

RESEARCH PAPER

Cardiopulmonary effects of a new inspiratory impedance threshold device in anesthetized hypotensive dogs

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Abstract

Objective To compare the hemodynamic and respiratory effects of an inspiratory impedance threshold device (ITD) in anesthetized normotensive and hypotensive dogs.

Study design Prospective randomized study.

Animals Ten adult dogs.

Methods Dogs were anesthetized with propofol followed by isoflurane. During spontaneous ventilation, tidal volume (\dot{V}_T), systolic (SAP), mean (MAP) and diastolic arterial blood pressure, central venous pressure, gastric PCO_2 as an indicator of gastric perfusion, subcutaneous oxygen tension, subcutaneous blood flow, cardiac index (CI), systemic vascular resistance and blood lactate were monitored. To monitor respiratory compliance (RC) and resistance (ResR), animals were briefly placed on mechanical ventilation. Dogs were studied under four different conditions: 1) normotension (MAP > 60 mmHg) with and without the ITD and 2) hypotension (target MAP = 40 mmHg) with and without ITD. These four conditions were performed during one anesthetic period, allowing for stabilization of parameters for each condition. Data were analyzed by ANOVA repeated measure mixed models.

Results No cardiovascular changes were detected between no ITD and ITD in the normotensive state. During hypotension, CI was higher with the ITD ($5 \pm 1.0 \text{ L minute}^{-1} \text{ m}^{-2}$) compared with no ITD ($4 \pm 1.3 \text{ L minute}^{-1} \text{ m}^{-2}$). During hypotension, SAP was increased with ITD ($80 \pm 14 \text{ mmHg}$) versus without ITD ($67 \pm 13 \text{ mmHg}$). There was an increase in ResR and decreased RC with the ITD in both normotensive and hypotensive state.

Conclusion and clinical relevance Impedance threshold device in dogs during isoflurane-induced hypotension improved CI and SAP but had negative effects on RC and ResR.

Keywords anesthesia, cardiac output, dog, hypotension, impedance threshold device.

Introduction

Cardiac output (\dot{Q}_t) is defined as the volume of blood delivered per minute by the heart. A reduction in pleural pressure (negative intrathoracic pressure) increases systemic venous return, ventricular preload and improves \dot{Q}_t (Cournand et al. 1948; Guyton et al. 1957).

An inspiratory impedance threshold device (ITD) is a non-invasive, disposable, small plastic device composed of a one-way valve and a set opening pressure that fits on the ET tube. It creates a

momentary airway resistance and therefore, augments negative intrathoracic pressure and improves venous return (Lurie et al. 2001). Currently, two types of ITD are commercially available: the *ResQPod* and the *ResQGard*.

The *ResQPod* was the original ITD and possess a high cracking pressure (-10 cmH₂O). It was designed to improve venous return during cardiopulmonary resuscitation (Lurie et al. 2000, 2003). The *ResQGard* is a new ITD designed with a lower cracking pressure (-7 cmH₂O) to be used in spontaneously breathing patients (Lurie et al. 2003). The effects of this ITD (*ResQgard*) have not been objectively assessed in dogs.

The ITD has been shown to improve systolic blood pressure, cardiac index (CI) and stroke volume (SV) in a hemorrhagic hypovolemic, hypotensive porcine shock model (Marino et al. 2004). However, during anesthesia, there are reasons aside from hypovolemia and hemorrhage that can lead to hypotension (Gaynor et al. 1999). Administration of isoflurane induces a reliable dose-dependent hypotension by causing vasodilation and myocardial depression (Stoelting & Miller 2007). Hypotension is one of the most frequent complications in canine anesthesia (Gaynor et al. 1999). A recent survey determined that 37.9% of dogs under general anesthesia had an episode of severe hypotension (Redondo et al. 2007). If not treated, hypotension can lead to a decrease in tissue perfusion and ultimately end-organ failure. An ITD device could be useful for the treatment of hypotension during anesthesia and in the immediate postoperative recovery period while a patient is still intubated. To the best of the authors' knowledge, this is the first study to use ITD in isoflurane-induced hypotension.

The objective of this study was to determine the effect of the new ITD on hemodynamic variables, respiratory variables, subcutaneous blood flow and gastric blood flow in normotensive and hypotensive anesthetized dogs.

Materials and methods

This study was approved by the University of Florida Institutional Animal Care and Use Committee.

Animals

Ten healthy cross-breed dogs were used in this study. Dogs enrolled in this study were older than 1 year of age and were healthy based on physical

examination, complete blood count and blood chemistry profiles. Animals were fasted for 12 hours prior to each experiment but had free access to water.

Animal preparation

A 20-gauge, 1-inch-length catheter was aseptically placed in the cephalic vein and anesthesia was induced with intravenous propofol (Propofol; Abbot Animal Health, IL, USA) to effect (calculated dose 12 mg kg⁻¹). An endotracheal tube was placed and the cuff inflated to eliminate air leak around the tube at 20 cmH₂O. Anesthesia was maintained with isoflurane (Isoflo; Abbott Animal Health, IL, USA) vaporized in oxygen and delivered via a circle system. Animals were placed in right lateral recumbency. All dogs received intravenous crystalloid solution (lactated Ringer's solution; Baxter Health Care, IL, USA) at 5 mL kg⁻¹ hour⁻¹. A 7-Fr 30-cm, double lumen catheter (Mila International Inc, CO, USA) was placed in the jugular vein and its tip directed to the junction of the cranial vena cava and right atrium. Length of the catheter was pre-measured (mid neck to RA chamber) and placement confirmed by the pressure waveform. A 20-gauge, 1.88-inch catheter was placed in the right medial metatarsal artery. Animals were allowed to breathe spontaneously throughout the experiment and were mechanically ventilated only for the determination of respiratory compliance (RC) and respiratory resistance (ResR). The ventilator setting attempted to mimic the patients' respiratory rate and tidal volume (\dot{V}_T). The ventilator was set at volume control with a respiratory pause; RR and \dot{V}_T equal to each of the patients' spontaneous breathing pattern. The pressure difference measured between two Pitot tubes facing in opposite directions during inspiration and expiration was used to calculate air flow velocity, \dot{V}_T , RC and ResR (Spirometry 88956 Kit; Datex-Ohmeda, MA, USA) with atmospheric pressure as the comparison pressure. Three to four breath cycles were usually needed to measure RC and ResR. Animals were instrumented (AS/5 Monitor; Datex-Ohmeda) for continuous monitoring of end-tidal CO₂ (P_E'CO₂), end-tidal isoflurane (E'ISO), \dot{V}_T , direct systolic, mean, diastolic arterial pressure (SAP, MAP, DAP respectively), central venous pressure (CVP), heart rate (HR) and respiratory rate (f_R). Blood lactate, hemoglobin, arterial and central venous blood-gas and oxyhemoglobin content were also measured (ABL 660 COxymeter and Blood

Gas Analyzer; Radiometer Inc, Denmark). Rectal temperature was maintained between 37 and 38 °C with the help of a circulating, warm water blanket.

Cardiac output was measured by the LidCO-lithium-dilution method (LidCOplus; LidCO Limited, UK). Lithium chloride (0.003 mmol kg⁻¹) was injected IV via the central vein. \dot{Q}_t was derived from the concentration *versus* time curve (LidCO CM 31-01; LidCO Limited) as described elsewhere (Corley et al. 2002). Animals' SV and systemic vascular resistances (SVR) were calculated by the LidCO computer. The SV was calculated as $\dot{Q}_t / \text{HR} \times 1000$ and SVR was calculated as $\{(\text{MAP} - \text{CVP}) \times 80\} / \dot{Q}_t$. Each dog's height (cm) was determined by measuring from the tip of the nose to the anus (Cowgill & Drabkin 1926). Body surface area (BSA) was determined by the modified DuBois equation: $\text{BSA (m}^2) = 0.0072 \text{ Height (cm)}^{0.725} \times \text{Weight (kg)}^{0.425}$. \dot{Q}_t was divided by BSA to calculate CI.

To evaluate peripheral perfusion, a tissue flow sensor (Oxylite oxygen and microvasculature flow probe; Oxylab Inc., UK) was placed subcutaneously in the flank area of the animal. The oxygen tension sensors are based on optical fluorescence technology for continuous quantitative monitoring of regional PaO₂ in mmHg. The tissue flow sensors are based on laser Doppler flowmetry technology for real time monitoring of tissue blood perfusion in units of blood flow (UBF). Both sensors are incorporated in one 20-gauge catheter. The Oxylite flow probe catheter allowed real time continuous monitoring of subcutaneous oxygen tension (SCTO₂) and subcutaneous microvascular tissue flow (SCBF).

A gastric tonometry catheter (Datex Naso-gastric Tonometry Catheter; Datex-Ohmeda) was inserted by mouth into the gastric cavity to estimate visceral blood perfusion (GBF). The length of the tube was pre-measured (tip of the nose to the stomach) and the gastric tonometry tube was placed blindly. Gastric tonometry estimates mucosal perfusion by measuring the amount of CO₂ produced by the gastric mucosa (Cerny & Cvachovec 2000; Sanchez et al. 2008). The rationale for this approach is that inadequate oxygen delivery to the stomach results in an increase of lactic acid and gastric CO₂ formation. Increased CO₂ indirectly reflects a decrease in tissue perfusion (Grum et al. 1984; Cerny & Cvachovec 2000; Sanchez et al. 2008). The gastric-to-arterial carbon dioxide gap reflects the mucosal blood supply to metabolic demand balance and is considered a marker of gastric perfusion (Cerny & Cvachovec

2000). The gastric tonometry module was calibrated using a CO₂ calibration gas of known concentration 5% (Datex-Ohmeda).

Experimental protocol

After instrumentation, dogs were evaluated during two arterial blood pressure (AP) states. A hypotensive state was obtained by titrating e¹ISO until MAP was stable at approximately 40 mmHg. For the normotensive state, isoflurane was titrated until MAP was >60 mmHg. For each blood pressure state, animals were maintained at that hemodynamic plane for 10 minutes prior to data collection. At each state, measurements were performed in duplicate with at least 3 minutes between measurements. If any two measurements for a given method varied by more than 20%, a third measurement was taken and the measurement outside the 20% variation was discarded. Cardiopulmonary variables, lactate, gastric tonometry and peripheral perfusion were recorded with and without the ITD in place. Animals were kept in a normotensive state first and then a hypotensive state was induced. A random number generator (1–2) determined the order of treatment (ITD *versus* no ITD). All animals received both treatments at each BP state.

Statistical analyses

Data were analyzed by ANOVA for repeated measures determined by least square analysis of variance, using the General Linear Modules procedures of SAS (SAS for Windows, version 9.3; SAS Institute Inc, NC, USA). For all analyses, $p < 0.05$ was considered significant. Data are expressed as mean \pm SD.

Results

A total of 10 dogs were used. Body weight ranged from 18.5 to 31 kg, with a mean of 22.40 ± 4.20 kg, dose of propofol used at induction was 9.7 ± 7.8 mg kg⁻¹. To determine \dot{Q}_t by LidCO, a total 0.8 ± 0.2 mmol of lithium chloride was used and the estimated total blood withdrawal was 152 ± 46 mL per dog. End-tidal isoflurane in the normotensive state was $1.1 \pm 0.2\%$ and e¹ISO required to induce hypotension was $2.4 \pm 0.2\%$.

There were no significant changes in any of the hemodynamic parameters [SAP/MAP/DAP, CVP, CI, HR, SVR, SV, SVR, GBF, subcutaneous oxygen tension (SCO₂) and SCBF] when using the ITD was

compared to no ITD in normotensive, anesthetized dogs (Tables 1 & 2). However, there was a significant increase in respiratory resistance (2.6 ± 0.7 versus 14.1 ± 1.6 cmH₂O L⁻¹ second⁻¹) $p < 0.01$ and compliance (33.2 ± 5.7 versus 16.1 ± 5 mL cmH₂O⁻¹) $p < 0.01$ with the ITD versus without, in normotensive dogs.

When normotensive dogs were compared to hypotensive dogs without ITD there was a significant decrease in SAP (100 ± 10 versus 67 ± 13 mmHg), MAP (62 ± 6 versus 46 ± 6 mmHg), DAP (52 ± 8 versus 35 ± 6 mmHg), CI (5 ± 1.2 versus 4 ± 1.3 L minute⁻¹ m⁻²) and SCBF (415 ± 280 versus 275 ± 140 UBF).

The use of ITD significantly increased CI by 19.5% (4 ± 1.3 versus 5 ± 1 L minute⁻¹ m⁻²) $p = 0.03$ (Table 1 & Fig. 1) and SAP by 15.6% (67 ± 13 versus 80 ± 14 mmHg) $p = 0.02$ in comparison to no ITD in the hypotensive state. Heart rate and SVR did not change significantly. There was a significant increase in respiratory resistance (3.2 ± 0.5 versus 14.2 ± 1.8 cmH₂O L⁻¹ second⁻¹) $p = 0.02$ and a decrease in compliance (27.0 ± 4.9 versus 12.6 ± 1.8 mL cmH₂O⁻¹) $p < 0.01$ with the ITD.

Discussion

The use of the ITD during spontaneous ventilation enhanced systolic arterial blood pressure and CI in anesthetized, hypotensive dogs. The improvement in CI was likely secondary to improved venous return and/or improved contractility as there was no change in SVR or heart rate. An ITD can improve venous return but does not dramatically change

vascular tone and SVR (Lurie et al. 2003). Diastolic blood pressure is in large influenced by changes in arterial tone and SVR (Guyton & Hall 1996). This in part explains why the use of the ITD significantly increased SAP but not DAP.

This study did not detect a change in GBF using gastric tonometry. Gastric tonometry is still a controversial method to assess visceral blood perfusion (Uusaro et al. 1995). Despite this, it is still widely used in humans as an assessment of intestinal mucosal perfusion (Grum et al. 1984; Cerny & Cvachovec 2000) and splanchnic perfusion (Masai et al. 2003). Two conclusions can be drawn out of this finding. One is that ITD improved central blood flow but not less vital organ (viscera) blood flow. A second explanation would be that gastric tonometry technology was not sensitive enough to detect changes in GBF. Sanchez et al. (2008), when validating gastric tonometry in neonatal foals, commented on the high standard deviation depending on the diet and gastric pH of the animal. All dogs in this study were fed the same diet and were not on any medication that would alter stomach acid production, but gastric pH was not evaluated in the current study.

The ITD did not improve peripheral subcutaneous perfusion. There was a high standard deviation seen in both SCBF, SCTO₂. As with GBF measurement, lack of change in SCBF and SCTO₂ can be a real finding or a technological problem. The oxygen/flow probe used in this study has been validated *in vitro* using rodent tissue (Braun et al. 2001) and has been successfully used in dogs before (Brurberg et al. 2005) but to the authors' knowledge, it has not yet been validated in this species. That said, the

Table 1 Comparison of cardiovascular variables: heart rate (HR) in bpm, direct systolic, mean, diastolic arterial pressure (SAP, MAP, DAP respectively) in mmHg, central venous pressure (CVP) in mmHg, cardiac index (CI) in L minute⁻¹ m⁻², systemic vascular resistance (SVR) in dynes seconds cm⁻⁵, stroke volume (SV) in mL minute⁻¹ and blood lactate concentration (Lactate) in mmol L⁻¹ studied under four different conditions: 1) normotension without impedance threshold device (Normal AP no ITD), 2) Normal AP with ITD (Normal AP ITD), 3) hypotension without impedance threshold device (Low AP no ITD), and 4) low AP with ITD (Low AP with ITD)

Treatment	HR	SAP*†	MAP*	DAP*	CVP	CI*†	SVR	SV	Lactate
Normal AP no ITD	96 ± 17	100 ± 10	62 ± 6	52 ± 8	-0.4 ± 2	5.1 ± 1.2	1410 ± 455	36 ± 9	0.5 ± 0.3
Normal AP ITD	95 ± 17	109 ± 7	67 ± 6	52 ± 5	-2 ± 2	5.5 ± 2.0	1343 ± 254	38 ± 8	0.4 ± 0.3
Low AP no ITD	102 ± 7	67 ± 13	46 ± 6	35 ± 6	2 ± 3	4.0 ± 1.3	1152 ± 422	29 ± 9	0.7 ± 0.6
Low AP ITD	100 ± 11	80 ± 14	52 ± 7	40 ± 5	1 ± 3	4.9 ± 0.9	1022 ± 228	33 ± 7	0.9 ± 0.7

*Statistical significance between condition (Normal AP versus Low AP); †statistical significance between treatment (ITD versus no ITD) in low AP state with $p < 0.05$.

Table 2 Comparison of the variables: respiratory rate (f_R) in bpm, end-tidal CO_2 ($PE'CO_2$) in mmHg and kPa, end-tidal volume (\dot{V}_T) in mL, respiratory resistance (RRes) in $cmH_2O L^{-1} second^{-1}$, respiratory compliance (RC) in mL cmH_2O^{-1} , subcutaneous oxygen tension (SCO_2) in mmHg, subcutaneous blood flow (SCBF) in units of blood flow (UBF), gastric CO_2 tonometry (GBF) in mmHg and arterial oxygen tension (PaO_2) in mmHg and kPa in studied under four different conditions: 1) normotension without impedance threshold device (Normal AP no ITD), 2) hypotension without impedance threshold device (Low AP no ITD), and 3) hypotension without impedance threshold device (Low AP with ITD) (Low AP with ITD)

Treatment	f_R	$PE'CO_2$	$PE'CO_2$ (kPa)	\dot{V}_T	RC [†]	RRes [†]	SCO_2	SCBF*	GBF	PaO_2	PaO_2 (kPa)
Normal AP no ITD	14 ± 8	46 ± 4	6.1 ± 0.5	250 ± 79	33 ± 6	2.6 ± 0.7	67 ± 16	415 ± 280	8 ± 2	520 ± 78	69.3 ± 10.4
Normal AP ITD	15 ± 6	46 ± 7	6.1 ± 0.9	239 ± 67	16 ± 5	14.1 ± 1.6	73 ± 25	670 ± 654	7 ± 2	495 ± 108	65.9 ± 14.4
Low AP no ITD	8 ± 4	58 ± 6	7.7 ± 0.8	239 ± 68	27 ± 5	3.2 ± 0.50	57 ± 21	275 ± 140	12 ± 10	498 ± 104	66.4 ± 13.8
Low AP ITD	10 ± 5	60 ± 8	7.9 ± 1.0	236 ± 82	13 ± 2	14.2 ± 1.9	55 ± 22	422 ± 338	9 ± 3	471 ± 116	66.8 ± 14.5

*Statistical significance between conditions (Normal AP versus Low AP); †statistical significance between treatments (ITD versus no ITD) with $p < 0.05$.

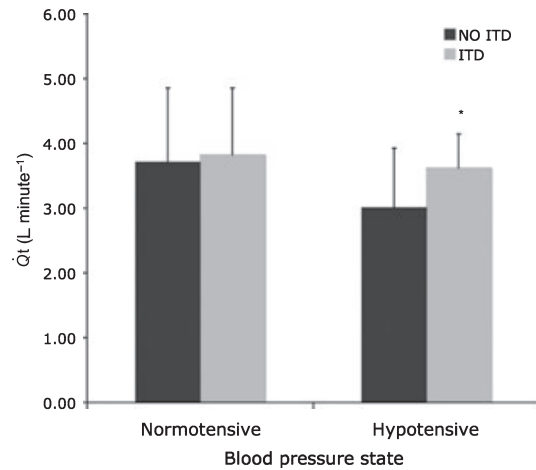


Figure 1 Changes in cardiac output ($L\ minute^{-1}$) expressed as mean and SD at normotensive state (normal BP) and hypotensive (low BP) in anesthetized dogs, with the impedance threshold device (ITD) and without (no ITD). *Statistical significance with $p < 0.05$.

laser Doppler should have been able to detect subcutaneous blood-flow changes very easily, if there were any.

This investigation suggests that the ITD does not improve hemodynamic values in normotensive, euvoletic patients. This is in disagreement with work carried out by Lurie et al. (2004) in which ITD improved blood pressure in normotensive pigs. The type of ITD used by the investigators may explain this discrepancy. Lurie's study (2004) used an ITD with a high cracking pressure (-12 and -20 cmH_2O) and this study opted to use an ITD with only -7 cmH_2O cracking pressure. The effect of a high cracking pressure ITD in dogs may be interesting to evaluate in the future.

The results in our study are in agreement with work carried out by Marino et al. (2004) and by Sigurdsson et al. (2006) in which the use of an ITD resulted in a rapid increase in CI and blood pressure in the hypotensive state. This study evaluated ITD for a short period of time (at least 10 minutes in each state). The improvement in blood pressure and CI may be temporary, but would allow the clinician time to institute a more definitive therapy (inotropes or fluid therapy) to correct hypotension. The physiologic benefit of the impedance valve is due to a decrease in intrathoracic pressure resulting in enhancement of venous return, and consequently SV, CI and finally systemic blood pressure (Marino et al. 2004).

This study shows that spontaneously ventilating patients breathing through an ITD will encounter increased resistance during inspiration resulting in decreased chest compliance and increased work of breathing (WOB) (Idris et al. 2007). For an ITD to be clinically useful, the effort for breathing through the device should not demand excessive WOB (Idris et al. 2007). The WOB is divided into three phases: work required to expand the lung against its elastic forces (lung compliance work), to overcome viscosity of the lung and chest wall (tissue resistance work) and to overcome airway resistance during the movement of air into the lungs (airway resistance work) (Stoelting & Miller 2007). In general, respiratory fatigue occurs when energy demand (oxygen consumption and blood flow) exceeds energy supply. For the ITD to be useful, the energy required for its operation should not exceed the patient's available energy reserves. Subjective observation in this study noticed that the animals would breathe with more abdominal effort when ITD was in place but we did not detect signs of decreased minute ventilation ($\dot{V}_T \times f_R$) or muscle fatigue (hypoventilation) when ITD was compared to no ITD. Animals were breathing through the ITD for a short period of time and this might have not been enough to induce muscle fatigue. Because the energy available for breathing can be significantly diminished in ill and injured patients, ITD should be avoided in animals with pulmonary disease, respiratory distress or any compromise to the chest wall integrity. If ITD is to be used, it is important that signs of ventilation and muscle fatigue be monitored and this device should be removed as soon as the patient is unable to adequately ventilate (Lurie et al. 1998), as indicated by hypercapnia and decrease in \dot{V}_T . Additionally, use of an ITD could lead to pulmonary overperfusion and decompensate or exacerbate pre-existing congestive heart failure.

There are limitations to this study: long-term organ function, including neurologic function after recovery was not assessed. Additionally, \dot{Q}_t was determined by lithium dilution and not pulmonary thermodilution (TD). The pulmonary TD method has been accepted as the gold standard for \dot{Q}_t monitoring for many years (Corley et al. 2002; Tibby & Murdoch 2003). However, measurement of \dot{Q}_t via lithium-dilution closely compares with TD (Chen et al. 2005), and is currently one of the most commonly used method in anesthetized dogs (Chen et al. 2005; Cooper & Muir 2007). We controlled variables that could have affected the hemodynamic

status of the dogs to minimize their effects on our results. Hemoglobin concentration, important for LIDCO determinations, varied minimally despite the blood loss invariably associated with this technique. Blood loss associated with arterial blood withdrawal for \dot{Q}_t determination was minimal and estimated at <5% total blood volume. Likewise, the total mean cumulative dose of lithium administered was low ($0.029 \pm 0.005 \text{ mmol kg}^{-1}$), and should not have affected our results (Corley et al. 2002; Mason et al. 2002).

By augmenting the negative intrathoracic pressure, ITD increases venous return and diastolic filling volume (preload) (Guyton et al. 1957). In theory, this negative intrathoracic pressure may also produce counteracting forces during systole (increase in afterload) and decrease contractility (Braunwald et al. 2001). This asynchronous effect is unlikely to cause a significant reduction in contractility, and the use of ITD did not decrease SV in our experiment. We did not measure real time beat-to-beat SV and cardiac compliance at each contraction cycle (systole and diastole). This would involve either the use of transesophageal echocardiogram (TEE) or use of flow/pressure probe to determine aortic impedance. Aortic impedance is the aortic pressure divided by aortic flow at the instance (Braunwald et al. 2001) and is a more accurate measure of the afterload at each contraction cycle. Neither option was available at the time of the experiment. Further studies looking at the ITD effect on real time beat-to-beat contractility and aortic impedance would be beneficial.

This model was very effective in producing euvolemic hypotension in dogs, but pH, lactate and mixed venous saturation remained normal during the low AP phase. Thus, the model was able to produce hypotension but not able to induce global tissue hypoxia and shock. Although there are no theoretical reasons that the impedance device will not work in a clinical hypotension setting (Marino et al. 2004), further study is needed to validate its use in different clinical situations in dogs.

In conclusion, the ITD not only improved CI and blood pressure in hypotensive dogs but also increased respiratory resistance and compliance. Each individual case will need to be evaluated to ensure that the advantages gained by improving cardiovascular function are balanced against negative effects on respiratory function. Further studies are needed to evaluate the benefits of ITD in veterinary medicine under a wide variety of conditions.

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