



EXPERIMENTAL PAPER

Effects of an inspiratory impedance threshold device on blood pressure and short term survival in spontaneously breathing hypovolemic pigs[☆]

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Summary

Background: The inspiratory impedance threshold device (ITD) has been shown to improve hemodynamic variables and survival outcomes during cardiopulmonary resuscitation in animals and humans. We hypothesized that use of an ITD, with a resistance of -10 cm H₂O, will improve hemodynamics and short-term survival rates during hypovolemic hypotension in spontaneously breathing pigs.

Methods: Female farm pigs (~ 26 kg) were intubated and anesthetized with propofol with the dose adjusted to permit spontaneous respirations. They were bled to 50% of calculated blood volume through an arterial catheter and then prospectively randomized to either treatment with an ITD or observation alone. Arterial and intratracheal pressures as well as arterial blood gases were measured. After 90 min the ITD was removed, normal saline was administered to all surviving animals, the anesthetic was discontinued, and animals were allowed to recover. Statistical analysis was performed with one-way repeated ANOVA and survival rates were calculated with Kaplan–Meier analysis.

Results: Treatment with the ITD resulted in lower intratracheal inspiratory pressure in the treatment group (-11 ± 0.4 mmHg versus -4 ± 0.7 mmHg, respectively, $P < 0.005$). Mean arterial pressure after 30 min of treatment with the ITD was higher in the treatment group (61.1 ± 5.5 mmHg versus 37.4 ± 2.1 mmHg, respectively, $P < 0.005$). All pigs in the control group died within 65 min of

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the initial bleed, whereas 7/8 (87%) treated with an ITD survived for >90 min ($P < 0.001$). During the recovery phase, 6/8 (75%) in the ITD group survived for >3 h and awoke without neurological deficit; one surviving animal in the ITD group never woke up. Arterial oxygenation was not compromised in the ITD group.

Conclusions: Use of an ITD improved blood pressure and short-term survival rates in a spontaneously breathing porcine model of hypovolemic hypotension.

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Introduction

It is well known that with normal inspiration intrathoracic pressure decreases. This results in the entrainment of respiratory gases into the lungs, a decrease in right heart pressures and an increase in venous return and cardiac preload.^{1–4} The inspiratory threshold device (ITD) was developed to augment this normal physiological cardiopulmonary interaction in order to increase preload and cardiac output further.³ This device requires an inspiratory pressure threshold of -10 cm H₂O (''cracking pressure'') to be reached before it allows inflow of air, thus functioning like a partial Mueller maneuver with each inspiration. It does not affect expiration.

The ITD was used initially to increase circulation during cardiopulmonary resuscitation after cardiac arrest, as it augments negative intrathoracic pressure during recoil of the chest.^{5–7} In this clinical setting it has been shown to increase circulation to the vital organs and increase short-term survival rates animals and humans.^{6–11} Subsequently the ITD was used in conjunction with phrenic nerve stimulation to increase blood flow and blood pressure during hypovolemia.¹² More recently the ITD has been used during spontaneous ventilation in animals and humans. In spontaneously breathing hypovolemic hypotensive pigs use of the ITD with a cracking pressure of -10 cm H₂O was well tolerated and resulted in an increase in systemic blood pressures and cardiac output.^{3,4} The ITD has also been demonstrated to increase blood flow in healthy human volunteers.¹

The purpose of this study was to determine if breathing through the ITD would improve blood pressure and short-term survival rates in spontaneously breathing pigs with significant hypovolemic hypotension.

Methods

The study was approved by local Committee of Animal Experimentation. The animals received care in compliance with the 1996 *Guide for the Care and Use of Laboratory Animals* by the National Research

Council. The study was performed on female Yorkshire-cross farm pigs (22–31 kg). The mean weights were similar between groups: 26.2 ± 0.9 kg in the ITD group and 26.5 ± 0.9 kg in the controls.

Preparatory phase

Sedation, intubation, and ventilation during the preparatory phase have been described earlier.⁵ Propofol anesthesia (Propofol®, Abbott, North Chicago, IL) was delivered by an intravenous infusion of $160 \mu\text{g/kg/min}$. Animals were positioned in the supine position. Bilateral femoral artery cannulation was performed. On one side central aortic blood pressures were recorded, using a micromanometer-tipped catheter (Mikro-Tip® Transducer, Millar Instruments, Inc., Houston, TX). On the other side a catheter was placed for controlled bleeding. All animals were treated with intravenous heparin (100 units/kg) once catheters were in place. Intratracheal pressures were measured with a micromanometer-tipped catheter positioned 2 cm below the tip of the tracheal tube. After the preparatory phase, the animals remained heavily sedated, but were allowed to breathe spontaneously by decreasing the dosage of the propofol to $50 \mu\text{g/kg/min}$. This dose was adjusted to target respiratory rate of 25–35 breaths/min and oxygen saturation above 90%, breathing room air. Once the animals were able to maintain normal oxygenation in the absence of mechanical ventilator support for 20 min the experimental protocol, described below, was initiated. Hoof pinching and canthal reflex were checked frequently to secure adequate sedation throughout the study.

Experimental protocol

Pigs were bled an estimated 50% (32.5 ml/kg) of their total blood volume¹³ at the rate of 60 ml/min over a period of 15–20 min. After a 5 min period of stabilization, the animals ($n=8$ per group) were randomized to either observation alone or ITD treatment (ITD™, Advanced Circulatory Systems, Inc., Eden Prairie, MN). Randomization was

performed after the bleed during the stabilization period by a blinded random draw. The ITD had a -10 cm H₂O cracking pressure, which was found to be well tolerated in a recent titration study.³ The airway dead-space associated with the ITD was an additional 25 ml. After a period of 90 min, the ITD was removed and the surviving pigs received 400 ml of intravenous normal saline solution at the rate of 60 ml/min. The arterial catheter was removed 15 min later and propofol infusion was also discontinued. Animals were allowed to recover from anesthesia in order to assess cerebral function. The level of consciousness was assessed 3 h after the bleeding phase using the 5 point Cerebral Performance Scoring system,¹⁴ where a score of 1 is for normal, 2 = slightly disabled, 3 = severely disabled but conscious, 4 = vegetative state and 5 = brain death.

At the end of each study protocol, animals were sacrificed with propofol 60 mg and bolus injection of 10 M potassium chloride. Limited necropsies of the thorax were performed.

Statistical analysis

Hemodynamic and respiratory parameters were analyzed using ANOVA. Survival analysis was performed using Kaplan–Meier methods with log–rank (Mantel–Cox) comparison of cumulative survival by treatment group. Data were calculated as the mean $\pm$ S.E.M. at each time point. A *P*-value of <0.05 was considered statistically significant.

Results

The average blood loss in the control group 858 ± 79 ml and in the ITD group 855 ± 98 ml (*P* = NS). Treatment with the ITD resulted in lower intratracheal pressure compared with the control group (-11 ± 0.4 mmHg versus -4 ± 0.7 mmHg, respectively, *P* < 0.005), without affecting PaO₂ (Table 1). The control group also had lower PaCO₂ values compared with the ITD treatment group.

As shown in Figure 1, animals treated with the ITD had higher mean arterial blood pressure compared with control animals (61.1 ± 5.5 mmHg versus 37.4 ± 2.1 mmHg, respectively, *P* < 0.005) 30 min into treatment. This effect was sustained for the entire 90 min period of ITD treatment. After removal of the ITD and simultaneous infusion of saline the mean arterial blood pressure returned to normal (Table 2).

Survival was significantly affected by treatment with the ITD. Seven of the eight animals (87%) survived to the end of the study period. By contrast,

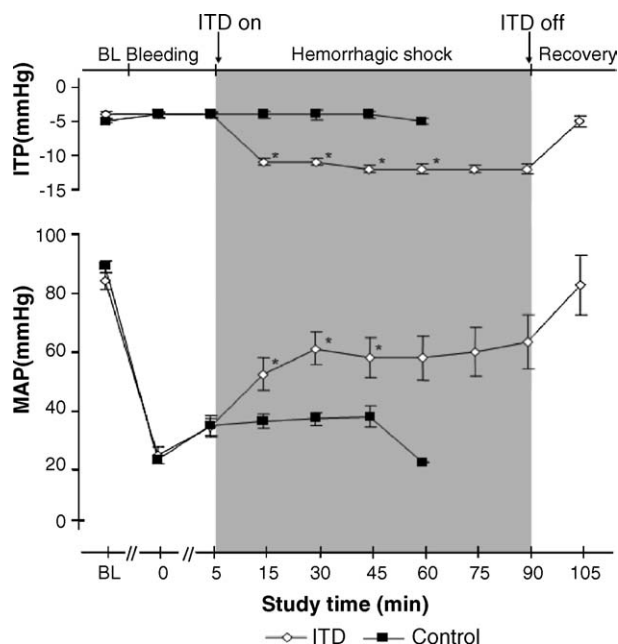


Figure 1 Following controlled blood loss the inspiratory threshold device (ITD), set to open at -10 cm H₂O, resulted in a significant decrease in intratracheal pressure (ITP) and a significant increase in mean arterial blood pressure (MAP), compared to controls. BL = baseline, **P* < 0.05 .

none of the pigs in the control group survived past 65 min (*P* < 0.0001). After discontinuation of ITD therapy and cessation of the anesthetic, 6/8 animals in the ITD group woke up. Three hours later 5/6 pigs had normal neurological function, and 1/6 had a Cerebral Performance Score of 2. This animal improved with time and also had normal neurological function 5 h after the bleeding phase. One animal in the ITD group died 80 min after the bleed. A limited necropsy study after each experiment showed no signs of confounding heart or lung disease. Pulmonary edema and hemorrhage were not detected in any animal.

Discussion

The results of this study demonstrate that use of an ITD for up to 90 min during hypovolemic hypotension improves hemodynamics and short-term survival rates in spontaneously breathing animals. The physiological effects of the ITD in this animal model result from enhancing the modest vacuum within the thoracic cavity with each inspiratory effort,^{3,4} thereby augmenting venous return, stroke volume, and blood pressure (Table 2). The increase in blood pressure was observed within several minutes of ITD treatment and was sustained for up to 90 min. It

Table 1 Measurements of respiratory rate (RR), intra-tracheal pressure (ITP) during inspiration, oxygen saturation (SO₂), arterial pH, arterial partial pressure of O₂ (PaO₂), CO₂ (PaCO₂), and base excess, at baseline and during treatment of hemorrhagic shock

	Treatment type	Baseline	End of bleed (0 min)	15 min	45 min	90 min	Recovery (105 min)
RR	ITD	41 ± 2	30 ± 3	31 ± 3	31 ± 3	31 ± 3	43 ± 5
	Control	41 ± 4	33 ± 2	40 ± 2*	35 ± 5		
ITP (mmHg)	ITD	-4 ± 0.5	-4 ± 0.4	-11 ± 0.5	-12 ± 0.5	-12 ± 0.7	-5 ± 0.9
	Control	-5 ± 0.3	-4 ± 0.3	-4 ± 0.4†	-4 ± 0.5†		
SO ₂ (%)	ITD	96.0 ± 0.5	97.0 ± 0.4	94.7 ± 0.4	94.6 ± 0.8	93.6 ± 0.9	95.7 ± 0.4
	Control	94.0 ± 0.8	95.8 ± 0.9	94.4 ± 1.1	96.8 ± 0.8		
Ph	ITD	7.44 ± 0.01	7.48 ± 0.01	7.37 ± 0.01	7.33 ± 0.03	7.29 ± 0.03	7.34 ± 0.03
	Control	7.42 ± 0.02	7.45 ± 0.02	7.40 ± 0.02	7.37 ± 0.04		
PaO ₂ (mmHg)	ITD	78.7 ± 3.5	87.3 ± 3.8	78.0 ± 2.5	80.0 ± 3.2	79.9 ± 3.9	86.8 ± 3.3
	Control	70.6 ± 3.0	79.6 ± 5.5	76.8 ± 4.4	86.2 ± 6.9		
PaCO ₂ (mmHg)	ITD	35.7 ± 0.8	30.8 ± 1.5	36.4 ± 1.2	34.7 ± 1.0	36.6 ± 2.8	30.5 ± 4.7
	Control	38.9 ± 2.7	32.6 ± 1.5	30.6 ± 0.6*	25.4 ± 3.1*		
Base Excess (mmol/l)	ITD	1.0 ± 1.0	-0.1 ± 0.8	-3.5 ± 1.0	-6.5 ± 1.3	-7.5 ± 2.2	-8.6 ± 3.4
	Control	2.4 ± 1.0	-1.0 ± 0.8	-4.9 ± 1.2	-10.9 ± 1.7		

ITD treatment was administered 5 min after the bleed and removed 90 min later.

* $P < 0.05$ between ITD and control.

† $P < 0.005$.

has been established previously that a mean arterial pressure of at least 40 and 60 mmHg is needed for effective coronary and cerebral autoregulation of blood flow, respectively.^{15–18} This level of arterial pressure was achieved with the use of the ITD but not observed in the control group.

The results suggest that the use of the ITD can be used to maintain “permissive hypotension”,¹⁹ if bleeding is under control but the clot is fresh.

While use of the ITD is not a substitute for transfusion or correction of the primary cause of the blood loss, it may be useful to “buy time” and to prevent the fatal consequences of severe blood loss, particularly when intravenous therapy is not readily available and the bleeding can be controlled (i.e. by direct compression). As with fluid resuscitation, clinical evaluation and use of the ITD must take into consideration the potential to worsen the patient’s

Table 2 Measurements of heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse pressure (PP) at baseline and during treatment of hemorrhagic shock

	Treatment type	Baseline	End of bleed (0 min)	15 min	45 min	90 min	Recovery (105 min)
Heart rate (beats/min)	ITD	135 ± 7	179 ± 10	211 ± 16	230 ± 15	243 ± 22	209 ± 14
	Control	137 ± 8	209 ± 15	233 ± 18	267 ± 2		
SBP (mmHg)	ITD	102.9 ± 2.5	35.4 ± 4.1	67.9 ± 6.2	76.7 ± 6.4	82.1 ± 7.3	105.6 ± 9.0
	Control	107.8 ± 2.6	31.8 ± 2.1	51.1 ± 3.4*	51.9 ± 4.5*		
DBP (mmHg)	ITD	74.3 ± 3.8	19.7 ± 2.6	45.0 ± 5.1	49.1 ± 7.0	54.1 ± 10.1	71.4 ± 11.4
	Control	82.3 ± 1.8	19.1 ± 1.1	29.2 ± 2.5*	31.2 ± 3.2		
MAP (mmHg)	ITD	84.0 ± 2.9	25.0 ± 3.0	52.6 ± 5.4	58.3 ± 6.7	63.5 ± 9.1	82.8 ± 10
	Control	90.7 ± 1.9	23.4 ± 1.4	36.5 ± 2.5*	38.1 ± 3.5*		
PP (mmHg)	ITD	28.4 ± 2.0	15.6 ± 2.5	22.9 ± 2.8	27.6 ± 3.2	27.9 ± 3.9	34.2 ± 3.8
	Control	25.5 ± 2.6	12.7 ± 1.4	21.8 ± 2.8	20.7 ± 2.3		

ITD was placed on 5 min and removed after 90 min.

* $P < 0.05$ between ITD and control.

clinical status if the blood pressure is increased when bleeding remains uncontrolled.

Analysis of the arterial blood gases demonstrated that oxygenation was adequate with use of the ITD. Arterial pH was also maintained within the normal range in both groups although a mild acidosis was observed in the treatment group. We speculate that the lower pH values in the ITD group could play a beneficial role since it allows for a left shift of the oxyhemoglobin dissociation curve that further enhances oxygen delivery to the tissue level.¹⁹ PaCO₂ was maintained constant around 36 mmHg in the ITD group and remained higher throughout the study compared with the control group. This may be secondary to a combination of higher pulmonary flow and mild increase of the dead-space (use of the ITD) in the treatment group. Finally use of the ITD slowed the decrease in the decline of base excess compared with the control group, which showed faster progression of metabolic acidosis. The differences observed in base excess, PaCO₂ and mean arterial pressure support the hypothesis that use of the ITD improved tissue perfusion.

The potential metabolic and hemodynamic effects of the anesthetic propofol may have contributed to the outcome of the study. Propofol, in high concentrations, can exacerbate metabolic acidosis and cause vasodilatation. This may have lowered arterial pressure in both groups. In preliminary studies we observed that there were differences in the respiratory rates and depth of inspiration between controls and ITD-treated animals. Under these conditions it would therefore be difficult, if not impossible, to maintain the same depth of anesthesia with the same amount of inhaled anesthetic. We chose propofol, therefore, to enable the pigs to breathe spontaneously, yet remain anesthetized using the same infusion rate of anesthetic between groups. Thus, while both groups received the same dose and type of anesthetic, it is possible that the propofol was a confounding variable.

The study limitations include the fact that we could not blind the study. We used a fixed volume, controlled bleeding model and our results should not be generalized in uncontrolled bleeding settings. Second, the work of breathing^{20,21} was not measured in this study. It has been measured in humans using the ITD and was found to be equivalent to doubling the work of normal breathing.²² Although an increase in the work of breathing with the use of ITD is a potential concern, at least in this pig model and in human volunteers it was well tolerated.¹ Third, we did not measure sympathetic activity. However, it has been recently shown that the inspiratory impedance resets the operational point for systolic blood pressure on

the baro-reflex stimulus-response relationship in healthy subjects.²³ The resetting of the cardiac baro-reflex allows blood pressure to increase without a reflex-mediated reduction in HR.²³ Finally we measured intratracheal pressures as a surrogate for intrathoracic pressures.

Conclusions

In the setting of hypovolemic hypotension and the absence of available intravenous fluids, use of the ITD (−10 cm H₂O) in spontaneously breathing pigs resulted in a sustained increase in blood pressure and an improvement in short-term survival rates without significant hypoxia or neurological impairment.

Disclosure

Keith G. Lurie is a co-inventor of the inspiratory threshold device and founded a company, Advanced Circulatory Systems, Inc., to develop this device.

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