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RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA (REBOA) AT ALTITUDE: EFFICACY AND EFFECTS

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14. ABSTRACT

BACKGROUND: Non-compressible torso hemorrhage remains a leading cause of death. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) placement may occur prior to transport; however, its efficacy has not been demonstrated at altitude. We evaluated REBOA and Partial REBOA (pREBOA) utilization. We hypothesized that changes in altitude would not result in blood pressure changes proximal to a deployed REBOA. We also that the pREBOA balloon would function similarly to the ER-REBOA and therefore would be safe at altitude. **CONCLUSION:** ER-REBOA and p-REBOA catheters-maintained MAP up to 22,000 feet ft in an inanimate model. In the porcine model, ER-REBOA deployment improved MAP and the balloon remained effective at altitude. The pREBOA results suggest that the pREBOA balloon is efficacious at altitude and reduces the ischemia-reperfusion injury while maintaining lower extremity perfusion compared to a fully occlusive aortic balloon. In addition, partial aortic occlusion allowed for the mitigation of the additional insult of altitude that would otherwise exacerbate the ischemia/reperfusion inherent to aortic occlusion for hemorrhage control.

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1.0. SUMMARY DSICLAIMER:

The following final technical report provides results regarding the use of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) and partial REBOA (pREBOA) at altitude. The funded study title "REBOA at altitude: Efficacy and Effects". The research efforts involving large pre-clinical models were reviewed and approved by the University of Cincinnati Institutional Animal Care and Use Committee as well as the Air Force Medical Support Agency Office of Research Oversight and Compliance. The final report will include information covering the methods, results for each research activity.

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2.0. ABSTRACT:

BACKGROUND: Non-compressible torso hemorrhage remains a leading cause of death. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) placement may occur prior to transport; however, its efficacy has not been demonstrated at altitude. We hypothesized that changes in altitude would not result in blood pressure changes proximal to a deployed REBOA. Additionally, while effective for hemorrhage control, REBOA deployment incurs the risk of ischemia reperfusion injury with prolonged use, which has been demonstrated both in animal models as well as in human studies. Therefore, a pREBOA balloon, has been developed with the intention to allow for life-saving hemorrhage control without non-survivable ischemia reperfusion injury. This study also evaluated the ability for pREBOA to maintain hemodynamic stability while maintaining structural efficacy at altitude has yet to be elucidated. Therefore, we designed a porcine model to evaluate the efficacy of a partially inflated REBOA catheter at altitude and physiologic temperature. We hypothesized that the pREBOA balloon would function similarly to the ER-REBOA and therefore would be safe at altitude.

Methods: To determine if ER-REBOA would affect blood pressure a simulation model for 7Fr guidewireless was utilized at altitudes up to 22,000 feet. Female pigs then underwent hemorrhagic shock to a mean arterial pressure (MAP) of 40 millimeters of mercury (mmHg). After hemorrhage, a REBOA catheter was deployed in the REBOA group and positioned but not inflated in the no-REBOA group. Animals underwent simulated aeromedical evacuation at 8,000 feet (ft) or were left at ground level. After altitude exposure, the balloon was deflated, and the animals were observed. To determine if pREBOA would be safe at altitude a commercially available simulation model for the 7-Fr guidewireless pREBOA-PRO was utilized, as previously described. Each pREBOA catheter underwent three flights for a total of 9 flights. Full occlusion was achieved by inflating the balloon with 8 milliliters (mL) of normal saline. Partial inflation was achieved by titrating the amount of saline introduced in the balloon to allow a mean arterial pressure (MAP) of 50 mmHg proximal to the balloon. Each flight consisted of 15 minutes each at 0 ft, 5,000 ft, 8,000 ft, 12,000 ft, and 22,000 ft before returning to ground level. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were measured every five minutes at each altitude, at the end of the experiment, and after the balloon was deflated and the animals were observed.

Results: Taking the ER-REBOA catheter to 22,000 ft in the simulation model resulted in a lower SBP but a preserved MAP. In the porcine model, ER-REBOA increased both SBP and MAP compared to no-REBOA ($p<0.05$) and was unaffected by altitude. No differences in post-flight blood pressure, acidosis, or systemic inflammatory response were observed between ground and altitude REBOA groups. The results of the pREBOA demonstrated significant differences SBP, MAP, and DBP, as expected. There were no differences in the SBP or DBP over the course of the flights, indicating that the balloon did not change in its compliance over the course of the flight in the simulation model. There was evidence of a slight decrease in the

MAP noted at the end of flight as detected above the balloon in both the partial and full REBOA groups.

Conclusion: ER-REBOA and p-REBOA catheters-maintained MAP up to 22,000 ft in an inanimate model. In the porcine model, ER-REBOA deployment improved MAP and the balloon remained effective at altitude. The pREBOA results suggest that the pREBOA balloon is efficacious at altitude and reduces the ischemia-reperfusion injury while maintaining lower extremity perfusion compared to a fully occlusive aortic balloon. In addition, partial aortic occlusion allowed for the mitigation of the additional insult of altitude that would otherwise exacerbate the ischemia/reperfusion inherent to aortic occlusion for hemorrhage control.

3.0 INTRODUCTION:

Hemorrhage remains a leading cause of early death after trauma, accounting for 25-40 percent (%) of the mortality rate overall and 80% of potentially non-lethally injured patient mortality. [1-3]. Non-compressible torso hemorrhage, as characterized by torso injury not amenable to control by direct pressure, accounts for approximately two thirds of preventable in non-lethal trauma in civilian and military populations.[4-6] and death is attributed to hemorrhage. [7]

While hemorrhage can only be definitively controlled by surgical intervention or angioembolization, the nearest center with such capabilities may be at a substantial distance from where the trauma occurred. In the United States, approximately 50 million people live at least 60 minutes away from the nearest Level 1 or Level 2 trauma center, which often necessitates aeromedical emergency transport services.[8] Aeromedical evacuation is also common in global combat scenarios, with 28,000 aeromedical evacuations performed in 2003 alone during Operation Iraqi Freedom.[9,10] Therefore, temporizing blooding control measures could be

implemented to ensure that patients survive transport to the nearest facility capable of definitive hemorrhage control.

In order to control bleeding in these patients, temporary aortic occlusion may be required. [11] While this maneuver has traditionally been achieved by open aortic cross-clamping, REBOA is increasingly used in military and civilian populations to achieve this goal through percutaneous placement of an endovascular balloon, thereby sparing patients the morbidity of a thoracotomy. Multiple trials comparing REBOA to resuscitative thoracotomy have demonstrated that REBOA has equal or superior clinical outcomes. [(12-15)] Moore *et al*. demonstrated in a retrospective study of 76 patients that REBOA utilization had a 16.7% mortality rate compared to a 62.5% mortality rate in the resuscitative thoracotomy patients. [13] Another larger retrospective study of 903 patients in Japan similarly demonstrated that patients who underwent REBOA had a lower mortality compared to thoracotomy (67% from 90%). [14]

Controlling non-compressible hemorrhage is particularly challenging in rural areas and in austere military environments where immediate operative intervention is not feasible, and resources are limited. Without the ability to provide definitive care, hemorrhage management shifts to temporizing measures known as damage control resuscitation (DCR). DCR is defined by actions that promote hemorrhage control and hemostasis while avoiding exacerbation of bleeding through iatrogenic harm, including minimizing crystalloid administration, providing balanced blood products, and permissive hypotension.[16] However, in the setting of devastating torso injury, these maneuvers have proven to not be sufficient in preventing deaths.

Classically, operative aortic control for the emergent management of non-compressible torso hemorrhage has been limited to resuscitative thoracotomy. Not only does this procedure carry a high mortality rate associated with it, ranging between 43% to 100%, but this operation should only be performed in close proximity to definitive surgical management. [(14,17,18)] A

percutaneous alternative to aortic cross clamping for occlusion of the aorta in torso hemorrhage is REBOA.[19] REBOA in these circumstances has been considered as a possible adjunct in the setting of patients in extremis, with one study even suggesting that upwards of 10% of patients who presented to a large Level I trauma center could have benefitted from pre-hospital REBOA.[20-21] Yet, there is a paucity of clinical data of pre-hospital REBOA usage to truly support its use without definitive care immediately available.[22]

When compared to aortic cross clamping, REBOA has been demonstrated to reduce morbidity and mortality.[12-15, 23] In spite of this advantage, the usage of ER-REBOA™ (Prytime Medical Devices Inc., Boerne, TX) is still limited to approximately 50% of US Level 1 trauma centers, and primarily for use in pelvic fractures as opposed to polytrauma or resuscitative efforts.[24] While effective for hemorrhage control, REBOA deployment incurs the risk of ischemia reperfusion injury with prolonged use, which has been demonstrated both in animal models as well as in human studies.[25-29]. Due to this lack of evidence, no REBOA catheter has yet been proven to be appropriate for pre-hospital use, and its efficacy has not been demonstrated at altitude. Demonstrating safety and efficacy in these circumstances is particularly vital in the setting of prehospital aeromedical evacuation and en route care. Moreover, aeromedical evacuation is ubiquitous in the military, particularly during foreign conflicts. In 2003, during Operation Iraqi Freedom, approximately 28,000 aeromedical evacuations were performed. [10] While it is not as common in the civilian trauma population, aeromedical transport of patients has demonstrated improved rates of survival compared to ground transport in select patients. [11] Therefore, we conducted a series of experiments, both in inanimate and porcine models, to examine the efficacy of a REBOA catheter at altitude and at physiological temperature. We hypothesized that changes in altitude would not induce blood pressure changes or exacerbate physiologic derangements with a deployed REBOA.

Additionally, a pREBOA balloon, has been developed with the intention to allow for life-saving hemorrhage control without non-survivable ischemia reperfusion injury.[19, 29] Whether pREBOA works to maintain hemodynamic stability while maintaining structural efficacy at altitude has yet to be elucidated. In both civilian and military flight, aircraft are pressurized to 8000 feet altitude, which raises concern around balloon efficacy. [30]Therefore, we designed a porcine model to evaluate the efficacy of a partially inflated REBOA catheter at altitude and physiologic temperature. We hypothesized that the pREBOA balloon would function similarly to the ER-REBOA ™ and therefore would be safe at altitude.

The remainder of this technical report will provide research methods, statistical findings, discussion and conclusion for each of the above hypothesis.

4.0. METHODS:

REBOA:

Simulation model and tactical flight

A commercially available simulation model for the 7 French guidewireless ER-REBOA ™ catheter (Prytime Medical Devices, Inc, Boerne, TX) was used. This model consists of a closed circuit with water that flowed in a pulsatile, arterial-like manner. The device was controlled by a tablet, with real-time display of pressure generated within the simulated aorta, which was calibrated to be consistent with human blood pressure. Blood pressure was calibrated to have a SBP between 70-80 mmHg and a DBP between 40-50 mmHg, for a MAP of approximately 50-60 mmHg prior to REBOA deployment. Each ER-REBOA ™ catheter underwent three 90-minute flights for a total of 9 flights, both at the room temperature and at the physiological temperature models.

In the room temperature model, the altitude chamber was set to ambient room temperature of approximately 22 degrees Celsius (°C) and the temperature of the water ranged from 23.9°C to 24.9°C. For the physiological temperature model, the altitude chamber was pre-heated to 37°C for four hours prior to experimentation. The simulation model was subsequently infused with water set to temperatures between from 36.9-38.5°C. Water temperatures were measured at the start and end of each flight to ensure consistency.

After the simulation model was infused with the appropriate temperature water, an ER-REBOA catheter was introduced, and 8 m of saline was used to inflate the balloon. For both models, the simulation model underwent three 90-minute simulated flights using a custom-built altitude chamber located in the Center for Surgical Innovation at the University of Cincinnati (Abbess Instruments and Systems, Ashland, Massachusetts). Each flight consisted of 15 minutes each at 0 ft, 5K (thousand K) ft, 8K ft, 12K ft, and 22K ft before returning to ground level. SBP, DBP, and MAP were measured every five minutes at each altitude, as well as at the end of experiment and after the balloon was deflated. After trials had been completed in the altitude chamber, the same model was placed on board a C130 military aircraft during an 82-minute tactical training flight reaching up to 35K ft. SBP, DBP, and MAP measurements were taken every ten minutes during the flight.

Animal housing and preparation

This study was reviewed and approved by University of Cincinnati Institutional Animal Care and Use Committee as well as the Air Force Medical Support Agency Office of Research Oversight and Compliance. Animals were cared for by a program approved by the Association for Assessment and Accreditation of Laboratory Animal Care International and in compliance with the National Research Council's 2011 Guide for the Care and Use of Laboratory Animals as well as Department of Defense Instruction 3216.1. Twenty female Yorkshire swine that

weighed a mean of 41.75 plus or minus (±) 1.6 kilogram (kg) were obtained from Isler Genetics (Prospect, OH) and were acclimated in our animal facility for 48-72 hours prior to experimentation. Animals were housed alone or in pairs and fed and watered without restriction, except for the night before study initiation in order to prevent aspiration during induction of anesthesia.

Experiments were performed at the surgical facility in the University of Cincinnati Center for Surgical Innovation. Pigs were sedated with tiletamine hydrochloride (*Telazol)* and xylazine hydrochloride (both given 5 milligram of medication per kilogram (mg/kg) intramuscularly, Henry Schein Animal Health, Dublin, OH). Sedated pigs were placed in a supine position and orotracheally intubated. Pigs were maintained on a ventilator (Ohmeda, Madison, WI) in pressure control mode during ground portions of the experiment and transferred over to Impact 731 Series Ventilator (IMPACT Instrumentation, West Caldwell, NJ) for flight.

Hemodynamic Monitoring, REBOA placement, and Laboratory Values

All animals were shaved and prepped in a clean technique. Prior to line placement, pigs were randomized to ground or flight. Flight animals were taken to an altitude of 8k ft. Pigs were also randomized to REBOA deployment or no-REBOA for a total of 4 groups (REBOA ground, REBOA flight, no-REBOA ground, and no-REBOA flight). In the no-REBOA groups, the catheter was inserted but the balloon was not inflated. All pigs underwent the same following procedures. A left carotid arterial line was placed via cutdown using an arterial catheterization set (Teleflex, Wayne, PA). The right internal jugular vein was cannulated with an 8 French size (Fr) introducer for central venous access. A 7Fr introducer sheath was placed via left femoral artery cut-down after gaining proximal and distal control of the femoral artery. After lines were placed, the right femur was fractured by dissecting through the soft tissue and firing a pressurized bolt gun directly against bone (Bock Industries, Philipsburg, PA). The pigs subsequently

underwent controlled hemorrhage by removing blood from the arterial access line. Hemorrhage began at 1.5 milliliter per kilogram per minute (ml/kg/min) for 7 minutes, followed by 0.75 ml/kg/min for 13 minutes to target a MAP of 40 mmHg (±5mmHg) for a total of 20 minutes of hemorrhage. Blood was collected for return to the pig during resuscitation in citrate-coated blood bags (Terumo Corporation Imuflex, Tokyo, Japan).

After hemorrhagic shock, the REBOA catheter was introduced via the left femoral sheath to Zone I, as defined by superior to the mesenteric arteries in the peridiaphragmatic aorta. REBOA pigs had the balloon immediately insufflated with 9 mL saline for 15 minutes prior to altitude. After 15 minutes at ground level, pigs were placed in the altitude chamber. Ground pigs remained in an open chamber without altitude increase. Simulated flight pigs were taken to an altitude of 8k ft for 15 minutes. Pigs were resuscitated with their shed citrated blood 10 minutes into flight. After flight was completed, the pigs were given 100 milliequivalents (mEq) sodium bicarbonate and 1 gram (g) calcium chloride as the balloon was deflated over three minutes at a rate of 3 milliliters per minute (ml/min). Pigs then underwent a four-hour observation, during which time a MAP was targeted to greater than 50 mmHg, allowing up to 2 liters (l) in boluses of crystalloid per hour.

Vitals signs (heart rate (HR), SBP, DBP, MAP, respiratory rate (RR), and temperature) were measured at baseline, then after hemorrhagic shock, REBOA placement, altitude, postflight, and hourly during the observation period. Arterial blood was collected at baseline, after shock, after flight, and hourly during the 4-hour observation period. An iSTAT ™ point-of-care analyzer (Abaxis, Union City, CA) was used to measure arterial blood gas, electrolytes, and prothrombin time international normalized ratio (PT/INR). Whole blood was then placed in a serum separator tube (BD Bioscience, San Diego, CA) and centrifuged at 1,000 relative centrifugal force (g.)for 10 minutes after which the porcine serum was collected and analyzed

for pro-inflammatory cytokines interleukin (IL) IL-1, IL-6, IL-8, and Tumor Necrosis Factor (TNF)-alpha (a) using a Q-Plex ™ Porcine Chemokine High Sensitivity enzyme-linked immunoassay (ELISA) assay according to the manufacturer's protocol (Quansys Bioscience, Logan, Utah).

Statistical Analysis

Continuous variables are displayed as mean ± standard deviation. For the simulator model, values were compared by Student's t-test and probability (p) less than (<) 0.05 was considered significant. Analysis of Variance (ANOVA) analysis was used to analyze porcine data to account for multiple pigs at different time points. All statistical analyses were performed with Prism 6 ™ (GraphPad Software, La Jolla, California).

pREBOA

Simulation model and tactical flight

A commercially available simulation model for the 7-Fr guidewireless pREBOA-PRO ™ (Prytime Medical Devices, Inc, Boerne, TX) was utilized, as previously described.[8] Briefly, the model was a closed model torso with a perfusion circuit filled with water that flowed in a pulsatile manner and was calibrated to correspond to human blood pressure. Unlike the ER-REBOA model used previously, this model was capable of monitoring pressure above and below the balloon. Each pREBOA catheter underwent three flights for a total of 9 flights using a custom-built altitude chamber at the University of Cincinnati (Abbess Instruments and Systems, Ashland, Massachusetts). Full occlusion was achieved by inflating the balloon with 8mL of normal saline. Partial inflation was achieved by titrating the amount of saline introduced in the balloon to allow a MAP of 50 mmHg proximal to the balloon. Each flight consisted of 15 minutes each at 0 ft,

5K ft, 8K ft, 12K ft, and 22K ft before returning to ground level. SBP, DBP, and MAP were measured every five minutes at each altitude, at the end of the experiment, and after the balloon was deflated.

Animal model and care

After demonstrating efficacy in the simulation model, a porcine model was developed in accordance with the University of Cincinnati Institutional Animal Care and Use Committee as well as the Air Force Medical Support Agency Office of Research Oversight and Compliance. Animals were cared for by a program approved by the Association for Assessment and Accreditation of Laboratory Animal Care International and in compliance with the National Research Council's 2011 Guide for the Care and Use of Laboratory Animals as well as Department of Defense Instruction 3216.01.

The study was also designed to conform with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines and a complete checklist has been uploaded as Supplemental Digital Content (SDC-1). No pigs were excluded from the study or the analyses. The determination of sample size was derived from the primary outcome of measure being serum lactate based off our previous investigation of ER-REBOA at altitude. Using previously published data, we estimated that serum lactate levels would be 50% lower in partial compared to full REBOA pigs with a 33.3% variance, so that a minimum sample size of 4 animals per group was established.

Twenty-four female Yorkshire swine were obtained from Isler Genetics (Prospect, OH) and were randomized into six different experimental groups – ground partial inflation, ground full inflation, 8K ft partial inflation, and 8K ft full inflation, sham REBOA ground, and sham REBOA 8K ft. Sham REBOA animals had the catheter inserted and positioned but the balloon was not inflated. The pigs were acclimated in our animal facility for 48-72 hours prior to

experimentation and fed and water ad lib but were made nil per os (NPO) the night prior to surgery in standard fashion.

Experiments were performed at a surgical facility in the Center for Surgical Innovation at the University of Cincinnati College of Medicine. Pigs were sedated with tiletamine hydrochloride (Telazol, dose 5mg/kg) and xylazine hydrochloride (5mg/kg)(Henry Schein Animal Health, Dublin, OH). Sedated pigs were placed supine and were orotracheally intubated. Pigs were maintained on a ventilator (Ohmeda, Madison, WI) in pressure control mode when not in the altitude chamber and transferred to the altitude-approved Impact 731 Series Ventilator (IMPACT Instrumentation, West Caldwell, NJ) for simulated flight.

pREBOA placement, central access monitoring, and laboratory values

As described previously, all animals were shaved and prepped in the typical fashion.[17] In the full REBOA groups, the balloon was inflated with 8mL of sterile saline. In the partial inflation group, the balloon was inflated to achieve a MAP of 50 mmHg above the balloon. All of the study arms underwent the same procedures. A left carotid arterial line was placed via an open cutdown approach for blood samples (Teleflex, Wayne, Pennsylvania). The right internal jugular vein was cannulated via an open cutdown approach for anesthesia infusion. For REBOA placement, a 7Fr introducer sheath was placed in the left femoral artery. After lines were placed, the right femur was fractured with a bolt gun (Bock Industries, Phillipsburg, Pennsylvania). The pigs underwent a controlled hemorrhage by removing blood from the arterial line. Hemorrhage began at 1.5ml/kg/min for 7 minutes, followed by 0.75ml/kg/min for 13 minutes with a target MAP of 40 mmHg (±5mmHg) or 50% of total blood volume. Blood was collected for return to the pig in citrate-coated collection bags (Terumo Corporation Imuflex, Tokyo, Japan).

After shock, the REBOA catheter was introduced via the left femoral sheath to Zone I. Full REBOA pigs had the balloon immediately inflated with 8mL of saline. pREBOA pigs had

the balloon inflated with a saline volume sufficient to achieve only a MAP of 50 mmHg. Pigs remained outside the chamber for 15 minutes and were then subsequently transferred into the altitude chamber and placed on a propofol infusion to maintain sedation during simulated flight. Ground pigs were transferred to the chamber, but the altitude was unchanged. Simulated flight pigs were taken to 8K ft altitude for 15 minutes. Pigs were resuscitated with shed blood 10 minutes into flight. Post-flight, pigs were given 100mEq sodium bicarbonate and 1g calcium chloride and the balloon was deflated over 3 minutes at a rate of 2.5mL/min. Pigs then underwent a 4-hour observation time.

Vital signs (temperature, HR, SBP, DBP, MAP, and RR) were measured at baseline, after hemorrhagic shock, at REBOA placement, altitude, postflight, and hourly during observation, with blood collection at baseline, after shock, after flight, and hourly during observation. An iSTAT^{TM} point-of-care analyzer (Abaxis Union City, CA) was used to measure blood gas, potassium, and PT/INR. Whole blood was analyzed for IL-1, IL-6, IL-8, and TNF-α using a ELISA assay according to the manufacturer's protocol (Quansys Bioscience, Logan, Utah).

Statistical analysis

For the simulation model, values were compared by Student's t-test; $p < 0.05$ was considered significant. ANOVA comparisons were used to analyze porcine data to account for multiple pigs at different time points. Continuous variables are displayed as mean ± standard deviation. Statistical analyses were performed with Prism 6 (GraphPad Software, La Jolla, California).

5.0 RESULTS:

REBOA

Effect of Altitude on SBP with REBOA simulator

In the room temperature model, inflating the REBOA led to an acute increase of mean SBP. As altitude increased, SBP decreased slightly but steadily at each altitude compared to ground level ($p<0.01$). No significant change was seen between pre- and post-flight SBP (Figure (Fig) 1A). The physiologic temperature model replicated these findings. Mean starting SBP for this model was 138 mmHg. Increasing the altitude from ground to 5K ft resulted in a decrease in SBP to 130 mmHg ($p<0.01$) and increasing to 8K ft decreased SBP further to 127 mmHg ($p<0.04$). Increasing altitude from 8K ft to 12K ft did not result in a significant change; however, increasing altitude to 22K ft induced an increase to 134mmHg ($p<0.03$). Post-flight SBP was 4mmHg lower than pre-flight SBP (Fig 1B).

Effect of Altitude on DBP with REBOA simulator

In the room temperature model, DBP started at 65mmHg post-REBOA inflation. Increasing the altitude to 5K ft raised the DBP. No significant changes were noted increasing altitude from 5K ft to 8K ft; however, increasing the altitude to 12K ft again increased the DBP. No significant difference was noted in increasing the altitude further to 22K ft and there was no significant change between the pre- and post-flight DBP. In the physiologic temperature model, increasing the altitude only had a significant effect from ground to 5K ft. No further changes were noted with increasing the altitude to 8K ft, 12K ft, 22K ft or between pre- and post-flight DBP. (Fig 1A and B)

Effect of Altitude on MAP with REBOA simulator

In the room temperature model, MAP was only noted to change significantly when increasing altitude from ground to 5K ft, where an increase from a MAP of 91mmHg to 102mmHg was noted ($p<0.01$). No further changes were noted. (Fig 1A)

In the physiologic temperature model, MAP at ground was noted to be 99mmHg. A change in MAP was only noted in bringing the model from 12K ft to 22K ft, where MAP increased to 107mmHg ($p<0.01$). (Fig 1B)

REBOA Performance in Active Military Aircraft

In taking the REBOA simulation model to 35K ft in a military aircraft, there was no significant difference in SBP (126mmHg and 127mmHg at ground and altitude, respectively). However, DBP increased from 91mmHg to 96mmHg ($p<0.01$) and MAP increased from 103mmHg to 106mmHg ($p<0.03$). (Fig 2)

Porcine REBOA Performance

Ground REBOA pigs were tachycardic compared to ground no-REBOA pigs; however, the REBOA pigs were actually more tachycardic prior to REBOA placement. In the no-REBOA groups, the flight pigs were tachycardic compared to the ground pigs; however, no difference was observed in the between ground or flight REBOA groups. No differences in HR were appreciated between any of the groups after REBOA was deflated, including the REBOA versus no-REBOA flight pigs. (Fig 3A)

In examining SBP, DBP, and MAP, the ground REBOA and flight REBOA pigs demonstrated the expected higher SBP, DBP, and MAP compared to their respective no-REBOA pigs from time of inflation until deflation. Importantly, within the REBOA pigs, there were no significant differences between the ground and flight groups. After deflation, however, REBOA pigs were more hypotensive compared to the no-REBOA pigs. The SBP in the REBOA flight pigs

remained lower for longer than the REBOA ground pigs. Ground REBOA pigs recovered from their post-balloon hypotension by observation hour two, whereas flight REBOA pigs had a lower SBP throughout the entire resuscitation period. (Fig 3B) DBP remained no different between the ground and flight pigs; however, REBOA ground pigs were found to have lower DBP than no-REBOA ground pigs at observation hours one and three. (Fig 3C) The trend for MAP demonstrated that the ground REBOA pigs were hypotensive compared to ground no-REBOA pigs through observation hour three and flight REBOA pigs remained hypotensive through the duration of their resuscitation period. Although there were differences in comparing how the REBOA pigs performed relative to their no-REBOA counterparts, there were no statistically significant differences in MAP throughout the entire experiment when comparing the flight REBOA to ground REBOA porcine groups. (Fig 3D)

REBOA pigs were persistently more acidotic compared to the no-REBOA pigs. Both the ground and flight pigs had a lower power of hydrogen (pH) after REBOA was removed through observation hour one in comparison to their respective no-REBOA counterparts. (Fig 4A) Bicarbonate levels were actually lower in the ground REBOA pigs from observation hour through observation hour four compared to no-REBOA pigs. (Fig 4B) Lactate was significantly higher in the ground REBOA pigs but cleared after observation hour three. In the flight REBOA pigs, lactate was elevated immediately after flight through observation hour four. (Fig 4C) Base excess was higher in both the flight and ground no-REBOA pigs throughout the observation period. (Fig 4D) On arterial blood gas, partial pressure of carbon dioxide (pCO2) was lower immediately post REBOA deflation and at observation hours two and three in both groups. Flight REBOA pigs also had a lower pCO2 at observation hour four and were notably hyperkalemic compared to no-REBOA pigs at observation hours two through four. Ground REBOA pigs were

hyperkalemic only at observation hour one. However, there were no differences in respiratory acidosis or hyperkalemia between the flight REBOA and ground REBOA groups (Fig 4E-F). No changes were seen between the pig groups in other electrolytes or coagulation studies, as there were no differences between hemoglobin, PT/INR. ELISA™ analysis of serum samples demonstrated no differences in the levels of IL-1b, IL-6, or TNF-alpha. IL-8 was found to be lower in ground REBOA compared to ground no-REBOA pigs immediately post flight. IL-8 was also found to be higher in the ground no-REBOA group compared to flight no-REBOA flight; however, this difference was also observed at baseline and therefore is unlikely to be related to flight.

FIG 1A: Room Temperature Model

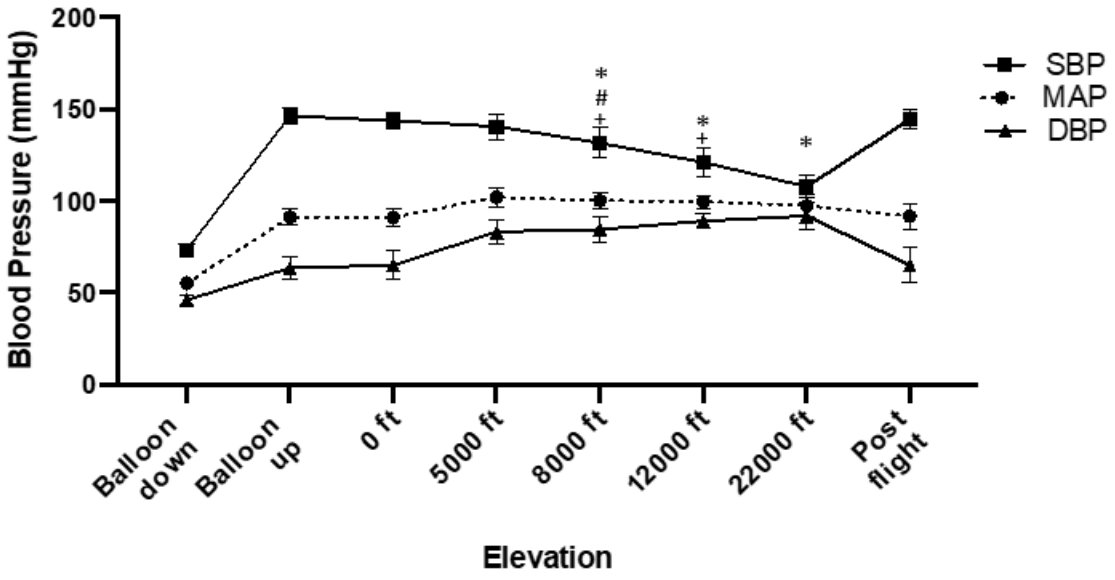


Fig 1B: Physiologic Temperature Model

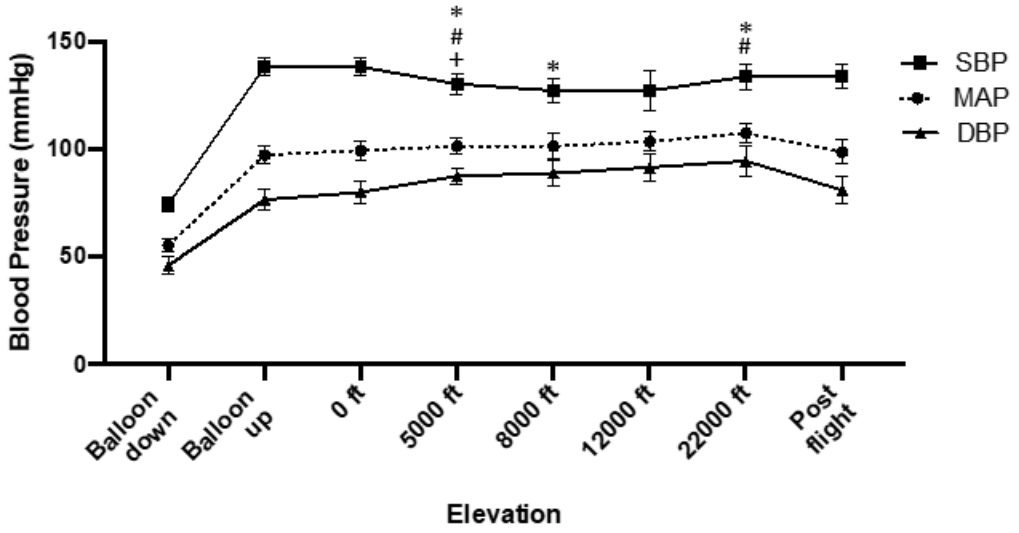


Fig 2: REBOA Performance in Active Military Aircraft

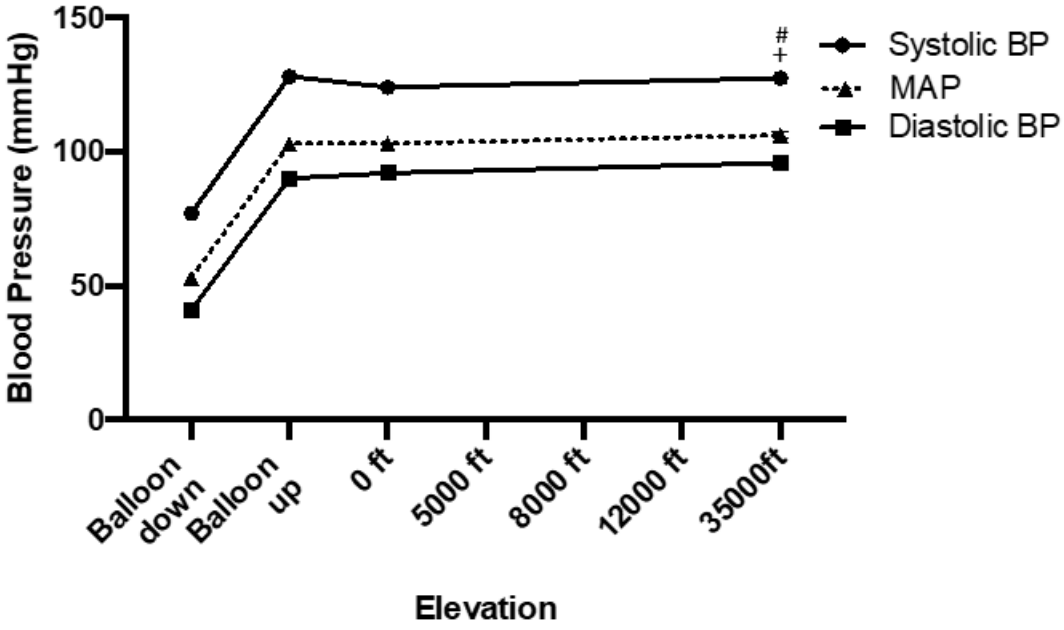


Fig 3A: Porcine REBOA Performance

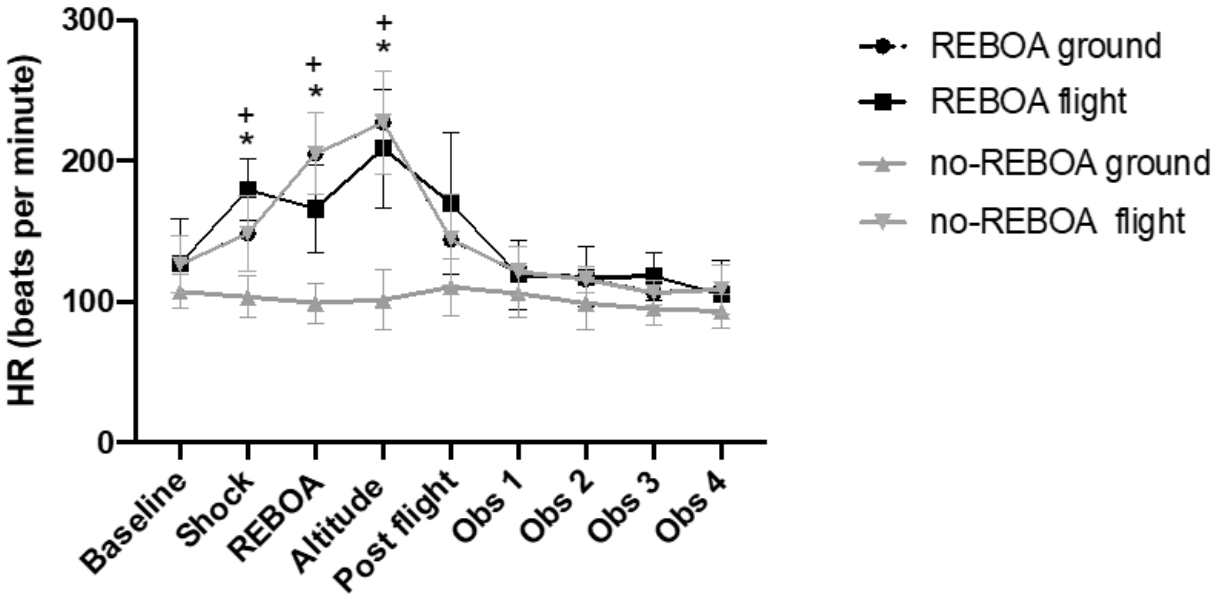


Fig 3B: Porcine REBOA Performance

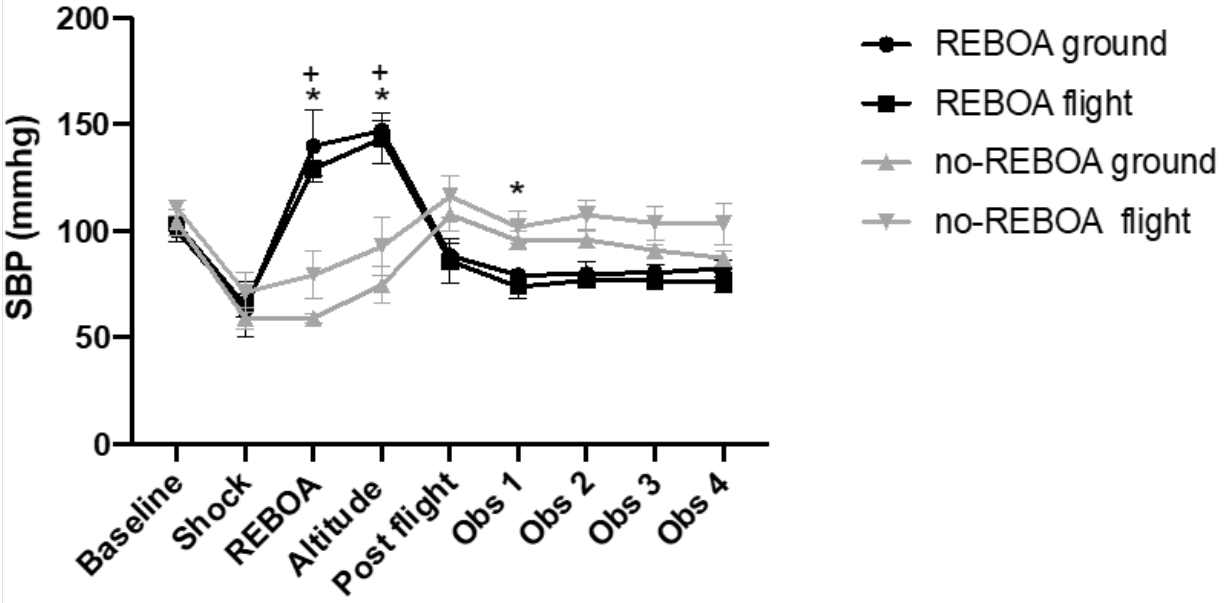


Fig 3C: Porcine REBOA Performance

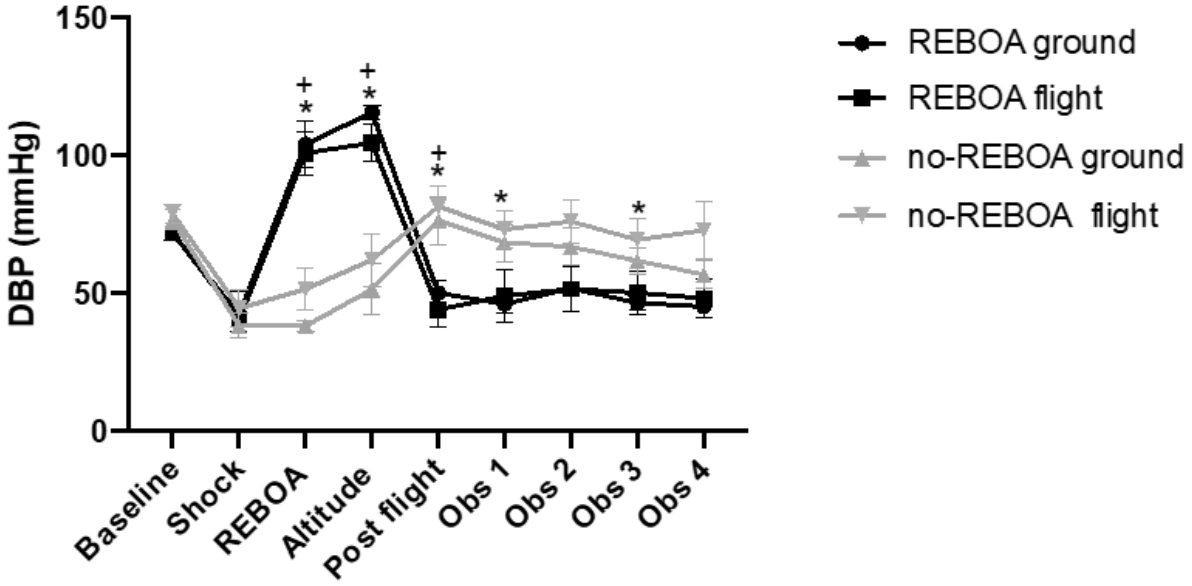


Fig 3D: Porcine REBOA Performance

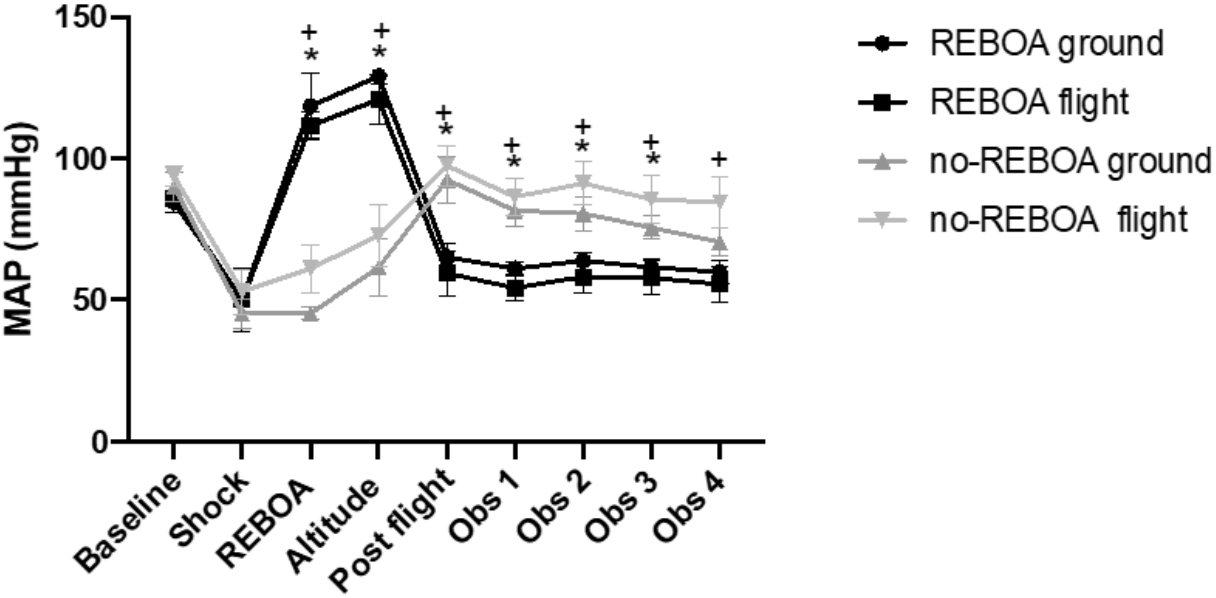


Fig 4A: Porcine REBOA pH Comparison

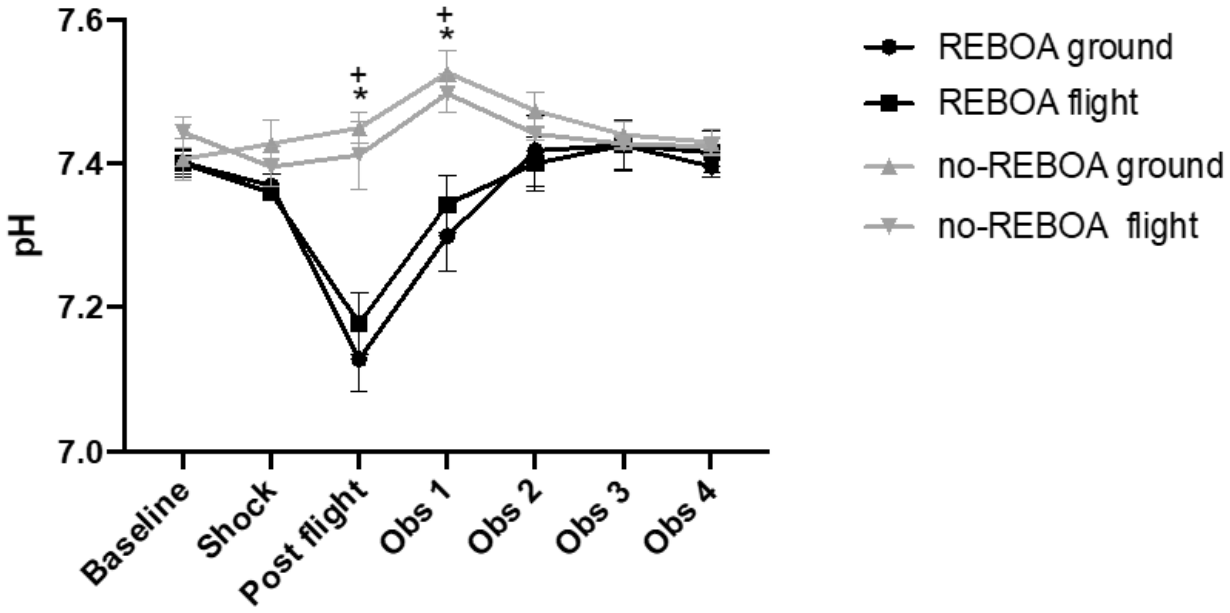


Fig 4B: Porcine REBOA Bicarbonate Comparison

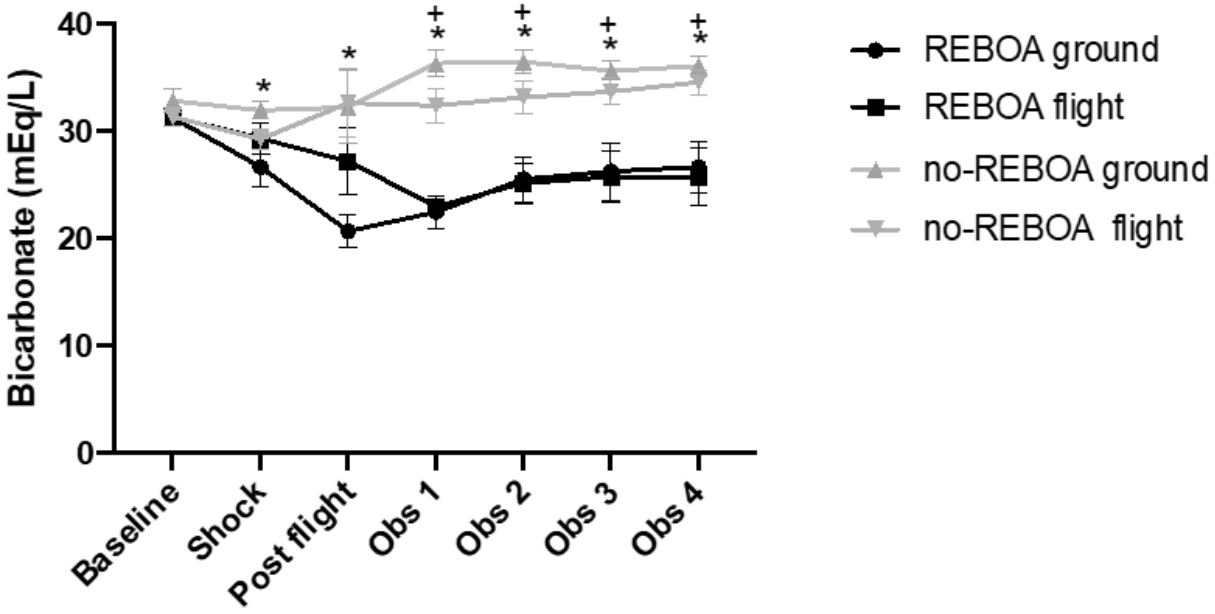


Fig 4C: Porcine REBOA Lactate Comparison

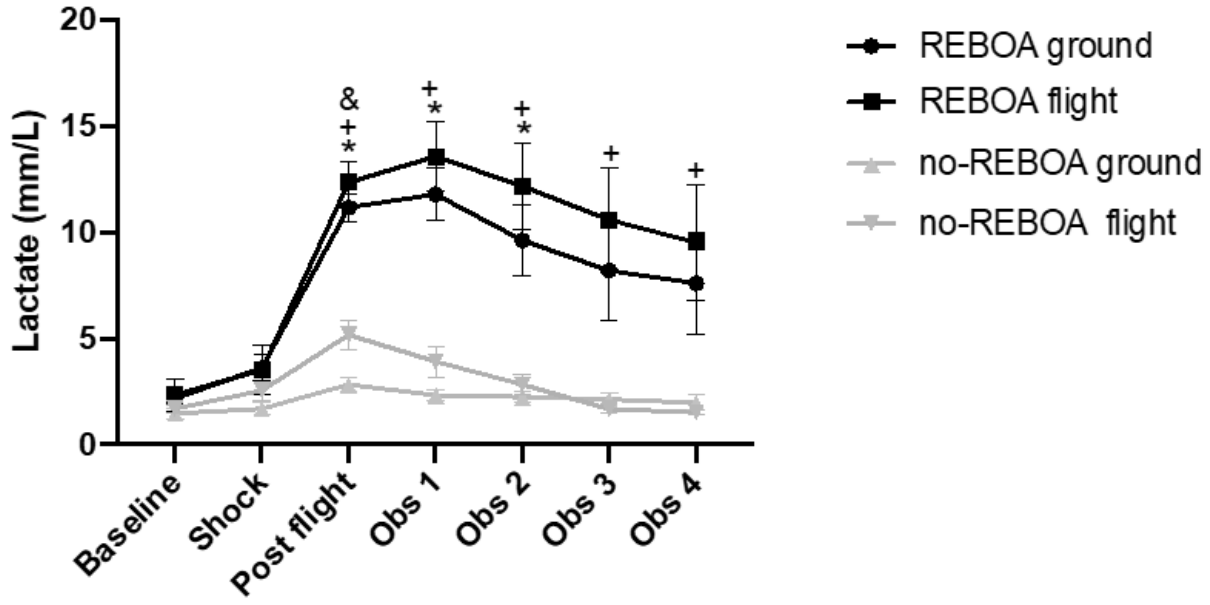


Fig 4D: Porcine REBOA Base Excess Comparison

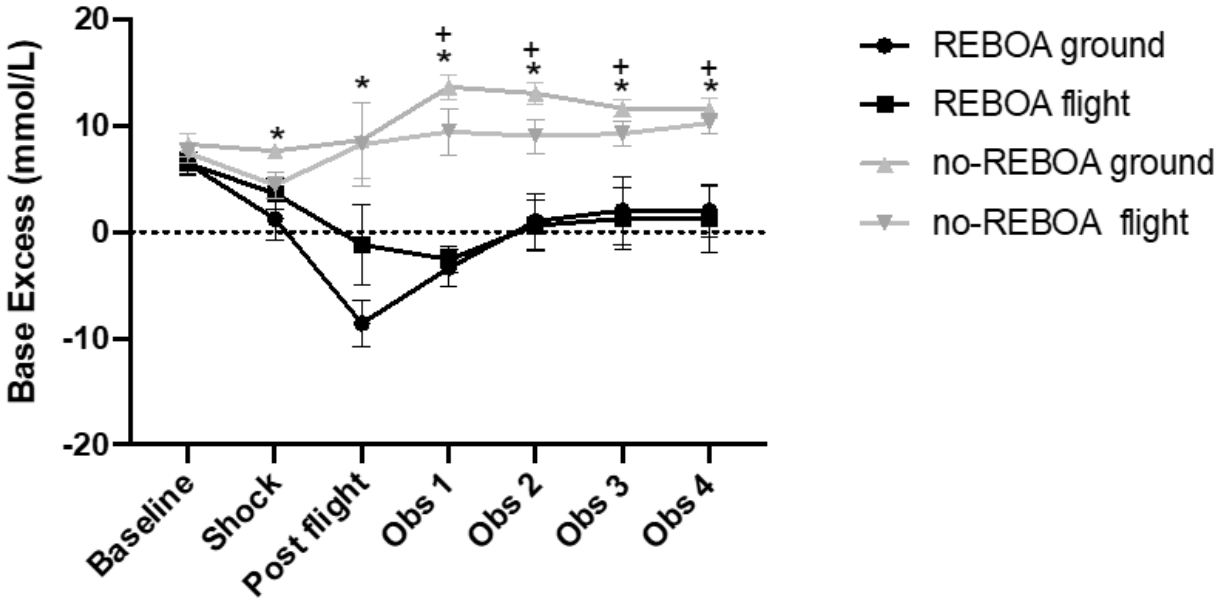


Fig 4E: Porcine REBOA pCO_2 Comparison

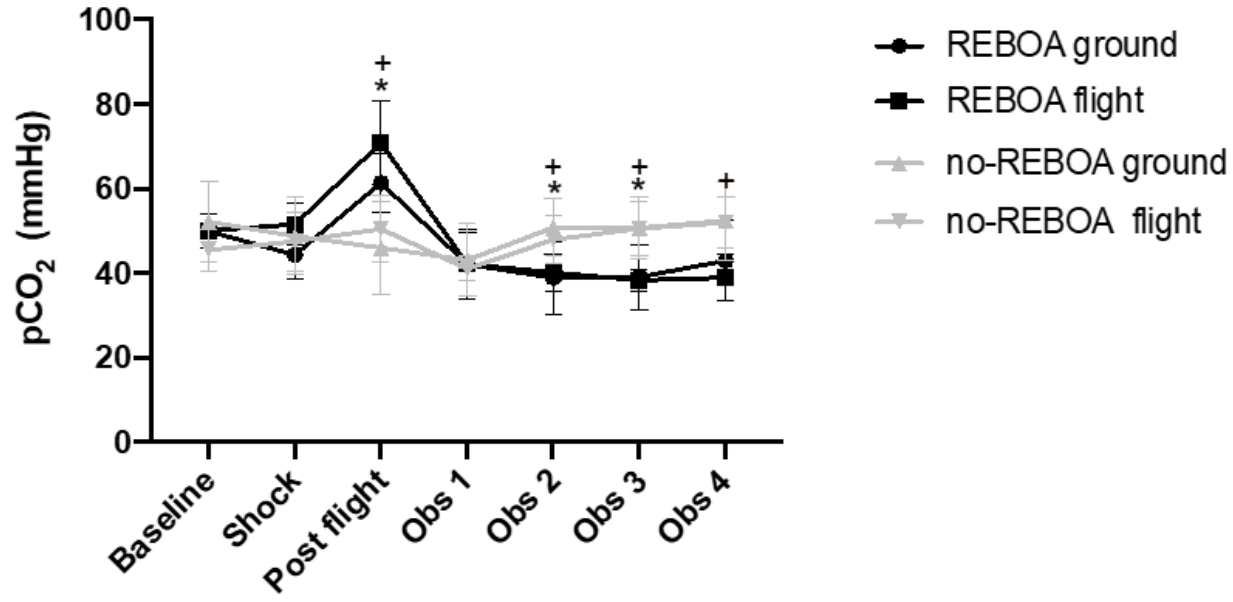
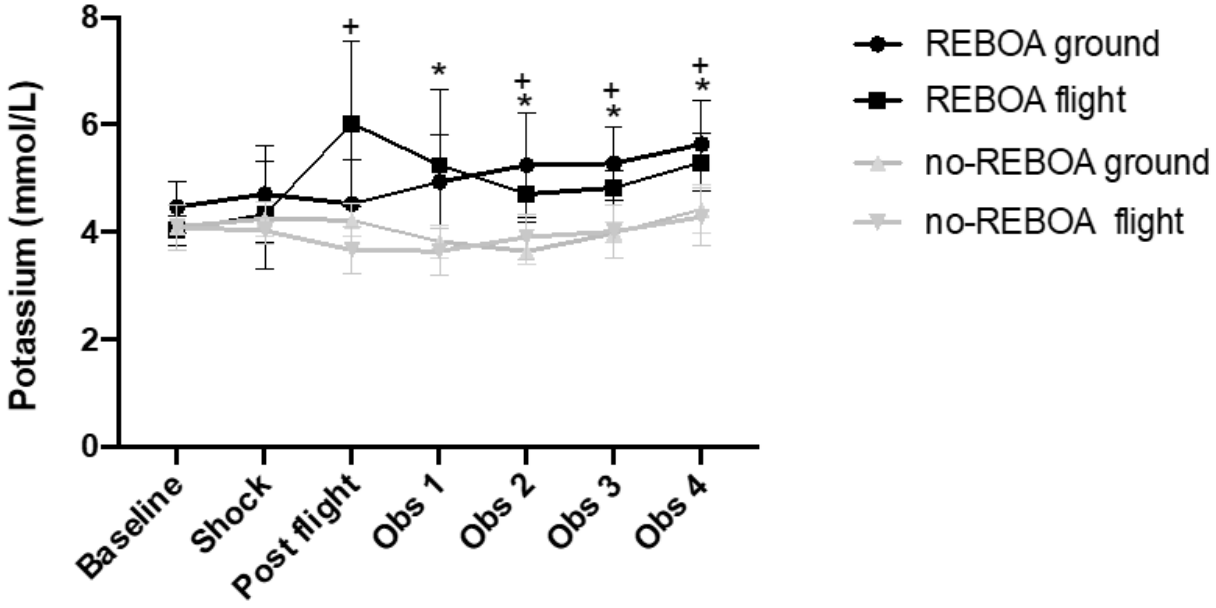


Fig 4F: Porcine REBOA Potassium Comparison



pREBOA

Simulator Flights

Upon inflating the balloon per protocol, significant differences were noted in the SBP, MAP, and DBP, as expected (Fig 5). There were no differences in the SBP or DBP over the course of the flights, indicating that the balloon did not change in its compliance over the course of the flight in the simulation model. Of note, there was a slight decrease in the MAP noted at the end of flight as detected above the balloon in both the partial and full REBOA groups.

Partial inflation REBOA pigs did not show increased tachycardia compared to sham

At time of femur fracture, all animals had comparable HR (Fig 6). After hemorrhagic shock, the full REBOA pigs were more tachycardic compared to sham groups, which persisted through altitude exposure. Post-resuscitation, full REBOA pigs at 8 K ft were more tachycardic than their ground counterparts. Among the ground pigs, the full REBOA pigs were more tachycardic than the pREBOA or sham animals. After deflation of the balloon, full REBOA 8K ft pigs were more tachycardic than the full REBOA ground pigs. Full REBOA pigs were also more tachycardic than the pREBOA or sham REBOA pigs. Of note, no differences were found between the pREBOA and sham REBOA groups.

Full inflation of REBOA resulted in a higher SBP, DBP, and MAP compared to partial inflation and sham

After shock, no significant differences in SBP, DBP, and MAP were appreciated between all porcine groups (Fig 7A-C) Full REBOA pigs had a higher SBP, DBP, and MAP after inflation compared to pREBOA and sham pigs. Ground full REBOA pigs continued to have a higher SBP and DBP than partial or sham pigs, however, pigs taken to 8K ft had a higher SBP than the sham pigs only and there were no differences between the pREBOA and full REBOA animals. Of

note, ground full REBOA pigs had a higher SBP, DBP, and MAP than those taken to altitude. For the pigs that went to 8K ft, differences in MAP and DBP were noted between full REBOA and sham as well as pREBOA and sham.

Distal perfusion pressures – SBP, MAP, and DBP – were all improved in partially inflated REBOA compared to fully inflated REBOA (Fig 8 A-C).

pREBOA had improved acidosis compared to full REBOA, particularly at altitude

Full REBOA animals had a lower pH than pREBOA pigs for both altitude and ground groups at observation hour 1 (Fig 9A). Lactate was also significantly higher in the full REBOA groups, particularly the group that went to altitude (Fig 9B). Full REBOA pigs sustained a higher lactate than pREBOA pigs from deflation through hour 3 for the ground group and through hour 4 for the 8K ft animals. Notably, full REBOA 8K ft animals had a higher lactate than full REBOA ground pigs for all observation hours. By observation hour 3, there was a difference between partial ground versus 8K ft and full ground versus 8K ft. pCO_2 was lower in full REBOA pigs at 8K ft versus partial at observation hour 3 and hour 4 (Fig 9C). At hour 4, differences were noted between the full REBOA ground versus 8K ft and the pREBOA ground versus 8K ft. Bicarbonate was also higher in the pREBOA 8K ft pigs compared to full REBOA animals starting immediately at balloon deflation and continuing through until observation hour 3 for ground groups and hour 4 for altitude groups (Fig 9D). Of note, differences were noted between the altitude and ground groups of both partial and fully inflated REBOA. Base deficit was worse in full REBOA at 8K ft compared to partial and sham at 8K ft starting at deflation of the balloon (Fig 9E). At hour 1-4 of observation, full REBOA pigs had a greater base deficit than partial or sham at 8K or ground. Of note, 8K ft pigs had a greater base deficit than their ground counterparts for both full and pREBOA .

Fully inflated REBOA had altitude had an increase in IL-6 compared to partially inflated REBOA

Full REBOA pigs that underwent flight had a greater IL-6 compared to ground full REBOA pigs from hour 1 through hour 3 of observation (Fig 10) Differences between full and pREBOA were only noted at altitude during observation hours 2 and 3. No differences were seen in IL-1b or IL-8 between the groups. TNF-α was elevated in the ground pREBOA groups in observation hours 3 and 4 compared to pREBOA 8K ft and full REBOA ground (Fig 10).

Fig 5: Deployment of simulation balloon effective at partial and full occlusion at altitude

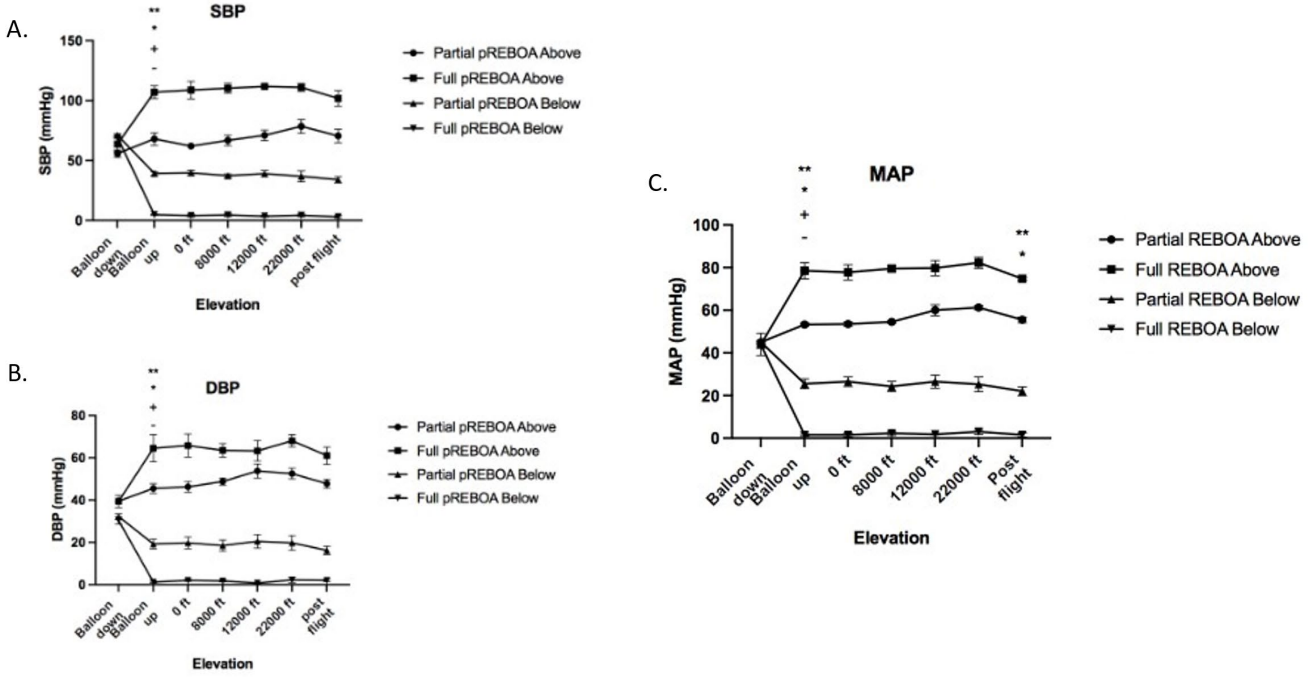


Fig 6: Full deployment of REBOA resulted in greater tachycardia compared to partial REBOA

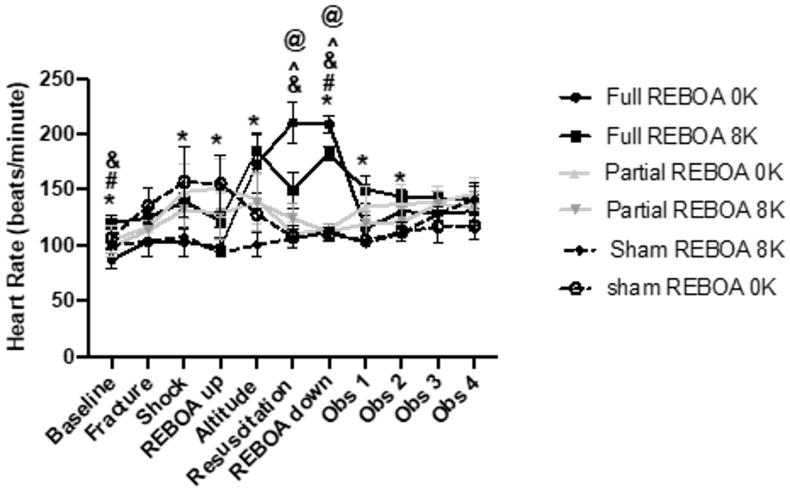


Fig 7: Full deployment of REBOA resulted in increased SBP, DBP, and MAP compared to partial REBOA and sham

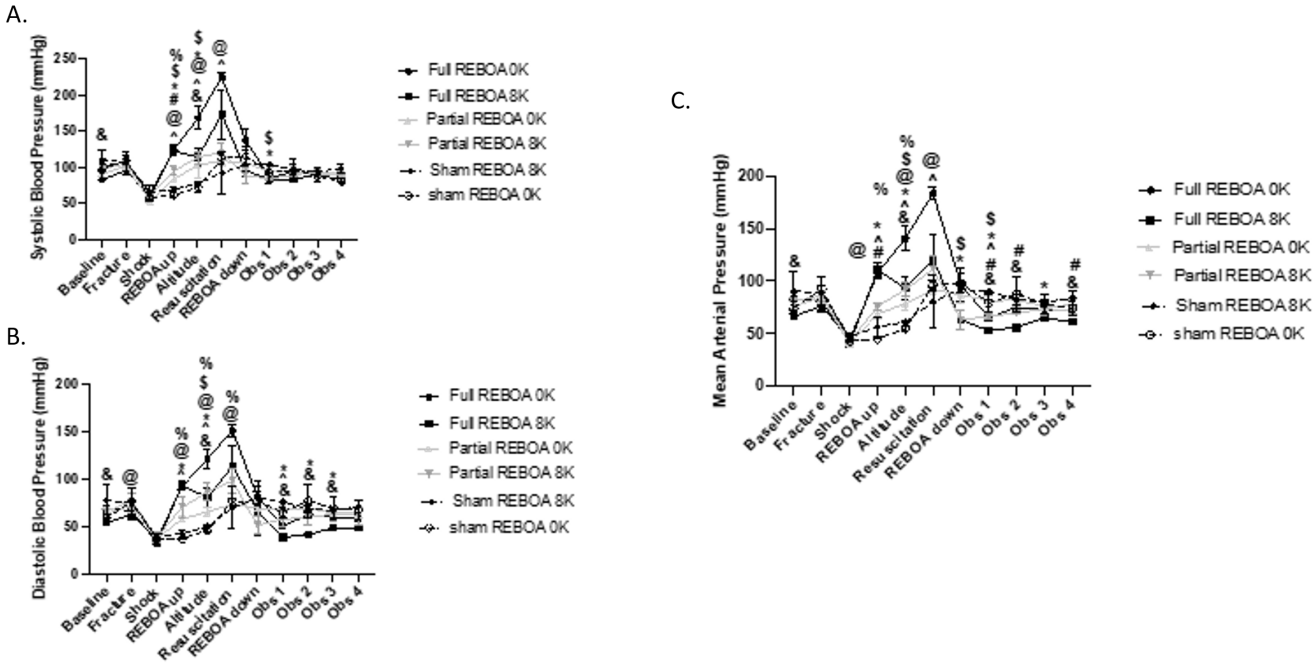


Fig 8: Partial REBOA improved distal perfusion compared to full occlusion

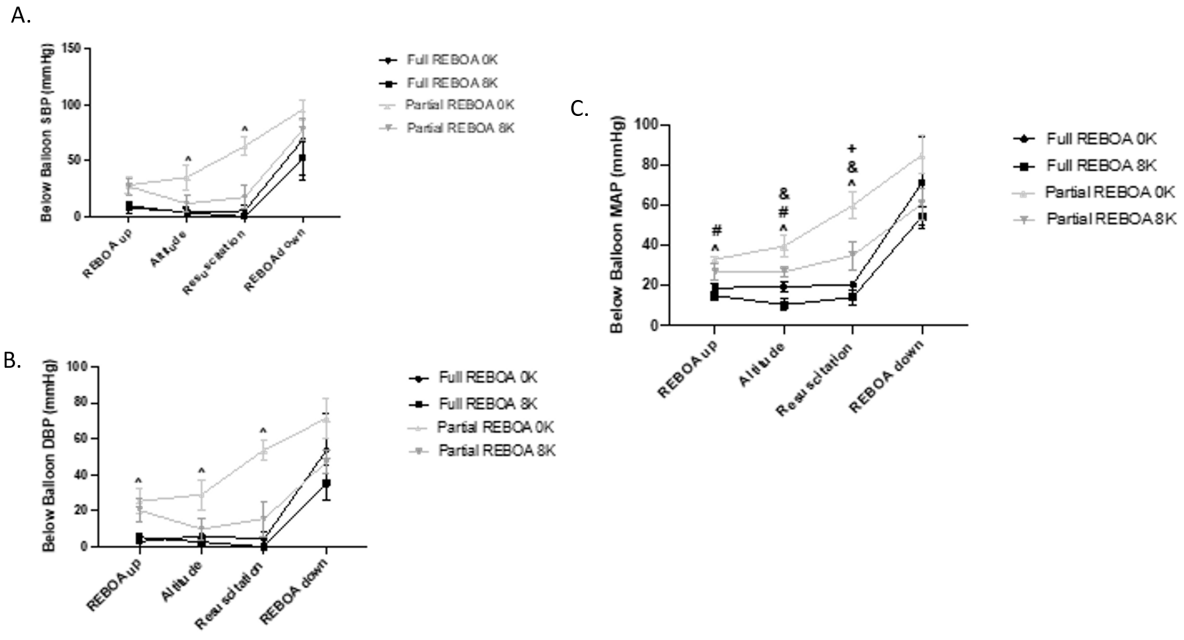


Fig 9: Partial REBOA resulted in less acidosis and reperfusion injury

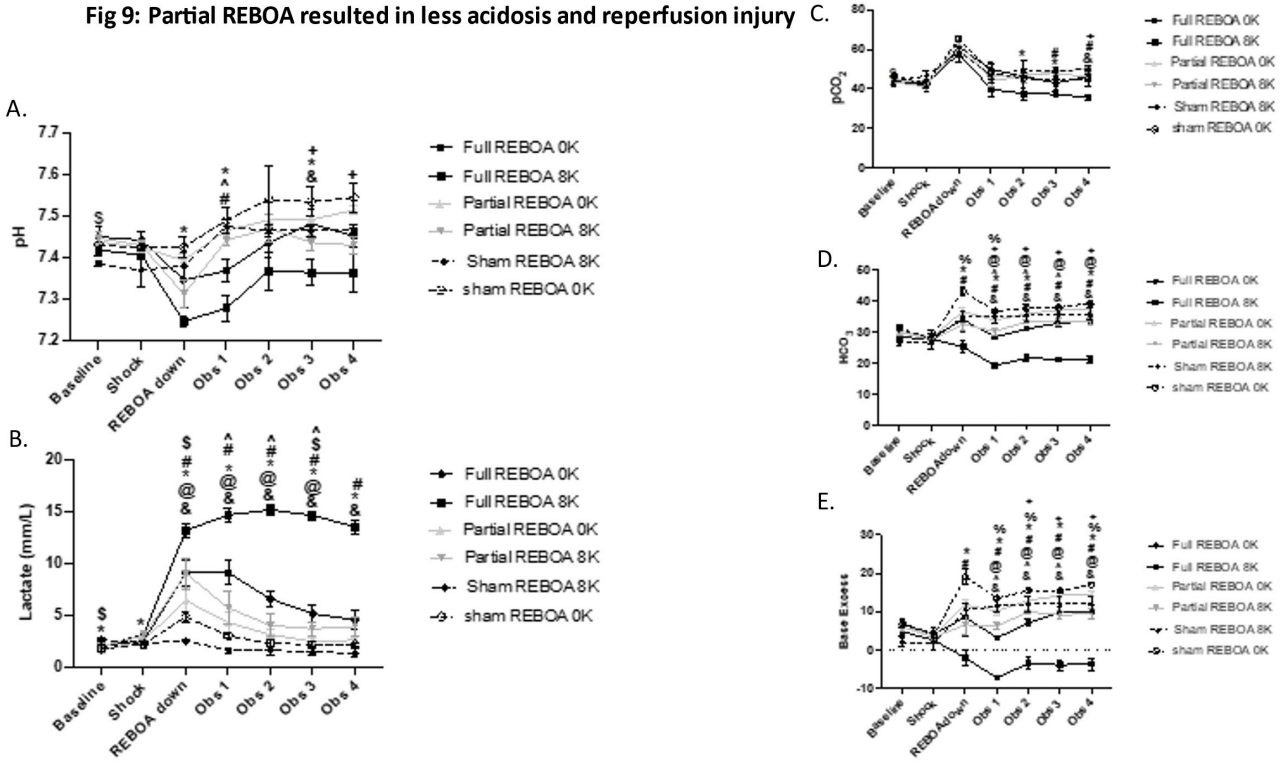
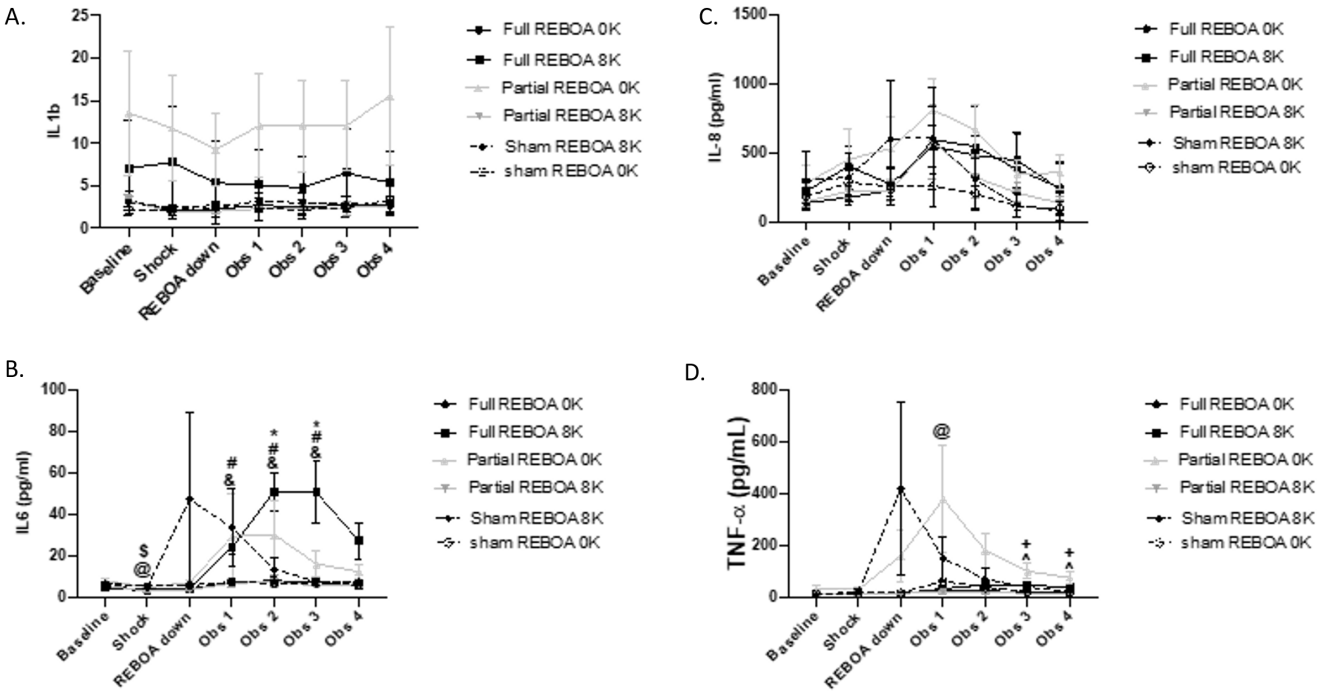


Fig 10: Partial REBOA improved IL-6 post-reperfusion compared to full REBOA



6.0 DISCUSSION:

REBOA

In this study, we examined the effects of REBOA in a simulator model as well as a porcine model in the setting of simulated aeromedical evacuation. The simulator data suggested that bringing a REBOA deployed catheter to altitude led to variation in SBP and DBP but MAPs remained unchanged or increased compared to blood pressures at ground level in both the room temperature and physiological temperature models. Simulated flight also did not influence hemodynamics in the porcine model. While deflating the balloon induced hypotension in REBOA pigs secondary to ischemia reperfusion injury, flight did not exacerbate this injury. Taken together, these data suggest that while REBOA may intentionally induce transient lower body ischemia and subsequent hypotension during reperfusion, these effects are independent of altitude, thereby suggesting that REBOA as safe in aeromedical evacuation as it is at ground level.

The box trainer data demonstrated REBOA catheter integrity at altitude, which led to variations in SBP and DBP but a MAP that remained unchanged or increased compared to blood pressure at ground. The SBP differences noted were unlikely to bear clinical significance, particularly in the setting of a stable MAP. Furthermore, these variations of blood pressure at altitude were not demonstrated in the in vivo model, suggesting that these changes were likely secondary to the interaction of the altitude chamber with the simulator device rather than true effects of the aortic balloon. Our results also suggest that the REBOA balloon performance is unaffected by temperature. While other studies on REBOA have noted that REBOA is commonly placed in hypothermic patients in extremis, this study is the first to examine a wider range of temperature that may be encountered when the catheter is stored in austere conditions. [31-32]

In spite of the resolution of hemorrhage-induced hypotension with deployment of REBOA,

there was significant ischemia-reperfusion injury as evidenced by the hypotension caused by deflating the balloon and the subsequent development of lactic and metabolic acidosis in the porcine model. However, these effects were independent of altitude. REBOA placement was also not found to be pro-inflammatory, either at ground or at altitude, as IL-8 was found to be lower in ground REBOA than ground no-REBOA. In previous clinical studies, REBOA placement has been shown to cause ischemia and reperfusion injury to all organs distal to the balloon placement, including to the bowel and kidneys when the REBOA is positioned in zone 1, as performed in this study.[33] Due to this concern, as well as the concerns of ability to safely and effectively place and troubleshoot the device itself, the American College of Surgeons Committee on Trauma does not currently endorse the use of REBOA during the transport of patients. [34-36] However, our study demonstrates that simulated flight did not exacerbate the metabolic acidosis caused by REBOA, indicating that the catheter could potentially be safe at flight and during pre-hospital transport.

However, the risks of REBOA utilization during en route care must be reconciled with the risk of not being able to address non-compressible hemorrhage in an austere setting. Two autopsy studies have shown that there is a patient population that may benefit from pre-hospital REBOA. One such study of 98 patients investigating resuscitative thoracotomy versus REBOA showed that the injuries in 45% of patients who underwent thoracotomy could have been addressed with REBOA. Interestingly, of patients with evidence of thoracic injury in the emergency room, which is a current contraindication to REBOA placement, 41% of patients still could have had some of their life-threatening injuries temporized by REBOA.[37] A recent retrospective study of the autopsies of 198 patients who were brought to Los Angeles County Hospital in cardiac arrest from trauma demonstrated that over 10% of those who died had injuries that could have anatomically been temporized by pre-hospital REBOA placement. [20]

Taken together, these studies indicate that REBOA could serve a purpose in these select patients in the hands of trained professionals with a plan for timely definitive management, whether within the same hospital or within an acceptance distance for aeromedical evacuation. There are several limitations to our study, mainly due to the inanimate and porcine nature of the training models. While our data demonstrate the effect of altitude on the balloon, it does not address how a REBOA balloon at altitude would work in human tissue and how it may impact ischemia and reperfusion injury not only immediately on balloon deflation but also sub acutely over the subsequent days to weeks. Furthermore, comparing the REBOA pigs to the no-REBOA pigs is an imperfect model of comparison, as the no-REBOA pigs did not continue to hemorrhage without the balloon in place.

pREBOA

This study used the pREBOA-PRO catheter to compare partial inflation to both full inflation and no inflation in the setting of post-injury simulated aeromedical evacuation. We found that partially inflating the pREBOA-PRO catheter significant decreased the post-deflation ischemia-reperfusion injury compared to full balloon occlusion, as evidenced by animals having an improved lactate, bicarbonate, and base deficit compared to the fully inflated REBOA balloon. In addition, altitude exposure exacerbated the physiologic impact of full but not partial balloon occlusion.

The development of a partially occlusive balloon is an important step in allowing for the REBOA technology to have greater utility, both in the hospital as well as in the pre-hospital setting. The profound ischemia-reperfusion injury that occurred with ER-REBOA balloon deflation has led to the Joint Trauma System Clinical Practice Guidelines recommending occlusion time to be limited to 15-30 minutes in Zone 1 (diaphragm) and 30-60 minutes in Zone 3 (pelvis).[38, 39] These times present a challenge for prehospital use of REBOA, as the average transport time for

emergency medical services in the United States is 12 minutes long. [40] Therefore, one could expect that surgeons at a receiving facility would have less than 20 minutes from time of arrival to achieve balloon deflation if Zone 1 is occluded. While a partially inflated REBOA in our study also induced an ischemia-reperfusion injury, the effects were far less severe, which could allow for the REBOA catheter to be utilized in the prehospital setting for longer periods of partial aortic occlusion.

Our simulation model with pREBOA demonstrated that the balloon was efficacious at altitude, with MAPs remaining unchanged throughout flight. Interestingly, these results were not completely replicated in our in vivo model, as the MAPs for the partial inflation increased with altitude. In an actual military evacuation, the amount of saline in the balloon can and should be titrated according to the physiologic needs of the patient. Unfortunately, this may be particularly challenging when considering vibration experienced in the aircraft, which this model did not address. While this is unlikely to affect the performance of the balloon, there may be inconsistent displays from the arterial line measurement making titrating the balloon a challenge.[41]

It is still important to note, however, that the effect of altitude on post-flight acidosis with deployment of the pREBOA-PRO stands in contrast to what our group had found previously with ER-REBOA. Using the original ER-REBOA model, we found that the ischemia-reperfusion injury was no worse in the altitude groups compared to the ground controls, suggesting that REBOA could be used safely at altitude with the same parameters as ground transportation.[17] However, the mechanics of the pREBOA-PRO balloon are different, with an intentional design change to allow channels within the balloon to allow partial perfusion with minimal inflation. The results of the present study are not necessarily surprising, as post-injury aeromedical evacuation has previously been found to exacerbate lactic acidosis.[(42-44)] However, it should be noted that using the pREBOA-PRO to full occlusion during flight may result in a more severe

ischemia-reperfusion injury than what is observed in the ground transport. By contrast, altitude exposure with partial aortic occlusion did not increase the post-reperfusion acidosis.

There are multiple studies comparing a partially occlusive REBOA to a fully occlusive REBOA model. Each one unsurprisingly demonstrates the superiority in ischemia-reperfusion injury with partial occlusion.[45-48] One study by Russo et al. conducted a study with 15 swine that demonstrated that full occlusion produced a greater lactic acidosis than partial occlusion.[45] They also examined the duodenum and renal cortex for histology and found that complete occlusion resulted in necrosis whereas partial occlusion did not. Importantly, there were a number of differences in design between our study and theirs. They euthanized the animals approximately 15 minutes after deflation of the balloon, whereas ours allowed for a 4 hour observation period. Therefore, their results only show a steady accumulation of lactic acid in their swine, whereas our studies demonstrate the relative rates of clearance between the groups. They also kept the balloons inflated for 90 minutes, which is significantly longer than these balloons are used in human patients. However, it is promising that even at 90 minutes with partial occlusion that distal end-organ perfusion was maintained. Forte et al. also performed a slow deflation of the balloon over two hours and showed superior performance of partial occlusion compared to full occlusion.[46] Interestingly, they also found that the administration of calcium correlated with improved survival, thought to be secondary to ability to tolerate hyperkalemia. In our model, we supplemented all study pigs with sodium bicarbonate and calcium as the balloon was being deflated, as our previous model developments demonstrated a high rate of mortality from ischemia-reperfusion without these adjunct treatments. These findings may be worth further investigation in future studies.

Our study is not without limitations, mainly secondary to the simulation model and limitations of our pig and chamber model. Unfortunately, we were unable to titrate the amount of saline in

the balloon during flight for the pREBOA models, as would be possible in actual aeromedical evacuation. This suggests that the benefits of the partial inflation may be even greater than what we showed in this study, as MAPs were consistently above goal during flight. Furthermore, this model also does not account for all environmental effects of flight, including the vibrational forces experienced during an actual aeromedical evacuation.

7.0 CONCLUSION:

REBOA

Taken together, we conclude that while simulator data suggested that there were systolic and DBP fluctuations with ER-REBOA at altitude, these results were not replicated in the porcine model and since MAP was preserved, altitude is unlikely to have clinically significant consequences for hemodynamics during REBOA deployment. Altitude does not appear to have a synergistic or additive effect on the ischemia reperfusion reaction from REBOA, and therefore, flight itself should not be considered a contraindication to the placement of the catheter.

pREBOA

Nevertheless, this study suggests that the pREBOA balloon is not only efficacious at altitude but also that it reduces the ischemia-reperfusion injury while maintaining lower extremity perfusion compared to a fully occlusive aortic balloon. pREBOA-PRO ™ maintains balloon occlusion without alteration at altitude as did ER-REBOA ™ in the previous study, even with a new balloon design. In addition, partial aortic occlusion allowed for the mitigation of the additional insult of altitude that would otherwise exacerbate the ischemia/reperfusion inherent to aortic occlusion for hemorrhage control.

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LIST OF SYMBOLS, ABBREVIATIONS and ACRONYMS

%	percent
±	plus or minus
<	less than
°C	degrees Celsius
ER-REBOA	ER- Resuscitative Endovascular Balloon Occlusion of the Aorta catheter
Fr	French size
ft	Feet
g	gram
K	thousand
kg	kilogram
l	liters
mEq	milliequivalents
mg/kg	milligram of medication per kilogram
mL	milliliters
ml/min	milliliters per minute
ml/kg/min	milliliter per kilogram per minute
mmHg	millimeters of mercury
NPO	nil per os
p	probability
ANOVA	Analysis of Variance
ARRIVE	Animal Research: Reporting of In Vivo Experiments
DBP	diastolic blood pressure
DCR	damage control resuscitation
ELISA	enzyme-linked immunoassay
Fig	Figure
HPW	Human Performance Wing
HR	heart rate
IL	interleukin
MAP	mean arterial pressure
pCO2	partial pressure of carbon dioxide
pH	power of hydrogen
pREBOA	partial REBOA
PT/INR	prothrombin time international normalized ratio
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
RR	respiratory rate
SBP	systolic blood pressure
SDC-1	Supplemental Digital Content
TNF	Tumour Necrosis Factor
U.S.	United States of America