''Fluidless'' resuscitation with permissive hypotension via impedance threshold device therapy compared with normal saline resuscitation in a porcine model of severe hemorrhage

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BACKGROUND: One approach to improve outcomes after trauma and hemorrhage is to follow the principles of permissive hypotension by avoiding intravascular overpressure and thereby preventing dislodgement of platelet plugs early in the clotting process. We hypothesized that augmentation of negative intrathoracic pressure (nITP) by treatment with an impedance threshold device would improve hemodynamics without compromising permissive hypotension or causing hemodilution, whereas aggressive fluid resuscitation with normal saline (NS) would result in hemodilution and SBPs that are too high for permissive hypotension and capable of clot dislodgement.

METHODS: Thirty-four spontaneously breathing anesthetized female pigs (30.6 ± 0.5 kg) were subjected to a fixed 55% hemorrhage over 30 minutes; block randomized to nITP, no treatment, or intravenous bolus of 1-L NS; and evaluated over 30 minutes. Results are reported as mean ± SEM.

RESULTS: Average systolic blood pressures (SBPs) (mm Hg) 30 minutes after the study interventions were as follows: nITP, 82.1 ± 2.9; no treatment, 69.4 ± 4.0; NS 89.3 ± 5.2. Maximum SBPs during the initial 15 minutes of treatment were as follows: nITP, 88.0 ± 4.3; no treatment, 70.8 ± 4.3; and NS, 131 ± 7.6. After 30 minutes, mean pulse pressure (mm Hg) was significantly higher in the nITP group (nITP, 32.3 ± 2.2) versus the no-treatment group (21.5 ± 1.5 controls) ($p < 0.05$), and the mean hematocrit was 25.2 ± 0.8 in the nITP group versus 19 ± 0.6 in the NS group ($p < 0.001$).

CONCLUSION: In this porcine model of hemorrhagic shock, nITP therapy significantly improved SBP and pulse pressure for 30 minutes without overcompensation compared with controls with no treatment. By contrast, aggressive fluid resuscitation with NS but not nITP resulted in a significant rise in SBP to more than 100 mm Hg within minutes of initiating therapy that could cause a further reduction in hematocrit and clot dislodgment. (*J Trauma Acute Care Surg*. 2013;75: S203–S209. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Hemorrhage; shock; intrathoracic pressure; impedance threshold device; permissive hypotension.

Human studies have demonstrated that aggressive fluid administration for treatment of prehospital trauma results in increased blood loss and mortality.[1,2] This has resulted in a shift in the clinical paradigm toward "hypotensive resuscitation." The objective of hypotensive resuscitation for the treatment of traumatic injury and hemorrhage shock is to maintain vital organ perfusion while avoiding intravascular overpressure that can cause increased hemorrhage and disruption of early platelet-fibrin clots.[3,4] This guiding principle, also termed *permissive hypotension*, has been examined in several animal models of uncontrolled hemorrhagic shock.[5–7] The results support the conclusion that hypotensive resuscitation to a systolic blood pressure (SBP) of no greater than 90 mm Hg to 100 mm Hg and a mean arterial pressure (MAP) of approximately 60 mm Hg will increase survival, reduce blood loss, increase hematocrit, and improve oxygen delivery as compared with animals treated with a target MAP value of 80 mm Hg.[2,5–8]

Recently, the investigators developed a new therapy to enhance circulation by augmenting negative intrathoracic pressure (nITP) in spontaneously breathing hypotensive patients. With each inspiration, this treatment harnesses the physiologic principles of breathing by enhancing venous blood flow back to the heart, increasing cardiac output and cerebral perfusion, and lowering intracranial pressures (ICP). This therapy is delivered with a simple-to-use device, the impedance threshold device (ITD). The ITD has a spring-loaded diaphragm that requires a certain threshold ("*cracking pressure*") before it opens to allow airflow during inspiration, thus functioning like a partial Mueller maneuver to augment nITP.[9] It has minimal expiratory resistance. In the spontaneously breathing patient, this device causes inspiratory resistance and creates a small vacuum within the chest, drawing blood from the extrathoracic venous system into the heart each time the patient takes a breath.[10–14] Treatment with nITP results in an immediate increase in systolic and diastolic blood pressure and improves vital organ perfusion.

There are several different ways to deliver this nITP therapy. One form of the ITD was initially used to increase myocardial and cerebral blood flow during cardiac arrest and cardiopulmonary resuscitation.[15] Subsequently another design of the ITD was shown to improve hemodynamics and organ perfusion in large animal models of hemorrhagic shock.[9,16,17] Physiologic

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improvements in hemodynamics have more recently been reported when the ITD was used in adult human volunteers with induced hypovolemia and in patients with hypotension.[10,13,14,18] One of the concerns raised by some clinicians about this new therapy is whether the ITD will increase blood pressure to such an extent that it could "pop the clot" in someone with hypotension secondary to recent trauma.

In this study, we hypothesized that nITP therapy would improve SBP in a porcine model of severe hemorrhage but at the same time achieve the goal of maintaining permissive hypotension. By contrast, we hypothesized that intravenous fluid therapy would improve SBPs but generate SBP levels that are too high for permissive hypotension and thus capable of clot dislodgement. While a number of adult animal and human studies have been performed with the ITD for the treatment of hypotension secondary to blood loss, its effect has never been directly compared with aggressive fluid replacement.

MATERIALS AND METHODS

The study was performed in compliance with the Institutional Animal Care Committee of the Minneapolis Medical Research Foundation at Hennepin County Medical Center, the 1996 Guide for the Care and Use of Laboratory Animals by the National Research Council, the USDA Animal Welfare Act, PHS Policy, and the American Association for Accreditation of Laboratory Animal Care.

Yorkshire crossbreed domestic pigs received intramuscular ketamine HCl (Ketaset, Fort Dodge Animal Health, Fort Dodge, IA) for initial sedation. The animals were anesthetized, the trachea was intubated with a 6.0 Fr cuffed tracheal tube, and the cuff was inflated to eliminate air leaking around the tube. During the preparatory phase, animals were anesthetized with 2% isofluorane and mechanically ventilated with room air using a positive-pressure ventilator (NarkoMed 2A, North American Drager, PA). It was discontinued at the end of this phase. The ventilator rate and tidal volume were adjusted to maintain an end-tidal CO_2 of 40 mm Hg. The depth of anesthesia was assessed by hoof withdrawal, tail pinch response, and canthal reflexes. Animals were placed in the supine position. Right atrial and aortic pressures were measured using a 5 Fr Millar micromanometer catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX) placed in the right internal jugular vein and the left femoral artery, respectively. An intracranial bolt was inserted into the animal's right hemisphere and ICPs were measured with a 3.5 Fr micromanometer pressure transducer (Mikro-Tip Transducer, Millar Instruments, Inc., Houston, TX). Cerebral perfusion pressure was calculated as the difference between the aortic pressure and ICP. The right femoral artery was used for arterial blood gas measurements and blood withdrawal. All animals were treated with heparin (100 U/kg intravenously administered) as a single bolus once catheters were in place. Continuous electrocardiographic monitoring was recorded with a lead II electrocardiogram. Intrathoracic pressures (intratracheal) were measured continuously with a micromanometer-tipped catheter positioned 2 cm below the tip of the endotracheal tube. Carotid artery flow was measured using an ultrasound flow probe attached to the internal carotid artery (Transonic Systems, Ithaca, NY). Intratracheal pressure, aortic pressure, right atrial pressure, ICP, carotid artery flow, and electrocardiograms (ECG) were digitized by a digital recording system (Biopac Systems Inc., Goleta, CA). Respiratory data were recorded continuously (CO2SMO Plus, Novametrix Medical Systems, Wallingford, CT). Rectal temperatures were maintained between 37.5°C and 38.5°C using a warming blanket. Intravenous access with an 18-gauge catheter was obtained through a lateral ear vein.

After the preparatory phase, the animals remained sedated but were allowed to breathe spontaneously with propofol anesthesia (PropoFlo, Abbott Laboratories, Chicago, IL), which was delivered as an intravenous infusion at a rate of 100 μg/kg per minute (propofol pump, model AS20GH-2, Baxter Healthcare, Hooksett, NH). This dose was further titrated to target spontaneous respiratory rates of 15 breaths per minute to 25 breaths per minute and oxygen saturation greater than 95%, within prospectively set parameters of heart rate (100–170 beats/min), mean arterial blood pressure (65–85 mm Hg), pH (7.35–7.45), P_{CO_2} (40–45 mm Hg), and P_{O_2} (100–200 mm Hg). Once the animals were able to maintain normal oxygenation within these parameters without mechanical ventilator support for 10 minutes, the study was initiated. The propofol infusion rate was decreased stepwise from 100 μg/kg per minute to 20 μg/kg per minute during the controlled hemorrhage and then increased to 60 μg/kg per minute during the study. If respiratory rate decreased to less than 10 breaths per minute, the propofol infusion was stopped while continuously monitoring for any signs of inadequate depth of anesthesia.

Experimental Protocol

With the use of a fixed bleed model, pigs were hemorrhaged to 55% of their calculated intravascular blood volume over 30 minutes (approximately 35 mL/min) (Easy Load II pump, Masterflex L/S, model 7523–50, Cole-Palmer Instrument, Barrington, IL), allowed to recover for 10 minutes and then randomized for 30 minutes to either no treatment (control), an ITD with a fixed 7 cm H_2O of inspiratory resistance, or 1 L of normal saline (NS) infused over 5 minutes. In pilot studies, it was recognized that no animals with a venous oxygen saturation (SvO_2) of less than 14% measured 10 minutes after the bleed could survive the hemorrhage protocol. As such, in this study, only animals with a SvO_2 of greater than 14% measured 10 minutes after the bleed were evaluated. Hemodynamic variables measured included heart rate, blood pressure (systolic, diastolic, and mean), pulse pressure, ICP, and right atrial pressure. Respiratory variables included descending aorta arterial and internal jugular venous blood gas measurement (mixed venous saturation from venous blood gas measured at the superior vena cava–right atrium junction), systemic arterial oxygen saturation, respiratory rate, expiratory tidal volume, and intratracheal pressure. Results are reported as mean ± SEM unless otherwise indicated. The primary study end point was a comparison between SBPs between the three groups 15 minutes after the study intervention was implemented. Statistical comparisons were made using one-way analysis of variance tests and unpaired *t* tests. A $p < 0.05$ was considered statistically significant. The study was powered by assuming that a sample size of 12 in each group has an 80% power to detect a difference between SBP means of 9.60 with a significance level (α) of 0.05 (two tailed).

RESULTS

After randomization, the number of animals per group and their respective weights were as follows: 12 pigs (31.0 ± 0.8 kg) in the nITP group, 12 pigs (30.7 ± 0.7 kg) in the no-treatment control group, and 10 pigs (29.6 ± 1.1 kg) in the NS group. Baseline as well as postbleed/pretreatment heart rate, blood pressure, base excess levels, and arterial blood gas parameters were similar between groups.

To test the primary hypothesis, we measured maximum SBP (mm Hg) during the initial 15 minutes of treatment: values were significantly higher in the NS group compared with the nITP and control groups (control, 70.8 ± 4.3 vs. nITP, 88.0 ± 4.3 vs. NS, 131 ± 7.6 $p < 0.05$) (Fig. 1). The SBP rose more rapidly to peak levels and remained greater than 98 mm Hg for more than 5 minutes after saline was completely infused in the NS group when compared with the nITP therapy group and untreated controls. Furthermore, MAP remained greater than 80 mm Hg throughout this same period. This sustained elevation in SBP and MAP has a high potential for dislodging a clot.

Comparisons of mean values for the key hemodynamic parameters measured are shown in Figure 2. Pigs treated with nITP and NS had significantly improved mean SBP compared with controls (untreated) throughout the course of treatment. NS resulted in higher mean cerebral perfusion pressures at the 15-minute time point as well as higher ICP levels and SBP values compared with untreated controls.

An important secondary end point was the SBP and MAP after 30 minutes of therapy. The findings are as follows: MAP (mm Hg) was significantly higher in the nITP group (nITP, 32.0 ± 3.0 vs. controls, 21.7 ± 1.8; $p = 0.01$). Cardiac output was also significantly higher in the nITP group compared with the control group at 30 minutes (nITP, 2.5 ± 0.11 vs. controls, 2.1 ± 0.04; $p = 0.008$). Additional hemodynamic and respiratory parameters are reported in Table 1. Throughout the study, airway pressures were significantly lower during inspiration in the nITP group (nITP, −7.4 ± 0.2; control, 0.1 ± 0.5; NS, 0.1 ± 0.2; $p < 0.001$). The respiratory rates were significantly higher in the NS group (35 ± 4 vs. nITP, 25 ± 2 and control, 25 ± 2; $p < 0.05$ at 30 minutes). Arterial and venous blood gas variables and metabolic markers are shown in Table 2. Mean hematocrit (%) was significantly higher in the nITP group compared with the NS group (nITP, 25 ± 0.6 vs. NS, 18 ± 0.5 after 30 minutes of therapy; $p < 0.05$). Pulse pressures, shown in Figure 2 were significantly higher in the nITP-treated pigs after 30 minutes of use compared with the control group. By contrast, ICP values were significantly lower in the nITP group versus the NS-treated group at 15 minutes. It is noteworthy that the cerebral perfusion pressure (CerPP) was significantly higher in the NS and nITP treatment groups compared with the untreated controls. After 30 minutes, all of the pigs were alive in all of the treatment and control groups.

DISCUSSION

Results from this study using a swine model of hemorrhage demonstrate that nITP treatment significantly improved hemodynamic parameters and provided permissive hypotension compared with untreated controls. As hypothesized, after application of nITP therapy, the maximal SBP did not exceed baseline values and did not result in arterial blood pressures associated with clot disruption. In animals, this has been reported with a MAP of 64 ± 2 mmHg and a SBP of 94 ± 3 mmHg.[6] Conversely, conventional fluid resuscitation treatment resulted in a rapid elevation in SBP to levels considered dangerously high in the setting of acute trauma and hemorrhage.[1,19] The elevation in SBP was sustained and at a magnitude sufficient to potentially

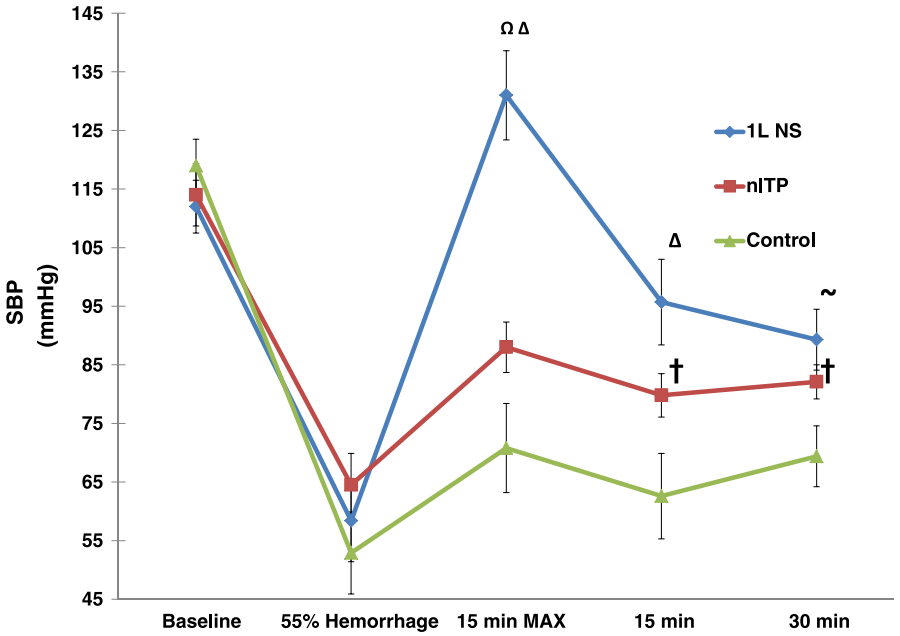

Figure 1. SBPs at baseline and during study. †$p < 0.05$ for control versus nITP, ~$p < 0.01$ for control versus NS, Δ$p < 0.001$ for control versus NS, Ω$p < 0.001$ for nITP versus NS.

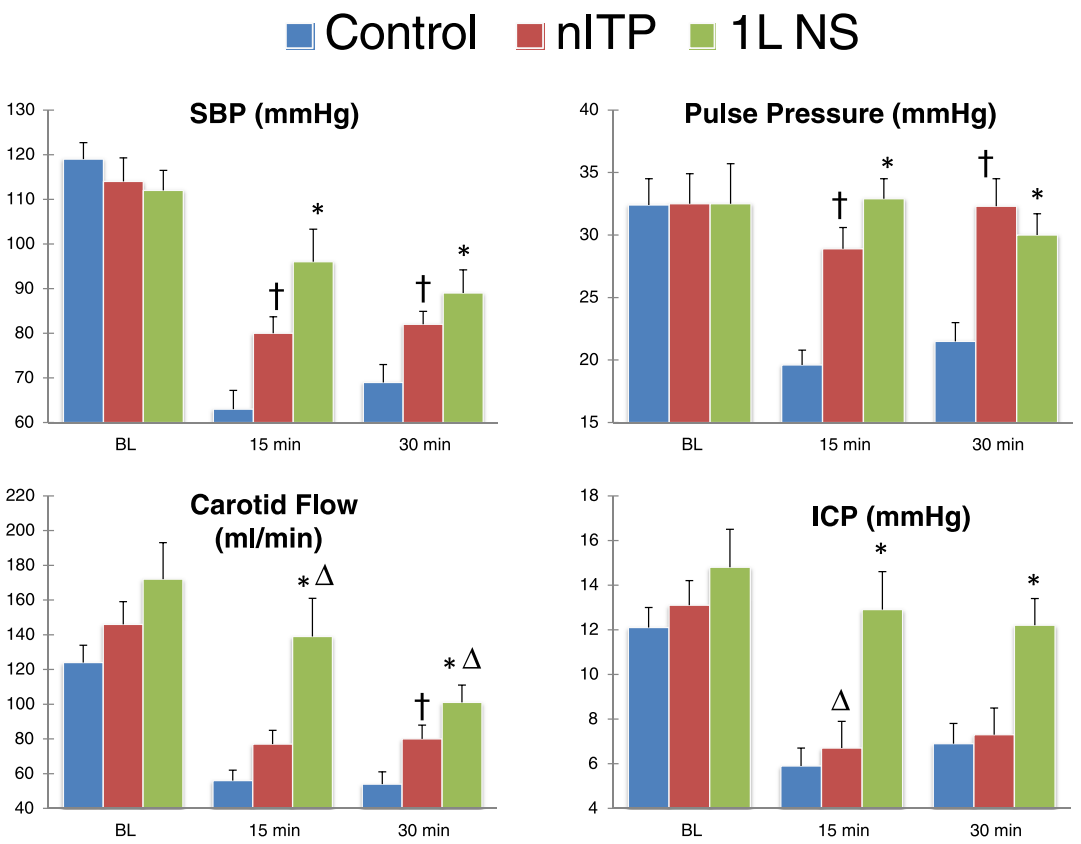

Figure 2. Key hemodynamic results. †$p < 0.05$ for control versus nITP, *$p < 0.05$ for control versus NS, Δ$p < 0.05$ for nITP versus NS.

TABLE 1. Additional Hemodynamic Results

	Treatment Group	Normovolemic Baseline	Postbleed Baseline	Intervention 15 min	Intervention 30 min
DBP	Control	86.4 ± 2.8	35.0 ± 4.3	43.1 ± 4.3	47.9 ± 4.6
	nITP	81.5 ± 4.8	41.1 ± 4.2	50.9 ± 3.5	49.7 ± 2.9
	NS	79.9 ± 5.1	37.3 ± 5.5	62.8 ± 7.0*	59.3 ± 5.4
MAP	Control	97.1 ± 2.9	41.0 ± 4.3	49.5 ± 4.3	55.0 ± 4.3
	nITP	92.4 ± 4.9	48.9 ± 4.6	60.5 ± 3.5	60.5 ± 2.7
	NS	90.8 ± 4.7	44.3 ± 5.9	81.8 ± 6.0**†	69.3 ± 5.3*
CerPP	Control	85.1 ± 3.4	35.8 ± 4.5	43.6 ± 4.7	48.1 ± 4.8
	nITP	79.2 ± 5.1	43.3 ± 4.6	53.8 ± 3.6	53.2 ± 3.0‡
	NS	76.4 ± 3.8	39.9 ± 6.2	62.0 ± 6.4*	58.0 ± 4.9**
HR	Control	101 ± 4	180 ± 13	196 ± 10	213 ± 5
	nITP	123 ± 11	194 ± 13	203 ± 11	208 ± 9
	NS	108 ± 7	180 ± 12	155 ± 14**†	166 ± 14†§
ITP (minimum)	Control	−0.1 ± 0.4	0.1 ± 0.4	0.1 ± 0.5	0.1 ± 0.5
	nITP	−0.1 ± 0.1	−0.6 ± 0.6	−7.4 ± 0.2‡	−7.4 ± 0.2‡
	NS	−0.2 ± 0.2	−0.2 ± 0.2	0.0 ± 0.3¶	0.1 ± 0.2¶

*$p < 0.05$ for control versus NS.
**$p < 0.001$ for control versus NS.
†$p < 0.01$ for nITP versus NS.
‡$p < 0.001$ for control versus nITP.
§$p < 0.01$ for control versus NS.
¶$p < 0.001$ for nITP versus NS.
CerPP, cerebral perfusion pressure; DBP, diastolic blood pressure; HR, heart rate; ITP, intrathoracic pressure; MAP, mean arterial pressure.

TABLE 2. Baseline and Study Blood Gas Results

	Treatment Group	Normovolemic Baseline	Postbleed Baseline	Intervention 15 min	Intervention 30 min
Arterial					
pH	Control	7.42 ± 0.01	7.44 ± 0.02	7.38 ± 0.03	7.40 ± 0.03
	nITP	7.42 ± 0.01	7.41 ± 0.01	7.40 ± 0.03	7.36 ± 0.01
	NS	7.41 ± 0.01	7.41 ± 0.01	7.35 ± 0.01	7.37 ± 0.01
$Paco_2$, mm Hg	Control	46 ± 2	33 ± 1	34 ± 1	32 ± 2
	nITP	42 ± 2	35 ± 1	35 ± 2	36 ± 2
	NS	46 ± 2	38 ± 2*	38 ± 1	36 ± 1
Pao_2, mm Hg	Control	73 ± 3	95 ± 8	87 ± 4	92 ± 9
	nITP	83 ± 3	86 ± 3	80 ± 3	80 ± 3
	NS	86 ± 8	88 ± 2	92 ± 3	89 ± 4
Hematocrit, %	Control	29 ± 1	25 ± 1	26 ± 1	26 ± 1
	nITP	30 ± 1	24 ± 1	24 ± 1**	25 ± 1**
	NS	31 ± 1	26 ± 1	17 ± 1†	19 ± 1†
HCO_3, mmol/L	Control	29.9 ± 0.8	21.8 ± 0.8	20.1 ± 0.9	19.5 ± 1.2
	nITP	26.7 ± 0.9	22.4 ± 0.7	20.3 ± 0.8	20.2 ± 0.8
	NS	28.9 ± 0.7	24.0 ± 0.9	21.0 ± 0.7	21.1 ± 0.9
BE ecf, mmol/L	Control	5.7 ± 0.9	−2.8 ± 1.1	−5.5 ± 1.6	−6.1 ± 1.3
	nITP	1.8 ± 1.0‡	−2.7 ± 0.9	−5.4 ± 1.0	−5.8 ± 0.9
	NS	4.3 ± 0.6	−0.6 ± 0.9	−4.6 ± 0.8	−4.2 ± 1.0
SaO_2, %	Control	94 ± 0.8	97 ± 0.5	96 ± 1.0	96 ± 0.6
	nITP	96 ± 0.7	96 ± 0.4	95 ± 0.5	95 ± 0.6
	NS	96 ± 0.8	97 ± 0.2	97 ± 0.4	96 ± 0.5
Venous					
SvO_2, %	Control	69 ± 2	22 ± 2	28 ± 4	30 ± 4
	nITP	73 ± 3	31 ± 2	30 ± 2**	30 ± 2**
	NS	75 ± 3	32 ± 4	54 ± 4†	54 ± 4†

*$p < 0.05$ for control versus NS.
**$p < 0.001$ for nITP versus NS.
†$p < 0.001$ for control versus NS.
‡$p < 0.05$ for control versus nITP.
BE ecf, base excess.

dislodge a clot. In addition, we also observed that animals receiving intravascular NS fluid replacement experienced significant hemodilution and a significantly higher ICP compared with nITP-treated or untreated control pigs.

This is the first study comparing nITP with fluid replacement therapy. We selected this fixed model with a controlled bleed over 30 minutes so that most of the pigs would survive, regardless of the treatment arm. We have previously used a similar but more aggressive model with a fixed 50% bleed over 15–20 minutes, to demonstrate a survival advantage with nITP therapy.[20] In that adult swine survival study, all pigs in the control group died within 65 minutes of the initial bleed, whereas 7 (87%) of 8 pigs treated with nITP survived for more than 90 minutes ($p < 0.001$), 6 (75%) of 8 pigs in the nITP group survived for more than 3 hours and awoke without neurologic deficit, and 1 surviving animal in the nITP group never woke up.[20] Other previous studies focusing on the mechanism of nITP therapy have shown that it increases blood pressure, stroke volume, cardiac index, and cardiopulmonary circulation in the absence of immediate fluid resuscitation in euvolemic and hypovolemic animals.[9,17] These effects seem related to increased left ventricular preload and not by increased systemic vascular resistance or heart rate. The findings in the current study are consistent with earlier studies: pulse pressure was significantly higher in the nITP group compared with NS treatment and untreated controls. This finding supports the underlying mechanism of the nITP therapy since pulse pressure can be used as a surrogate for stroke volume. In addition, the reduction in ICP during inspiration observed with the nITP therapy in the current study is similarly consistent with its previously described mechanism of action.[14,21]

In human models of orthostatic stress and hypotension, nITP therapy is well tolerated and increases SBP by increasing stroke volume and cardiac output. Clinically, the nITP treatment provides short-term protection against cardiovascular collapse induced by orthostatic stress or hypotension from other causes including blood loss in humans.[10,12,13,18] A recently published review on the physiology and effects of inspiration through a low level of resistance for the treatment of hypotension further supports the concept of using nITP to provide a physiologic boost to circulation.[14]

The benefits associated with harnessing inspiratory efforts with nITP therapy provide a novel way to deliver "permissive hypotension," thus avoiding the potential adverse effects of early aggressive resuscitation.[22] The current study provides additional support that nITP could be used as a bridge therapy in the setting

of hypotension secondary to acute blood loss, thus expanding its potential use to spontaneously breathing patients after trauma. Furthermore, this approach may also decrease the frequency of secondary acute compartment syndrome in patients with extremity injuries.[23] The current study and previous studies have clearly demonstrated that nITP therapy maintains permissive hypotension and thus provides a new way to enhance tissue perfusion and a potential way to reduce compartment syndrome. In addition, the current study suggests that nITP therapy may be of benefit in patients with traumatic brain injury and spinal injuries: treatment with nITP in these patients has several potential unique advantages because of its ability to increase SBP and simultaneously lower ICP, thereby improving cerebral perfusion pressure through two different mechanisms.[21] In each of these clinical states, another advantage of the use of nITP over aggressive fluid resuscitation is the absence of hemodilution. Data in this study demonstrate, for the first time, that it is possible to increase blood pressure but prevent hemodilution with nITP technology. As such, a hemoglobin target of 7 g/dL to 9 g/dL is easier to achieve when the patient is not diluted before blood transfusion.

LIMITATIONS

There are several study limitations. The work was conducted using a fixed and controlled hemorrhage model without splenectomy and with the anesthetic propofol. Both the presence of the spleen and use of propofol could have impacted the outcomes. Actual demonstration of clot dislodgement with the use of aggressive fluid resuscitation was not possible. In addition, we only evaluated the effect of 0.9-M NS in these studies and have not evaluated colloids, hypertonic saline, freeze-dried plasma, whole blood, or vasoconstrictors. This study was limited to 30 minutes, and we did not demonstrate a survival benefit with nITP in this study. However, this was not the intent as we designed the study so that most of the untreated control pigs would survive for at least 30 minutes. Survival with nITP has been previously demonstrated.[20,24]

CONCLUSION

In this porcine model of severe hemorrhagic shock, when compared with intravenous NS resuscitation, inspiration through 7 cm H_2O of resistance significantly improved SBP, carotid artery blood flow, and pulse pressure for 30 minutes without hemodilution or generation of excessive transient elevations in arterial pressure associated with clot dislodgment.

AUTHORSHIP

All authors contributed to the preparation of this article. A.M. and V.C. designed the study, analyzed the data, and prepared the manuscript. R.T.G. critically reviewed the manuscript and revised its contents.. N.S., J.R., S.M., and T.M. performed the studies and analyzed the data.

DISCLOSURE

A.M. is an adjunct assistant professor in the University of Minnesota's Department of Emergency Medicine. She is also employed by Advanced Circulatory Systems Inc., the manufacturer of the ITD used in this study to provide the nITP therapy. K.G.L. is the founder and chief medical officer of Advanced Circulatory Systems, and J.R. is a research associate at Advanced Circulatory Systems. The other authors have no conflicts of interest. This study was supported by the US Army (W81XWH-10-1-0019).

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