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CLINICAL RESEARCH



## A randomized controlled study comparing high-dose insulin to vasopressors or combination therapy in a porcine model of refractory propranolol-induced cardiogenic shock

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### ABSTRACT

**Context:** Although cerebral perfusion (CP) is preserved across a wide range of mean arterial pressures (MAP) through cerebral-vascular autoregulation, the relationship between MAP and CP in refractory poison-induced cardiogenic shock (PICS) has never been studied. We compared the effects of therapies used in PICS: high-dose insulin (HDI), HDI plus norepinephrine (NE), and vasopressors alone (NE plus epinephrine (Epi)) on cerebral tissue oxygenation ( $P_tO_2$ ).

**Methods:** Fifteen swine were randomized to either HDI, HDI + NE, or NE + Epi. All animals received a propranolol infusion using an established model of toxicity. At primary toxicity ( $P_1$ ), defined as a 25% reduction in heart rate (HR) multiplied by MAP, the HDI and HDI + NE groups received HDI and the NE + Epi group received NE. Once a sustained MAP < 55 mmHg was reached ( $P_2$ ), the HDI group received saline (NS), the HDI + NE group received NE and the NE + Epi group received Epi until death or censoring.  $P_tO_2$  and hemodynamic parameters including MAP, cardiac output (CO) and central venous pressure (CVP) were measured every 10 minutes. Glucose and potassium were measured at predetermined intervals.

**Results:** Animals treated with HDI + NE maintained  $P_tO_2$  over time more than the HDI-alone group. Due to rapid hemodynamic collapse, we were unable to analyze  $P_tO_2$  data in the vasopressor only animals. Mean survival time was 1.9, 2.9 and 0.1 hours for the HDI, HDI + NE and NE + Epi groups, respectively. Survival time from  $P_2$  (sustained MAP < 55 mmHg) to death or censoring was not different between HDI and HDI + NE groups.

**Conclusions:** HDI + NE treatment was superior to HDI-alone at preserving  $P_tO_2$  when MAP < 55 mmHg. We were unable to compare the  $P_tO_2$  between the NE + Epi to the HDI or HDI + NE due to rapid decline in CO and death. If MAP is sustained at < 55 mmHg after maximizing HDI, adjunctive treatment with NE should be considered to preserve  $P_tO_2$ .

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Overdose; beta-adrenergic blockers; cardiogenic shock; cerebral perfusion; high-dose insulin; vasopressors

### Introduction

Despite significant advances in the management of poison-induced cardiogenic shock (PICS), toxicity from the ingestion of cardiovascular drugs such as beta-blockers (BB) and calcium channel blockers (CCB) is still associated with significant morbidity and mortality. In spite of accounting for only 4.2% of the 2.5 million exposures reported to the National Poison Data System (NPDS) in 2017, cardiovascular drugs (calcium antagonists, beta blockers specifically) accounted for a disproportionate 8.8% of all deaths [1]. Cardiovascular drugs rank third behind sedative-hypnotic xenobiotics, opioids, and miscellaneous street drugs in terms of fatalities and are the seventh most frequently involved substance in exposure calls. BBs and CCBs are responsible for the majority of deaths attributed to cardiovascular medications [1].

Clinical hallmarks of beta-blocker poisoning are primarily an extension of their therapeutic effects, including hypotension and bradycardia from myocardial depression due to

decreased inotropy. Without treatment, this can progress to profound cardiogenic shock [2]. Historically, therapy has been focused on restoring hemodynamic function and subverting the hypoperfusion by administering intravenous (IV) fluids, atropine, glucagon, calcium, and vasopressor support. However, despite aggressive resuscitation measures, refractory cardiovascular failure may occur [3–5]. In animal models of poison-induced cardiogenic shock (PICS), high-dose insulin (HDI) has been shown to be superior to vasopressors in both improving hemodynamic parameters and increasing survival [6–10].

Previous authors have shown that insulin causes vasodilation at the capillary level [11,12]. We hypothesize that the improved survival that has been seen with HDI therapy is not only due to an increase in inotropy, but also due to its ability to increase blood flow to cerebral tissue. Using an animal model, the primary goal of this study was to determine the effects on cerebral oxygenation between treatment with HDI alone, HDI plus a vasopressor (NE), and vasopressors

alone (NE plus epinephrine) in the treatment of BB-induced PICS after maximizing HDI therapy. The secondary outcome evaluated was time to death or censoring (euthanization of animal at the end of the study protocol).

## Methods

### Animal preparation

The Institutional Care and Use Committee of the HealthPartners Institute approved all protocols. We performed the experimental protocol in the HealthPartners Animal Care Facility, which is a secured animal care facility, that is United States Department of Agriculture licensed and accredited with the American Association for Accreditation of Laboratory Animal Care.

The animal model is based on a previously described protocol for the purpose of monitoring cardiovascular and cerebral oxygenation in severe propranolol toxicity refractory to HDI therapy [6,8–10]. The investigators sedated 15 healthy Yorkshire–Duroc cross swine ( $43.9 \pm 5.23$  kg) with an intramuscular injection of tiletamine and zolazepam, followed by an inhaled combination of 50% nitrous oxide and isoflurane for the duration of the protocol. We monitored the animal's response to a brief toe pinch during induction of anesthesia to ensure adequate sedation (if the animal responded to the stimulus, sedation was increased). Once adequately sedated, we aimed to avoid over-sedating the animal to minimize cardiovascular depressant effects. We performed a tracheostomy on each animal, after which they were placed on a ventilator (positive end-expiratory pressure of 5 mmHg, tidal volume 10 ml/kg). Animals were ventilated with 50% FiO<sub>2</sub> which was adjusted accordingly to maintain O<sub>2</sub> saturation >90% and pCO<sub>2</sub> near baseline. Continuous electrocardiogram monitoring occurred for the duration of the protocol. Further, we maintained baseline temperature by external techniques. A cut-down incision to the right upper neck was done, and a Swan-Ganz catheter was inserted into the pulmonary artery for monitoring of CVP and CO (as determined by thermodilution technique). We placed a femoral arterial line for continuous systolic, diastolic, and mean arterial pressure monitoring. Femoral venous access was obtained to allow for medication and fluid administration as well as venous blood sampling. Finally, we placed a suprapubic urinary catheter in each animal and urine output was monitored.

Next, after the identification of surface landmarks, the scalp was reflected to expose the calvaria for placement of the Licox® for intracerebral monitoring. According to the manufacturer, the Licox probe (Integra LifeSciences Corporation, Plainsboro, NJ) is an electrode introduced into the brain parenchyma that measures oxygen tension (oxygen enters the probe through an oxygen-permeable membrane where it is reduced, generating a current that is measured). In this paper, we have assumed that the Licox measurement reflects the brain tissue oxygenation of the tissue in contact with the probe. We placed the Licox monitor approximately 1 cm caudal to the coronal suture and 1 cm left lateral to the sagittal cranial suture. Once secured and calibrated, we monitored the P<sub>t</sub>O<sub>2</sub> until stable readings were obtained. We

then paused for another stabilization period of 30 minutes prior to the induction of toxicity and making baseline measurements. Along with continually monitoring animal hemodynamics (CO, CVP, calculated SVR, calculated pulmonary vascular resistance (PVR), MAP, BP, and HR), we recorded a P<sub>t</sub>O<sub>2</sub> measurement every 10 minutes. Point-of-care testing occurred every 30 minutes (iSTAT CG8+, Abbott Laboratories, Chicago, IL) to quantify sodium, potassium, chloride, ionized calcium, hematocrit, pH, pCO<sub>2</sub>, pO<sub>2</sub>, and HCO<sub>3</sub>.

### Experimental design

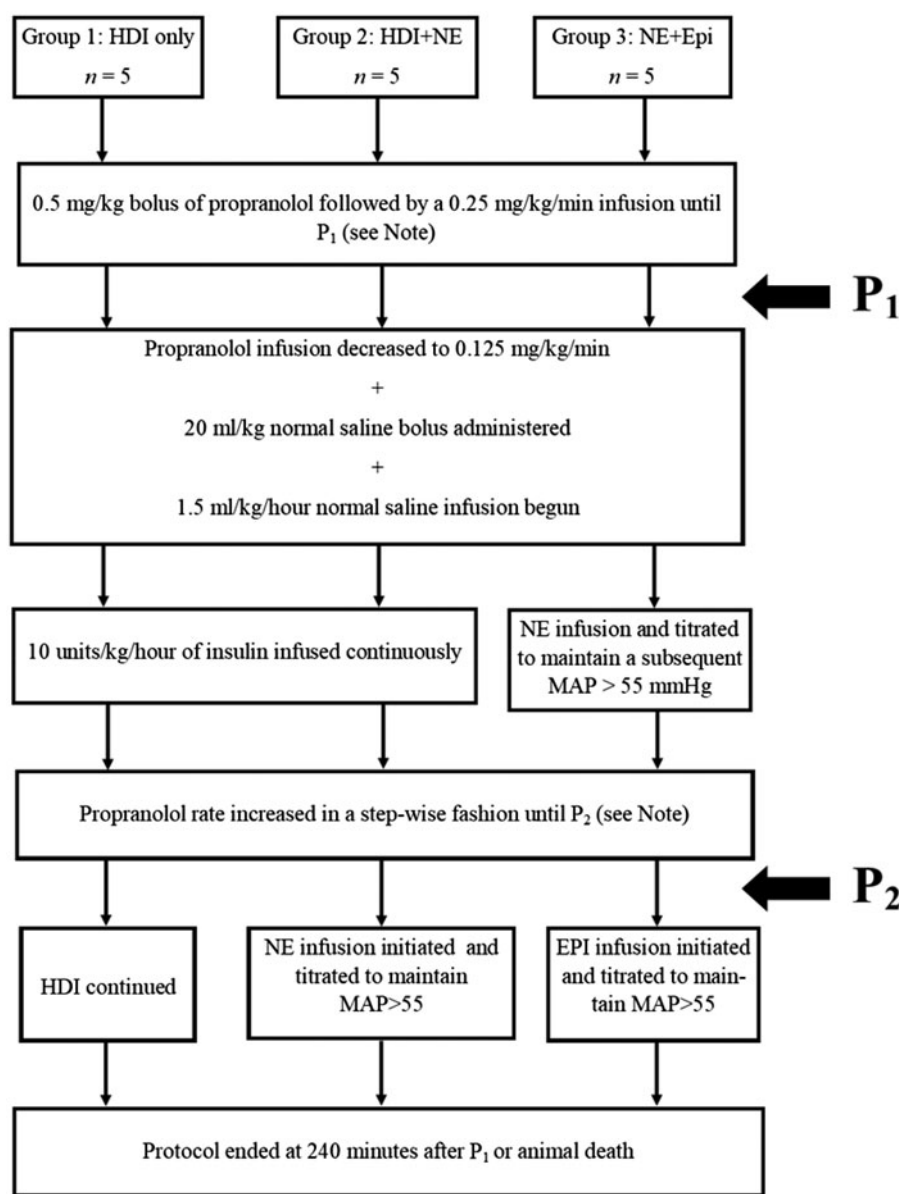
This was a blinded study of propranolol-induced PICS. The study investigators (with the exception of the pharmacist administering the medications and running/recording laboratory tests) were blinded to the interventions. We randomized 15 pigs to three different groups. A flowchart of interventions is displayed in Figure 1. As mentioned, the model of refractory propranolol toxicity is based on a previously reported protocol [6,8–10]. A 0.5 mg/kg bolus of propranolol was administered to all animals, followed by a 0.25 mg/kg/min infusion until the initial point of toxicity (P<sub>1</sub>) was reached. This point (P<sub>1</sub>) was defined as a 25% reduction from baseline MAP multiplied by HR. This point marked the start of the 240-minute protocol. After reaching P<sub>1</sub>, we decreased the infusion rate of propranolol to 0.125 mg/kg/min to simulate ongoing absorption that would occur with oral ingestion.

We also initiated and maintained throughout a 1.5 ml/kg/h normal saline (NS) infusion in all three groups to mimic clinical practice. At the initial P<sub>1</sub>, a 20 ml/kg bolus was pushed rapidly in each of the three groups to prevent hemodynamic collapse.

The pigs in groups 1 and 2 received HDI at 10 U/kg/h after this initial fluid bolus resuscitation. Animals were then allowed to stabilize on HDI therapy for 30 min after P<sub>1</sub>. We started group 3 pigs on a NE infusion at 0.1 mcg/kg/min and titrated by 0.1 mcg/kg/min up to a maximum of 0.5 mcg/kg/min to maintain a subsequent MAP > 55 mmHg. Once the stabilization period had been completed, the propranolol rate was increased in a stepwise fashion by 1/32nd of the dose, allowing 30 min between each subsequent dose increase, until a secondary point of toxicity (P<sub>2</sub>) was reached. We defined this point as a sustained MAP < 55 mmHg for >5 min.

At P<sub>2</sub>, we maintained group 1 pigs on HDI at 10 U/kg/h and a second placebo bag of saline was started with sham titrations to mimic the titrations occurring in groups 2 and 3 (and maintain the blinding for the study investigators). Group 2 pigs received HDI at 10 U/kg/h followed by an NE infusion that was started at 0.1 mcg/kg/min after P<sub>2</sub> was reached. We titrated NE from 0.1–0.5 mcg/kg/min to maintain subsequent MAPs > 55 mmHg. Once group 3 pigs reached P<sub>2</sub>, an Epi infusion was started at 0.1 mcg/kg/min and titrated up by 0.1 mcg/kg/min to a maximum dose of 0.5 mcg/kg/min to maintain a subsequent MAP > 55 mmHg.

We performed serum glucose checks every 10 minutes in all three groups. 12.5 grams of dextrose (25 ml of 50%



**Figure 1.** Intervention flowchart by group. Note:  $P_1$  was defined as a 25% reduction from baseline MAP multiplied by HR.  $P_2$  is defined as a sustained MAP  $<55$  for  $>5$  min.

dextrose IV) was administered if the blood sugar was between 40 and 60 mg/dl. 25 grams of dextrose (50 ml of dextrose 50% IV) was administered IV push if the blood glucose was noted to be  $<40$  mg/dl. If a bolus of IV dextrose was required, then we started a continuous infusion of IV dextrose at 12.5 g/h and each time an additional bolus of IV dextrose was required, the dextrose infusion was doubled. We simulated the administration of “dextrose boluses” to group 3 pigs to mimic dosing in groups 1 and 2 to maintain blinding of the primary investigator. Extrapolating dextrose requirements from previous studies wherein animals received HDI at 10 U/kg/h, we mimicked infusion rates as a placebo in group 3.

We monitored serum potassium levels every 30 minutes and potassium was administered at a rate of 5 mEq/h if potassium level fell below 2.8 mEq/L. If potassium levels did not increase to  $>2.8$  mEq/L within 30 min, then the potassium concentration was increased by an additional 5 mEq/h every 30 min until potassium was  $>2.8$  mEq/ml. Groups 1

and 2 typically received small amounts of potassium due to HDI therapy, therefore the non-blinded pharmacist started a placebo bag mimicking potassium administration in Group 3 to keep the other investigators blinded and to match total fluid administration between groups. We recorded  $P_tO_2$  every 5 min from the initial  $P_1$ . Surviving pigs at 240 min following  $P_2$  were euthanized with a standard euthanasia solution (containing sodium pentobarbital and sodium phenytoin).

### Statistical analysis

Linear mixed models with repeated measures were used to compare changes in brain oxygenation  $P_tO_2$  from  $P_2$  to death or censoring between the groups. Locally weighted scatterplot smoothing regression (LOESS) curves were used to illustrate means and 95% confidence intervals of  $P_tO_2$  over time.

We used Kaplan–Meier survival curves to plot the survival time for each group. Proportional hazards compared survival time from

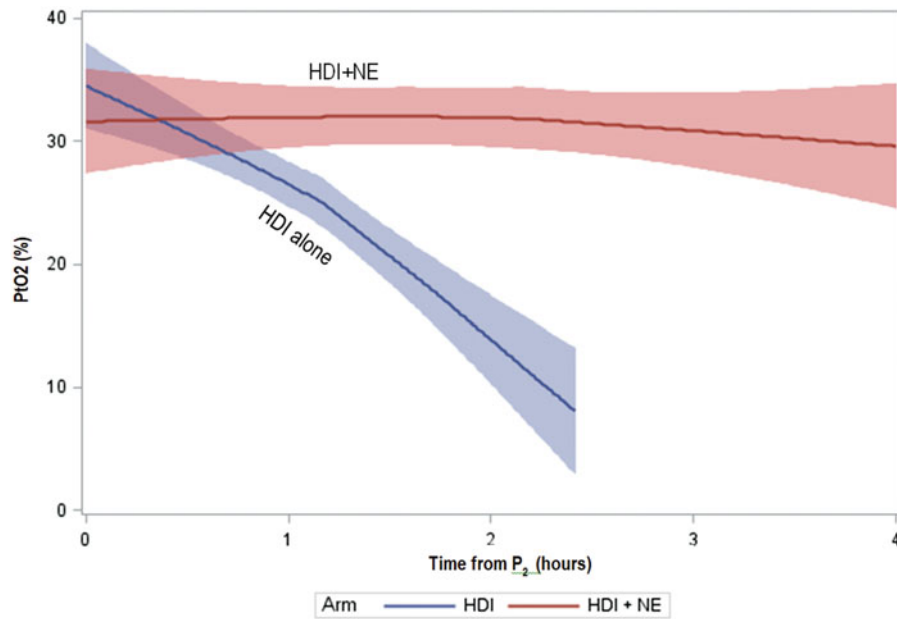


Figure 2.  $P_tO_2$  from  $P_2$  to death or censoring. Loess curves (95% CI) by group.

$P_2$  to death or censoring between the study groups. We tested differences in survival across groups with likelihood ratios.

A power calculation was completed prior to the study with regard to the primary outcome. Using data from a pilot study done at our institution [9], we conservatively assumed that the baseline difference at  $P_2$  would be 10 mmHg, the interclass correlation coefficient (within pig) for  $P_tO_2$  was 0.84, and that we would observe data at 19 time points per pig. We estimated that with 4 pigs in each of the two arms, there would be 87% power to detect a change in the rate of change of  $P_tO_2$  equal to 0.56 mmHg/h (1/3rd the magnitude observed in the pilot study). The study was not powered to explicitly find differences in the secondary outcomes.

## Results

With regard to the primary outcome (cerebral oxygenation), the animals in group 2 (HDI + NE) maintained cerebral oxygenation over time to a greater degree than group 1 (HDI only). The tissue oxygenation over time for the group 1 and group 2 animals can be seen in Figure 2. The difference in change in  $P_tO_2$  over time between the two study groups was significant at 9.9 mmHg per hour (95% CI of 5.9–13.9 mmHg per hour,  $p < .0001$ ). Regarding each group, group 1 showed a statistically significant decreased rate (10.4 mmHg per hour, 95% CI 6.7–14.0 mmHg per hour,  $p < .0001$ ), while the difference in group 2 was not (95% CI of 1.1–1.9 mmHg per hour,  $p = .58$ ). Although we attempted to compare the change in  $P_tO_2$  from  $P_2$  to death or censoring in all groups, the animals in group 3 (vasopressor only) did not survive long enough to make an adequate comparison.

Time to death or censoring from  $P_2$  to death or censoring (after the 4-hour protocol), for each animal is shown in Table 1. The mean survival time was 1.9 h (SD 0.4 hours) for group 1, 2.9 h (SD 1.5 h) for group 2, and 0.1 h (SD 0.1 h) for group 3.

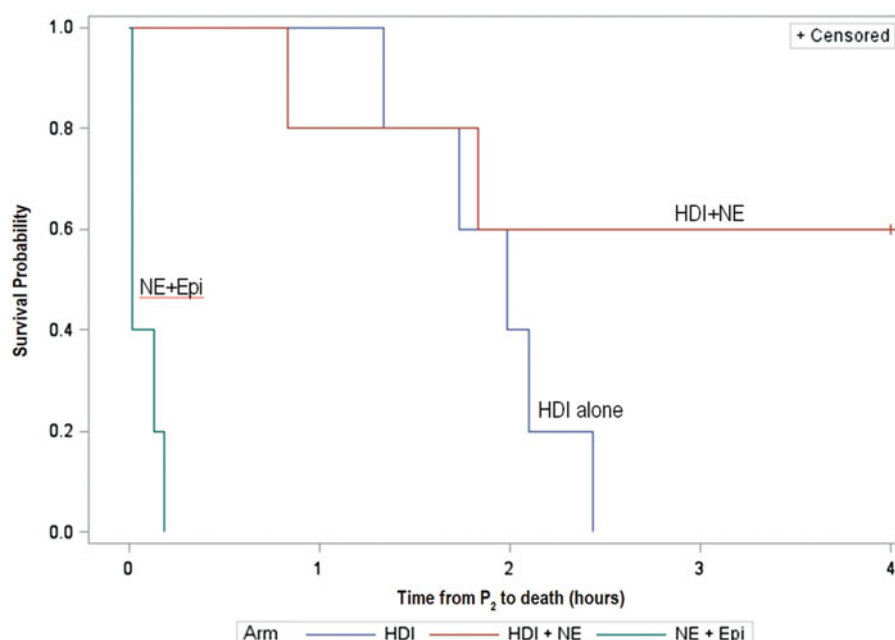
Table 1. Hours from  $P_2$  to death or censoring.

Animal	Intervention	Survival Time
1	HDI	1.3
2	HDI	1.7
3	HDI	2.0
4	HDI	2.1
5	HDI	2.4
	Mean (SD)	1.9 (0.4)
6	HDI/NE	0.8
7	HDI/NE	1.8
8	HDI/NE	4.0
9	HDI/NE	4.0
10	HDI/NE	4.0
	Mean (SD)	2.9 (1.4)
11	NE + Epi	0.02
12	NE + Epi	0.02
13	NE + Epi	0.02
14	NE + Epi	0.13
15	NE + Epi	0.2
	Mean (SD)	0.1 (0.1)

Kaplan–Meier survival curves are shown in Figure 3. None of the animals in group 1 survived to the end of the protocol, with survival times ranging from 1.3 to 2.4 h. In group 2, all animals survived to the end of the protocol with the exception of 2 that died at 0.8 and 1.8 h, respectively. In group 3, all pigs died by 0.2 h. Survival time from  $P_2$  to death or censoring was not different when comparing group 1 to group 2 (estimated hazard ratio = 0.31, 95% CI: 0.06–1.65,  $p = .15$ ). Survival time from  $P_2$  to death or censoring was also compared between the other groups (1–3 and 2–3), but an estimated hazard ratio could not be computed due to the small size in group 3 (two animals died between  $P_1$  and  $P_2$ ). Nevertheless, the differences in survival time between the other two groups were significant (likelihood ratio  $p = .001$ ).

## Discussion

This study demonstrates the following three important findings about the treatment of PICS in an animal model. First,



**Figure 3.** Survival from  $P_2$  to death or censorship.

vasopressor therapy alone had no survival benefit and animals died so rapidly that  $P_tO_2$  could not be analyzed. Second, animals treated with NE after maximizing HDI therapy had improved brain tissue oxygenation over time as compared to HDI-treated animals alone. Third, survival to death or censoring was not significantly different between the HDI and HDI + NE-treated animals. These findings suggest that introducing NE after maximizing HDI therapy provides the best treatment benefit in this model when compared to HDI alone and vasopressors alone in terms of cerebral oxygenation and survival.

There has been at least some debate as to whether HDI therapy in the setting of PICS is superior to other therapies, such as vasopressors alone. Over two decades ago, Kline published a canine model of verapamil toxicity in which animals were given HDI therapy (4 units/min) versus epinephrine (1 mcg/kg/min) versus glucagon (0.2–0.25 mg/kg bolus infusion followed by 150 mcg/kg/min infusion). After 240 min of monitoring, all six animals treated with HDI survived while only one-third of the epinephrine animals survived, and none of the glucagon-treated animals survived [13]. Several years later, Kerns published an animal model of beta-blocker toxicity in which animals were given HDI therapy (4 units/min) vs epinephrine (1 mcg/kg/min) [7]. After 240 min of monitoring, all six animals treated with HDI survived while only one of the vasopressor animals survived. In the interim, multiple animal studies [6,9,10,14], as well as a human case series [15], have shown the effectiveness of HDI in this setting. A recent systematic review of the literature concluded that: in animal models of PICS, vasopressors not only impaired hemodynamic function but also increased mortality [16].

Prior to this study, we hypothesized that the increased mortality in vasopressor-treated animals was, at least in part, due to severe vasoconstriction in vital end-organs, namely the brain, kidneys, and intestines. This suspicion was largely

based on personal observations as well as the work published by Levine et al. They found, in a patient population treated primarily with vasopressors for PICS, ischemic complications in a total of 10% of the 48 patients they reviewed. These complications included cerebral ischemia, gastrointestinal bleeds, ischemic bowel, and acute tubular necrosis. It is worth noting that the authors of this retrospective study argue that there was evidence of a majority of these complications prior to the initiation of therapy [17].

Our study not only reproduced the finding that HDI therapy is superior to vasopressor alone, but also probed whether adding vasopressors when shock is refractory to HDI alone (as is done frequently in the clinical treatment of human patients with refractory PICS) affects the survival of the animals. We further departed from previous literature on this topic to shift the focus away from hemodynamic parameters (MAP, SVR, etc.) to what is ultimately the most important measure of end-organ health – brain tissue oxygenation.

We demonstrated that the addition of vasopressors to HDI therapy improved hemodynamics and one measure of end-organ oxygenation (brain tissue) as compared to HDI alone and vasopressor alone therapy. Although cerebral oxygenation (assumed to be proportional to  $P_tO_2$ ) was measured from  $P_2$  to death or censoring in all groups, it could only be compared between the HDI and the HDI + NE groups due to early death in the NE + Epi group (Figure 2). Between the two HDI-treated groups, the group that received HDI alone had a more steady decline in cerebral oxygenation over time compared to those that additionally received NE.

The explanation for the improved oxygenation demonstrated in the HDI groups compared to vasopressors alone is likely related to the specific mechanism of action of HDI. At high doses, insulin increases tissue perfusion through positive inotropy ( $\beta_1$  effects) and smooth muscle relaxation ( $\beta_2$  effects) [18], vasodilating not only in the periphery but also in the pulmonary vasculature and at a microcapillary level as

well [12]. In addition, HDI increases myocardial glucose transport, decreases insulin resistance, and inhibits lactate oxidation [19–21]. The aforementioned studies are limited by being largely animal and *in vitro* studies – outside of a strict PICS model as in our study. We are unaware of studies that have directly investigated these effects in humans.

Knowing this, we were surprised to find that by adding NE (a medication known to cause vasoconstriction in end-organ capillary beds) to HDI therapy led to improved brain tissue oxygenation. The reason for this is unclear. The answer may be related to balancing increased perfusion via cerebral microcapillary vasodilation with the autoregulation phenomenon of cerebral perfusion. Autoregulation of cerebral blood flow is the ability of the brain to maintain relatively constant blood flow and as a result, maintain cerebral oxygenation despite changes in cerebral perfusion pressure [22,23]. In humans, literature suggests that cerebral blood flow is maintained provided that the cerebral perfusion pressure is within 50–150 mmHg [24,25]. In refractory PICS, the MAP falls below the lower limit of autoregulation and cerebral ischemia occurs [26]. While insulin may maintain the vasodilation in the brain to avoid microcapillary ischemia, the peripheral vasoconstriction and resultant increased MAP affected by the addition of the vasopressor may better maintain the animal in this range of autoregulation and stave off a drop in cerebral perfusion pressure.

In our study, this improved brain tissue oxygenation translated to a clear survival benefit. The mean survival time in the HDI and HDI+NE groups was 19 and 29 times longer than the vasopressor alone group, respectively. Given that the mean survival times between the HDI alone and HDI+NE groups was not statistically significant, our study suggests that the addition of a vasopressor along with prior initiation of inotropic support from HDI may neither increase mortality nor cerebral ischemia – although this was not explicitly studied here and an *a priori* power analysis was not completed to assess whether the study was powered to find a difference. Therefore, in the clinical management of patients with PICS, vasopressors should be considered if HDI alone does not lead to adequate tissue perfusion.

### Limitations

The primary limitation of this study is that it is an animal model. We chose a porcine model based on previous studies which have shown that cerebral autoregulation and cardiovascular parameters in swine have marked similarity to that of humans. Despite many studies demonstrating swine to be adequate models in cardiovascular toxicity, there are certainly differences between swine and humans that we do not understand or have not yet been identified.

Various other model-specific characteristics of the study represent study limitations – namely, the use of anesthetic agents. These medications are known to have cardiovascular depressing effects. These medications may also interact with the intervention medications. Given some animals required more sedation than others, this may have confounded our results. We attempted to mitigate this limitation by

minimizing the use of anesthetic agents (albeit prioritizing animal comfort).

Further, the number of animals per group was limited. This limitation was mitigated by an *a priori* statistical power analysis which suggested that even with small sample sizes, a significant difference in change in  $P_tO_2$  between the groups could be found.

We chose to administer propranolol intravenously, rather than orally via orogastric tube, to ensure a continuous infusion that would mimic ongoing drug absorption in an overdose scenario and allow the precise titration of infusion rate. However, this may not accurately represent what occurs with an oral ingestion. Further, we did not verify serum propranolol concentrations due to cost limitations.

The choice of beta blockers also presents a possible limitation. Propranolol is a unique beta blocker, exhibiting membrane stabilizing effects and greater lipophilicity which accords greater central nervous system penetration. This study did not evaluate and compare other beta blockers or calcium channel blockers.

The choice of a single constant infusion of insulin (10 U/kg/h) may not directly mirror the clinical practice of all toxicologists and may limit the interpretation of the study results. The constant infusion rate was chosen because it matches our local clinical practice (a rapid titration to 10 U/kg/h in patients as sick as the animals in this study), and also simplified the logistics of the study. Further, we were not aiming to determine whether HDI is superior to other therapies, rather which therapy is most beneficial when the shock is refractory to HDI.

Two further points may have biased our study against showing benefit in the HDI groups. First, the optimal dose of HDI has not been determined. The HDI infusion of 10 U/kg/h was chosen based on the results of a dosing study completed by Cole et al. [6]. This study found that a 10 U/kg/h infusion was better than both 5 and 1 U/kg/h at preserving hemodynamic parameters in propranolol-poisoned swine. However, a plateau in CO and MAP was not determined and higher doses were not evaluated. Second, it must be noted that the onset of the effect of vasopressors occurs within minutes while the effect of HDI occurs over 10–30 min. Therefore, the HDI treatment groups may have had 10–30 min of propranolol infusion without discernible pharmacological effect – allowing for increased time for toxicity as compared to vasopressor therapy.

In light of the limitations of the study design, future studies should be aimed at increasing doses of insulin beyond the generally accepted maximum dose of 10 U/kg/h. The goal of such an approach would be to find the balance between insulin therapy and vasopressor therapy that maximizes survival and cerebral oxygenation. Further, we aim to do a subgroup analysis of the period prior to  $P_2$  in order to confirm results from the previous Orozco study on which this work builds [9].

### Conclusion

Our data suggest that the addition of NE to maximal HDI therapy provides both a survival benefit and improvement in

cerebral oxygenation as compared to either HDI or vasopressors alone, within the limitations of the study. When comparing HDI therapy with or without the addition of NE to the use of vasopressors alone in refractory PICS, we have found significantly increased mortality in the vasopressor-alone group. We, therefore, recommend against the use of isolated vasopressors in PICS.

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