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Acute right heart failure after hemorrhagic shock and trauma pneumonectomy – a management approach: A blinded randomized controlled animal trial using inhaled nitric oxide

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Abstract

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Background—Hemorrhagic shock and pneumonectomy causes an acute increase in pulmonary vascular resistance (PVR). The increase in PVR and right ventricular (RV) afterload leads to acute RV failure, thus reducing left ventricular (LV) preload and output. iNO lowers PVR by relaxing pulmonary arterial smooth muscle without remarkable systemic vascular effects. We hypothesized that with hemorrhagic shock and pneumonectomy, iNO can be used to decrease PVR and mitigate right heart failure.

Methods—A hemorrhagic shock and pneumonectomy model was developed using sheep. Sheep received lung protective ventilatory support and were instrumented to serially obtain measurements of hemodynamics, gas exchange and blood chemistry. Heart function was assessed with echocardiography. After randomization to study gas of iNO 20 ppm (n = 9) or nitrogen as placebo (n = 9), baseline measurements were obtained. Hemorrhagic shock was initiated by exsanguination to a target of 50% of the baseline mean arterial pressure. The resuscitation phase was initiated, consisting of simultaneous left pulmonary hilum ligation, via median sternotomy, infusion of autologous blood and initiation of study gas. Animals were monitored for 4 hours.

Results—All animals had an initial increase in PVR. PVR remained elevated with placebo; with iNO, PVR decreased to baseline. Echo showed improved RV function in the iNO group while it remained impaired in the placebo group. After an initial increase in shunt and lactate and decrease in SvO₂, all returned towards baseline in the iNO group but remained abnormal in the placebo group.

Conclusion—These data indicate that by decreasing PVR, iNO decreased RV afterload, preserved RV and LV function, and tissue oxygenation in this hemorrhagic shock and pneumonectomy model. This suggests that iNO may be a useful clinical adjunct to mitigate right heart failure and improve survival when trauma pneumonectomy is required.

Keywords

Inhaled nitric oxide; hemorrhage; pneumonectomy; pulmonary vascular resistance; cardiac function

Background

While pneumonectomy in the setting of trauma is a rare occurrence, in the presence of pulmonary hilar vascular or extensive main stem bronchial injury, pneumonectomy may be the only option. Of the few case series in the literature demonstrating outcomes of these patients, mortality associated with trauma pneumonectomy has been reported to range from 50-100%¹⁻⁴. Moreover, when pneumonectomy is performed on the background of hemorrhagic shock, the mortality rate is even higher than the mortality rate for pneumonectomy in the setting of isolated bronchial injury¹. Overall, the high mortality rates have been attributed to right heart failure¹⁻⁴.

Right heart failure following combined hemorrhagic shock and pneumonectomy occurs secondary to an acute increase in pulmonary vascular resistance (PVR)^{2, 4}. In animal studies, the increase in PVR seen in pneumonectomy and hemorrhagic shock models has been shown to be greater than the additive effects of each of these situations on their own and irreversible⁴. Additionally, pneumonectomy and resuscitation have the potential to cause

acute lung injury². This can lead to alveolar hypoxia, a major contributor to pulmonary vasoconstriction and increase in PVR². Ultimately, these risk factors lead to an increase in right ventricular (RV) afterload and a dysfunctional scenario of which compensatory mechanisms are exceeded, resulting in RV failure, decreased cardiac index, systemic hypoperfusion, tissue hypoxia and death. An effective mechanism for mitigating this problem would include a treatment focused at the source of the increase in PVR, specifically, selective vasodilation of the pulmonary vasculature.

Inhaled nitric oxide (iNO) has been shown to be a selective vasodilator of pulmonary vascular smooth muscle, with minimal or no hemodynamic systemic effects^{5, 6}. The reduction in pulmonary vascular tone and consequently PVR leads to decreased pulmonary arterial pressure and ultimately decreased RV afterload, which mechanistically decreases the workload of the right ventricle and has the potential to prevent right heart failure⁶. These beneficial properties of iNO have been used to induce vasodilation in primary pulmonary hypertension, ARDS and secondary pulmonary hypertension due to congenital heart disease⁷. In a non-randomized study of patients with acute right heart failure, iNO was shown to increase cardiac output, stroke volume and mixed venous oxygen saturation, thereby improving hemodynamic parameters, and while not directly measured, has been related to improving RV dysfunction⁵.

While sparse, the few case studies of the use of iNO in hemorrhagic shock patients requiring trauma pneumonectomy have reported improved cardiac output, reduced pulmonary artery pressures and ultimately improved survival^{7, 8}. However, the impact of iNO to mitigate right heart failure in the presence of hemorrhagic shock and trauma pneumonectomy has not been systematically or directly studied. With this in mind, the purpose of this study was to test the hypothesis that iNO could be used to decrease PVR, unload the right ventricle, and attenuate alterations in right heart function, thereby reduce right heart failure in an animal model of hemorrhagic shock and trauma pneumonectomy.

Methods

All methods were approved by the Temple University animal care and use committee in accordance with National Institutes of Health guidelines. Animal Preparation: Sheep (n = 19; weight: 23.7 ± 0.71 kg) were anesthetized with intramuscular (IM) injections of buprenorphine hydrochloride (0.005 mg/kg) and ketamine/xylazine (20/2mg/kg), restrained in the supine position, intubated (8.0 mm), immediately instrumented with electrocardiogram leads, pulse oximetry, and an orogastric tube, and placed on lung protective ventilatory support (Servo 300; Siemens, Solna, Sweden) initiated with pressure-controlled (peak inspiratory pressure [PIP] = 18 cmH₂O, positive end expiratory pressure [PEEP] = 8 cmH₂O), synchronized intermittent mechanical ventilation at a rate of 12 br/min with heated and humidified F_IO₂ (0.40 – 0.60) titrated to SpO₂ target of > 90%. Bilateral peripheral leg veins were isolated and cannulated for administration of anesthesia (guaifenesin/ketamine/xylazine at 50/2/0.1 mg/ml; 0.25-2.5 ml/kg/hr), maintenance fluids, and autologous blood. The right carotid artery was cannulated (8 Fr) for continuous blood pressure monitoring and serial sampling of arterial blood chemistry. The left femoral artery (8 Fr) and internal jugular vein (16 Fr) were cannulated for blood withdrawal. The right

external jugular vein was cannulated with a thermodilution catheter (7.5 Fr) that was advanced into the pulmonary artery under transduced pressure guidance for continuous monitoring of pulmonary pressures and serial measurement of mixed venous blood chemistry and cardiac output. All sheep were placed on a temperature controlled water-circulating pad and under a warming blanket for temperature support as continuously measured by rectal probe.

Following baseline measurements (blood pressure, heart rate, pulmonary artery pressures, cardiac output, systemic arterial pressures, ventilator settings, arterial and venous blood chemistries), a lung protective strategy was supported by changing the ventilator mode to time-cycled, pressure-limited (plateau pressure < 30 cmH₂O), tidal volume monitored ventilation (~6 mL/kg), and a median sternotomy was performed. As previously described by Cryer et. al., the left pulmonary hilum was isolated by gentle positioning of umbilical tape to be used subsequently during the resuscitation phase for ligation as an experimental hemodynamic surrogate of pneumonectomy⁴, and the chest was covered with plastic wrap to minimize temperature and evaporative water loss. Animals were given warm lactated Ringer's (10 ml/kg) to support pre-hilar manipulation of mean arterial pressure and allowed to stabilize for 15-20 mins. Then, previously described baseline measurements were repeated and echocardiography was performed (Zonare z. one ultra-Ultrasound system; 10-3 probe; Zonare Medical Systems, CA, USA). During echocardiography, the animals were randomized to receive placebo (nitrogen; n =9) or study gas (iNO at 20 ppm; n = 9) delivered just proximal to the inspiratory wyre by the modified iNOmax DSIR delivery system for blinded studies (Ikaria/Mallincrodt; software version 1.05). Only one member of the study team knew the randomization result; this member was responsible for initiating the placebo or study gas.

The surgical table was elevated to the highest point, transducers were re-zeroed and hemorrhagic shock was then created by passive blood flow from the left femoral artery and internal jugular vein into blood collection bags (JorVet™, Jorgensen Laboratories, Inc. Loveland, CO) positioned 114 centimeters below the animal until a target of 50% of baseline mean systemic arterial pressure (MAP) was reached and sustained for 5 mins. Baseline measurements were then repeated. Within 15 mins of hemorrhagic shock, the resuscitation phase was initiated. Resuscitation consisted of simultaneous ligation of the left pulmonary hilum, infusion of withdrawn blood and initiation of placebo or iNO study gas. To account for single lung ventilation, lung protective ventilation was maintained by monitoring tidal volume via pneumotachography and end-tidal carbon dioxide (NICO CO₂ monitor, Philips-Respironics, Wallingford, CT), reducing inspiratory pressure-support thus tidal volume by 33% (plateau pressure < 30 cmH₂O), increasing frequency to prevent hypercapnea (PaCO₂ 60 mmHg), and titrating F_IO₂ to maintain SpO₂ > 90%. Warm lactated Ringer's solution was infused as needed after completion of blood infusion, to return MAP to baseline. In addition to continuous monitoring of vascular pressures, pulse oximetry, and ECG, blood chemistry and cardiac function were serially measured immediately, 30 minutes, then hourly post-resuscitation to 4 hours post injury or until death.

Pulmonary vascular resistance was calculated from mean pulmonary arterial pressure - pulmonary capillary wedge pressure/cardiac output⁹. All echocardiographic analysis was

performed in a blinded manner following the American Society of Echocardiography guidelines. Cardiac function was assessed using eccentricity index as an indication of RV pressure overload, RV dP/dT and LV ejection fraction as a measure of RV and LV systolic function, respectively, and RV and LV fractional area of change (FAC) as an indicator of respective global ventricular function.

Eccentricity index is a measurement of RV pressure vs. volume overload that is based on interventricular septum movement^{10, 11}. Two measurements of the left ventricle are taken, one perpendicular to the septum and one parallel to the septum¹¹. The ratio of these measurements is taken at end systole and end diastole. In a normal patient, the ratio is 1. If RV volume overload is present, the ratio at end systole is 1, but is >1 at end diastole. If RV pressure overload is present, this ratio will be >1 at both end systole and end diastole. RV fractional area of change (FAC) is a measure of global RV function that has been correlated to RV ejection fraction using MRI¹⁰. RV FAC is calculated as (RV end diastole area- RV end systolic area)/ RV end diastole area $\times$ 100¹¹. This is measured by tracing the RV endocardium in systole and diastole in an apical four chamber view in the following order: from the annulus, the free wall to the apex, back to the annulus along the intraventricular septum¹⁰. A similar measurement is made of the LV cavity. A FAC less than 35% is indicative of systolic dysfunction¹⁰.

Data and statistical analyses were performed using Microsoft EXCEL and Graph Pad PRISM. Physiological variables were evaluated by multifactorial ANOVA for time and treatment group with repeated measures on time. Treatment group means were compared vertically using the Dunn-Bonferroni procedure and horizontally to their respective baseline and last injury value using linear contrast. Data are presented as mean $\pm$ SEM and significance was accepted at the $p < 0.05$ level.

Results

As shown in Table 1, there were no significant group differences in body weight, baseline systemic or pulmonary arterial pressures, hematocrit, hemoglobin or blood volume withdrawn to achieve 50% mean arterial pressure. Following instrumentation and initiation of study gas, two animals died prior to the 4 hr end-point. Both animals were in the placebo group. One animal died immediately after ligation of the pulmonary hilum in which there was immediate and extensive right ventricular dilation and cardiac arrhythmia. This animal was excluded from complete statistical analysis. The other animal died from systemic hypotension and arrhythmia at the 2 hr time point. All animals in the iNO treated group survived to 4 hrs. As shown in Figs 1-4 and Table 2 respectively, there were no significant intergroup differences in baseline values for PVR, any measure of cardiac function, shunt, lactate, SvO₂, PaO₂, or PaCO₂.

Upon initiation of the resuscitation phase, PVR (Fig 1) increased significantly in all animals. In the placebo group, PVR remained elevated from baseline over time. In the iNO group, PVR decreased back towards baseline over time. As shown in Table 2, shunt and lactate increased significantly, SvO₂ and PaO₂ decreased significantly from baseline initially with the resuscitation phase in both groups. Over time and by 4hr, with placebo, shunt remained

elevated relative to baseline, lactate continued to increase, and PaO₂ and SvO₂, while increasing significantly from the initial resuscitation phase, remained significantly lower than baseline, and PaCO₂ was greater than baseline, suggestive of impairment in gas exchange and tissue oxygenation over time. With iNO, shunt, SvO₂ and PaO₂ improved, and lactate stabilized, reflecting improved tissues oxygenation as compared to placebo treated animals.

Cardiac function profile is shown in Figs. 2-4 . During the initial resuscitation phase, both placebo and iNO treated groups demonstrated an increase in eccentricity index at end systole (Fig 2) and diastole (not shown), reflective of RV pressure overload. This increase was significantly less in the animals treated with iNO. In the placebo group, the eccentricity index at end systole and diastole continued to increase over time, consistent with a continued increase in RV pressure overload. In contrast, the iNO treated group demonstrated a return to baseline values within 2-3 hours post resuscitation, reflective of return to normal RV pressure loading conditions.

With respect to systolic contractile function, RV dP/dt (Fig 3b) decreased significantly initially post resuscitation in both groups, continued to decrease in the placebo treated animals, and returned to baseline within 2 hrs in animals treated with iNO, reflective of preserved RV contractility. There were significant group differences in bilateral ventricular contractile function as reflected by RV and LV FAC, measurements of global ventricular systolic function. As shown in Fig 3d and Fig 4b respectively, both RV and LV FAC were significantly lower in animals treated with placebo gas as compared to iNO. In addition, while continuing to decrease over time in placebo treated animals suggesting continual impairment of function, RV and LV FAC remained relatively stable in the iNO treated animals. As shown in Fig 4c the group difference in LV function was further demonstrated by the significantly lower and continual decrease in LV ejection fraction over time in animals treated with placebo gas in contrast to the relative stability of this parameter in animals treated with iNO.

Discussion

This study demonstrates that iNO mitigated the increase in pulmonary vascular resistance, thus decreasing right ventricular afterload and risk of right ventricular failure following combined hemorrhage and pneumonectomy in the sheep. Our animal model, similar to the pig model previously reported by Cryer et. al.⁴ simulated the clinical situation of patients who have central hilar injuries causing hemorrhagic shock and who require pneumonectomy for control. Upon ligation, with the removal of one of the two parallel circuits of the pulmonary circulation, there was an acute and robust increase in PVR in both groups of animals. Cardiac instability, including right ventricular dilation, and hemodynamic compromise was observed as previously reported in both animal and humans^{1-4, 7, 8}. In our study, animals treated with placebo gas demonstrated progressive right heart failure as has been demonstrated in humans with hemorrhagic shock and trauma pneumonectomy³; whereas, animals treated with iNO demonstrated the return of elevated PVR back to baseline and preserved right ventricular function.

The return of PVR towards baseline supports the notion that iNO was effectively delivered to the alveolar-capillary membrane to diffuse into the pulmonary smooth muscle cells, activate soluble guanylate cyclase to convert GTP to cGMP thereby increasing intracellular concentrations of cGMP thus facilitating pulmonary vascular smooth muscle relaxation and decrease in PVR. Animals that received iNO had less RV pressure overload (eccentricity index), preserved RV systolic function (RV dp/dt, RV FAC), and preserved LV function (LV EF, LV FAC). Functionally, an interpretation of this finding is that this translated to preserved tissue oxygenation, as demonstrated by the stabilized lactate values and the return of mixed venous oxygen saturation to baseline values. Preservation of RV function and tissue oxygenation seen with iNO in the present study is consistent with that previously demonstrated in humans with acute right heart failure. In this regard, patients in acute right heart failure treated with iNO were reported to respond with a decrease in PVR, pulmonary pressures, increased cardiac output and ultimately improved tissue perfusion⁵. Several case studies suggest the salutary effect of iNO on survival following hemorrhagic shock and pneumonectomy^{7, 8}. One report described survival following pneumonectomy subsequent to bilateral blunt thoracic injury in which iNO was initiated post-operatively and maintained for 4 days⁸. Another case study reported a 24 year old patient with a right pulmonary artery injury who received pneumonectomy with initial worsened RV function, who was then treated with iNO experienced reduced pulmonary artery pressures, improved cardiac output and ultimately survived⁷.

In contrast, in animals that received placebo gas (nitrogen), PVR remained elevated which was associated with worse RV function than animals treated with iNO. The placebo animals experienced continued RV pressure overload, decreased global RV systolic function, abnormal motion of the interventricular septum and ultimately reduced LV EF. This translated to poorer tissue oxygenation, as demonstrated by the blood lactate levels, which remained elevated in these animals and the persistently low mixed venous oxygen saturation. The impaired right heart function seen in the placebo animals is consistent with current theories that increased RV afterload (via increased right ventricular end diastolic volume) ultimately decreased RV ejection fraction^{4, 5}, leads to decreased left ventricular end diastolic volume (preload) and ultimately decreased cardiac output⁵. Additionally, RV afterload in this scenario may be increased due to the combination pulmonary vasoconstriction, decreased vascular compliance and microvascular plugging⁴. This is likely exacerbated by hemorrhagic shock, in which thromboxane release and leukostasis have the potential to interfere with vascular recruitment, leading to vasoconstriction and plugging that further reduces the ability of the RV to compensate ultimately leading to RV failure⁴. These vascular effects also have the potential to lead to pulmonary edema, precipitating worsening hypoxemia and potentially worsening pulmonary hypertension². This vicious cycle of hypoxemia and pulmonary hypertension leading to RV failure contributes to the demise of these patients as the RV is not able to compensate for the vast increase in PVR.

Our data suggest that iNO is able to selectively vasodilate the pulmonary vasculature, thus decreasing PVR in the setting of hemorrhagic shock and pneumonectomy. This decrease in PVR leads to reduction in RV afterload and preserved RV and LV function. Ultimately, this yields improved tissue oxygenation and potentially survival, in cases when the right heart struggles to compensate in the face of increased afterload.

There are several unique strengths of this study. In contrast to previous pre-clinical studies, we chose to initiate iNO treatment simultaneous with surgical and volume resuscitation. In this regard, our study offers insight to the potential prophylactic application of iNO in the setting of hemorrhagic shock and pneumonectomy. In addition, in an attempt to minimize confounding variables which could impact interpretation, we chose to restrict rescue management to surgical resection, return of autologous blood, and iNO rather than to other additional support of hemodynamic and metabolic status with vasopressors and buffers. Some limitations of the present study should be noted. We recognize that in comparison to massive hilar hemorrhage our method of hemorrhage from central and peripheral vessels does not present the same clinical challenges with respect to surgical, vascular control, and blood collection for autotransfusion. Based on our interest in the immediate hemorrhagic shock and pneumonectomy resuscitation period, we chose a 4 hour study window as previously described⁴. As such, from this observation period we can speak only to the short-term benefits of iNO. Nonetheless, our degree of hemorrhage, study period and alterations in lactate levels paralleled the acuity and intensity experienced by our clinical Trauma team and lends insight to the salutary rescue potential of this approach. Other potential considerations are related to echocardiography. Whereas all measurements were performed by experienced sonographers, they were performed with the open-chest approach which may limit translation to the clinical experience. We recognize that certain echocardiography measurements are load dependent and that loading conditions are likely to change over time in a study of this nature. With this in mind, given that both groups were managed in the same way apart from the study gas, we submit that this would impact each group comparably. By nature, there is an element of subjectivity in echocardiogram analyses which may potentially lead to variations in interpretation. This variation was minimized by having all echocardiograms evaluated by the same skilled sonographer. As such, we believe that this is not a likely source of bias in our study.

Summarily, these data provide strong evidence that iNO can be a useful treatment to decrease PVR and reduce RV afterload. Within this context, this study suggests that iNO can be a useful clinical adjunct to mitigate right heart failure and potentially improve survival in the face of hemorrhagic shock when pneumonectomy is required. Further research is warranted to determine iNO management strategies (ie. dose, duration, weaning; longer durations of shock, with hilar hemorrhage) in this patient population.

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Figure 1. Pulmonary Vascular Resistance

Pulmonary vascular resistant (PVR) in the placebo and iNO treated groups every 30 minutes from Baseline through 4hrs post resuscitation. (●) placebo (n=9) and (■) iNO (n=9) treated groups. Data shown as mean $\pm$ SEM (* p< 0.05 vs baseline; # p< 0.05 vs group)

Figure 2. Eccentricity Index

(A.) Representative 2D short axis echocardiographic images of the left ventricle (LV) in diastole and systole at 4 hr post resuscitation. The placebo images in diastole and systole (top row) shows deformation of the septal wall vs. the iNO treated animal who has maintained a normal cardiac dimensional ratio (bottom row). (B.) The mean eccentricity index (EI) systole (ratio) at baseline, 1,2,3, and 4 hrs post resuscitation in the (●) placebo (n=9) and (■) iNO (n=9) treated groups. Data shown as mean $\pm$ SEM (* $p < 0.05$ vs baseline; # $p < 0.05$ vs group)

Figure 3. RV Cardiac Function

(A.) Representative 2D color (left column/continuous wave (CW) (right column) Doppler images of the right ventricular (RV) inflow tract 4 hrs post resuscitation in a placebo (top row) and an iNO (bottom row) treated animal. The placebo animals had greater regurgitation during systole vs. the iNO treated animals. (B) RV dP/dT, was calculated from the CW Doppler of the regurgitation flow at baseline, 1,2,3, and 4 hrs post resuscitation. (C) Representative traces of the RV areas in diastole and systole in a placebo (top row) and iNO (bottom row) treated animal. These areas were used to calculate the (D) RV fractional area of change (RV FAC%) at baseline, 1,2,3 and 4 hrs post resuscitation in each group. (●) placebo (n=9) and (■) iNO (n=9) treated groups. Data shown as mean ± SEM (* p< 0.05 vs baseline; # p< 0.05 vs group)

Figure 4. LV Cardiac Function

(A) Representative traces of the LV areas in diastole and systole in a placebo (top row) and iNO (bottom row) treated animal. These areas were used to calculate the (B) LV fractional area of change (FAC %) and (C) LV ejection fraction (LVEF), over time. (●) placebo (n=9) and (■) iNO (n=9) treated groups. Data shown as mean $\pm$ SEM (* p< 0.05 vs baseline; # p< 0.05 vs group)

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Table 1

Group comparisons of body weight, baseline vascular pressures, and blood profile.

	Placebo	iNO
Weight	23.1	23.6
kg	0.78	1.2
Baseline MAP	79	78
(mmHg)	5.4	7.1
Baseline mPAP	27	26.6
(cm H ₂ O)	2.9	1
Baseline HcT	30	29
(%)	1.1	2.4
Baseline HgB	10.3	10.2
(g/dL)	0.47	0.84
Blood Withdrawn	21	22
(mL/kg)	2.8	3.2

mean ± SEM; n=9/group; MAP: mean arterial pressure; mPAP: mean pulmonary artery pressure; HcT: hematocrit; HgB: hemoglobin

Table 2

Group differences in Shunt, Lactate and Mixed Venous Oxygen Saturation as a function of protocol time period.

	Baseline		Initial RP		4 Hours	
	Placebo	iNO	Placebo	iNO	Placebo	iNO
Shunt	4.9	4.5	22 *	21 *	17.5 *	8.5 ^{\$} #
(%)	1.6	1.1	4.4	6	4.2	3.5
Lactate	1.11	1.12	3.4 *	2.95 *	6.3 *	3.9 ^{\$} #
(mmol/L)	0.34	0.26	0.75	0.67	1.4	1.3
SvO2	60	61	27.5 *	29 *	43.2 ^{\$}	61 ^{\$} #
(%)	4.7	6.5	4.3	3.6	5.3	3.3
PaO2	162	154	81.7 *	89.5 *	135.9 ^{\$}	237.9 ^{\$} #
(mm Hg)	13	12	9.7	16	25	21
PaCO2	43.2	38.3	44.5	42.2	53.6 *	39.1 #
(mm Hg)	2.7	2.4	6.9	3.1	4.5	3.3

mean ± SEM; n = 9/group; RP: resuscitation phase

*
p < 0.05 vs BL

^{\$}
p < 0.05 vs Initial RP

p < 0.05 vs group