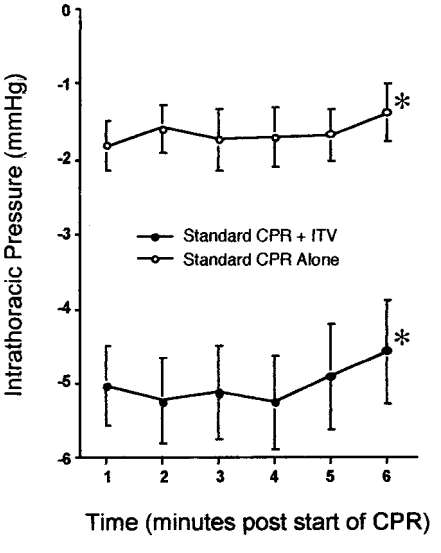

Figure 5. Intrathoracic pressures were recorded continuously during 6-minute study period. Values represent mean±SEM for time period indicated on each graph. Standard CPR was performed with either a sham or active ITV. *$P \leq 0.05$.

TABLE 3. Arterial Blood Gas Values

	Sham Valve			Active Valve		
	pH	P_{CO_2}	P_{O_2}	pH	P_{CO_2}	P_{O_2}
Baseline	7.45±0.03	32.8±1.2	93±3.2	7.46±0.01	34.2±1.1	86±2.9
VF+10 min	7.29±0.04	31.3±1.9	153±24	7.33±0.02	31.7±2.5	220±36
ROSC	7.13±0.03*	38.8±2.7	199±35	7.23±0.03*	36.05±2.7	198±31

VF indicates ventricular fibrillation.
*$P<0.05$.

Arterial blood gas measurements suggest that pulmonary function was not compromised by the impedance valve. As shown in Table 3, the P_{O_2} values after 10 minutes of ventricular fibrillation and 4 minutes of CPR, as well as ROSC, were not significantly different between groups. The arterial pH, however, was significantly higher in the active valve group than the sham group.

Potential Complications

Device failure (eg, breakage of the device) was monitored throughout the study. All valves were tested before and after use. There was no evidence of device failure.

Animals underwent necropsy to evaluate for potential complications, including damage to the rib cage and evidence of lung, heart, and other vital organ damage secondary to the CPR. There were no differences between the animals treated with the sham versus active impedance valve. In addition, we did not observe any evidence of pulmonary edema, as judged by the presence of pink frothy exudate in the endotracheal tube during or after CPR.

Discussion

The results from this pig study demonstrate that when blood return is enhanced to the heart during the decompression phase of standard CPR with an inspiratory impedance valve, 24-hour survival and neurological outcome are significantly improved. By harnessing the kinetic energy associated with the natural recoil of the chest during standard CPR, the inspiratory impedance valve transiently prevents the inflow of respiratory gases, thereby creating a greater vacuum in the chest with each decompression phase recoil of the chest wall. The results from this study demonstrate, for the first time, that a device developed to enhance blood return to the thorax during the relaxation, or decompression, phase of standard CPR can improve survival rates and neurological function. The results are consistent with reports demonstrating that use of an inspiratory impedance valve significantly enhances coronary perfusion pressure, myocardial perfusion, and cerebral perfusion during standard CPR.[2,4–6]

A recent study in humans[10] suggests that a brief period of "priming the pump" before the delivery of defibrillatory shocks can significantly improve overall survival. This stands to reason, because the fibrillating heart, in the absence of closed-chest cardiac massage, has a high metabolic rate and limited metabolic stores. Movement of blood through the coronary arteries during CPR provides a means to renew energy supplies and remove metabolic byproducts, especially lactic acid, that are toxic to the myocardium. The results demonstrating higher arterial blood pH values in the active valve group provide metabolic evidence in support of the improved perfusion with the valve.

The natural recoil of the chest results in the development of a -5.3 ± 0.6 mm Hg decrease in intrathoracic pressure with the active valve compared with -1.8 ± 0.4 mm Hg decrease with the sham valve. Relatively speaking, these changes in negative intrathoracic pressure are quite small. The negative intrathoracic pressures generated with the ITV, however, are sufficient to enhance blood return to the right heart during the decompression phase of CPR, which can be circulated during the subsequent compression phase, thereby priming the pump with each complete compression-decompression cycle.

We observed no significant adverse effects from the use of the inspiratory impedance valve. The blood gas data suggest that oxygenation was adequate in the active valve group, and no differences were observed between groups on autopsy. Previously, we had demonstrated that the use of the valve resulted in a decrease in minute ventilation and arterial oxygen tension compared with standard CPR alone.[2,4] In the previous studies, however, as well as in the present study, the P_{O_2} measured in arterial blood was always >85 mm Hg. Moreover, it is possible that the decrease in arterial P_{O_2} we previously observed when the ITV was used was the result of lower flow through the pulmonary vasculature in the control group, resulting in a paradoxically higher P_{O_2}, as was observed by Idris et al[11] in another model of cardiac arrest.

This study was designed to evaluate the potential impact of the inspiratory impedance valve on 24-hour survival and neurological function in a pig model. It is limited in that we did not assess myocardial function 24 hours after recovery, but there was no clinical evidence of heart failure in either group. In addition, we used only a single dose of epinephrine. This may have altered the outcome.

Conclusions

There was a statistically significant increase in 24-hour survival and neurological function when the functional ITV was used during standard CPR. The impedance valves worked well during and after the study, without evidence of failure. Moreover, P_{ETCO_2} appeared to be a promising and potentially meaningful predictor of outcome in cardiac arrest when the ITV was used. On the basis of this study, further evaluation of the ITV during standard CPR seems warranted.

Acknowledgments

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