Comparative Medicine
Copyright 2022
by the American Association for Laboratory Animal Science

Vol 72, No 1
February 2022
Pages 38–44

Original Research

Hemodynamic Effects of Cardiovascular Medications in a Normovolemic and Hemorrhaged Yorkshire-cross Swine Model

Jacob H Cole,[1,2,4] Scott B Hughey,[1,2,4] Phillip G Geiger,[1,2,4] Kamala J Rapp-Santos,[3] and Gregory J Booth[1,2,4]

The Yorkshire-cross swine model is a valuable translational model commonly used to study cardiovascular physiology and response to insult. Although the effects of vasoactive medications have been well described in healthy swine, the effects of these medications during hemorrhagic shock are less studied. In this study, we sought to expand the utility of the swine model by characterizing the hemodynamic changes that occurred after the administration of commonly available vasoactive medications during euvolemic and hypovolemic states. To this end, we anesthetized and established femoral arterial, central venous, and pulmonary arterial access in 15 juvenile Yorkshire-cross pigs. The pigs then received a series of rapidly metabolized but highly vasoactive medications in a standard dosing sequence. After completion of this sequence, each pig underwent a 30-mL/kg hemorrhage over 10 min, and the standard dosing sequence was repeated. We then used standard statistical techniques to compare the effects of these vasoactive medications on a variety of hemodynamic parameters between the euvolemic and hemorrhagic states. All subjects completed the study protocol. The responses in the hemorrhagic state were often attenuated or even opposite of those in the euvolemic state. For example, phenylephrine decreased the mean arterial blood pressure during the euvolemic state but increased it in the hemorrhagic state. These results clarify previously poorly defined responses to commonly used vasoactive agents during the hemorrhagic state in swine. Our findings also demonstrate the need to consider the complex and dynamic physiologic state of hemorrhage when anticipating the effects of vasoactive drugs and planning study protocols.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance

DOI: 10.30802/AALAS-CM-21-000080

Biomedical research using animals is a critical element in the advancement of human healthcare worldwide. Pigs are an important species for translational research, because their physiologic responses to hemorrhage, traumatic brain injury, and other traumatic injuries simulates the human response more closely than any other nonprimate animal model.[12] Yorkshire-cross swine demonstrate cardiovascular responses to physiologic insult that are similar to the responses of people.[18,24,27,32] These pigs have been used to evaluate several abnormal hemodynamic states, including those found in cardiac disease,[20,29,36] vascular disease,[3,21,25] and shock.[26,30,35] Swine models are particularly important in military and combat research for study of the complex physiology during hemorrhage,[10,17,19] especially given that traumatic hemorrhage remains the leading cause of potentially survivable mortality in both civilian and military populations.[7-9,16]

The effects of vasoactive medications in healthy swine have been well described and in general are similar to those observed in humans.[6,15] However, the effects of these medications have been less studied during hemorrhagic shock, and those studies have typically been limited to the effects that develop after the administration of vasoactive medications[4,5,22] as compared with medications that have direct inotropic or chronotropic activity. In normovolemic subjects, most vasoconstrictive medications have predictable responses that can be quantified by measuring changes in blood pressure, systemic vascular resistance (SVR), stroke volume, heart rate (HR), and cardiac output. However, hemorrhage can induce significant changes in these indices[28,31] and in how vasoactive medications affect these indices. For example, hemorrhage tends to decrease systemic blood pressure, with a compensatory increase in heart rate.

This study sought to expand the utility of the swine model by characterizing the hemodynamic changes observed after the administration of commonly used vasoactive medications during euvolemic and hypovolemic states. All of the study medications are highly selective, with rapid pharmacokinetics, and were chosen to selectively modify isolated components of cardiovascular physiology (e.g., preload, contractility, afterload).

The first agent, phenylephrine, is a rapidly metabolized selective α1 adrenergic agonist that we selected for this study because of its broad use in both research and human clinical settings and its selective ability to increase SVR through direct arteriolar vasoconstriction. Previous studies in euvolemic swine with phenylephrine-induced hypertension showed significant increases in mean pulmonary artery

Submitted: 16 Aug 2021. Revision requested: 16 Sep 2021. Accepted: 10 Oct 2021.
[1]Department of Anesthesiology and Pain Medicine, Naval Medical Center Portsmouth, [2]Naval Biotechnology Group, [3]Clinical Investigation Department, Naval Medical Center Portsmouth, Portsmouth, Virginia, and [4]Uniformed Services University of the Health Sciences, Bethesda, Maryland
[*]Corresponding author. Email: jacob.h.cole2.mil@mail.mil

pressure, mean arterial pressure (MAP), and SVR, with minimal influence on cardiac output and HR.[34] Second, nicardipine is a rapidly metabolized dihydropyridine calcium-channel blocker that is commonly used in human clinical practice. Its primary mechanism of action is direct arteriolar vasodilation. In previous studies of euvolemic swine, nicardipine decreased MAP and SVR.[11] Third, dobutamine is a rapidly metabolized β-adrenergic agonist that increases both cardiac ionotropy and chronotropy. Previous investigations in euvolemic swine found profound increases in HR, cardiac output, and MAP after dobutamine administration.[2] Fourth, esmolol is a highly selective β1 adrenergic antagonist that undergoes extremely rapid metabolism by nonspecific esterases in blood and tissue. It decreases both cardiac inotropy and chronotropy, and its administration leads to overall myocardial depression and decreased HR and MAP. Previous studies in swine showed decreased cardiac excitability and increased thresholds for the onset of malignant arrhythmias.[33] Finally, nitroglycerine increases venous capacitance through venous dilation, thereby causing a functional decrease in preload. The hemodynamic effects of nitroglycerine can vary depending on the subject's physiologic state. In general, intravenous administration of nitroglycerine decreases MAP due to decreased cardiac output. This effect was demonstrated in euvolemic swine and was accompanied by a compensatory increase in HR.[1]

Materials and Methods

Animals. The study protocol was approved by the IACUC of Navy Medicine Readiness and Training Command, Portsmouth. The work was performed in a USDA-registered and AAALAC-accredited animal facility in accordance with the *Guide for the Care and Use of Laboratory Animals* and federal animal welfare laws and regulations.[13] Juvenile female Yorkshire cross pigs (*Sus scrofa domestica*; $n = 16$; weight, 45 ± 5.8 kg [mean ± 1 SD]) were obtained from a commercial production herd (Smithfield, Wakefield, VA) and transported to the animal facility at least 3 d prior to use. Demographic information for these animals is shown in Table 1. Swine were socially housed in groups of 2-3 pigs per pen in indoor pens of approximately 5 m^2 (Carter2 Systems, Beaverton, OR) in environmentally controlled rooms maintained at 20 to 23 °C, a relative humidity of 40% to 60%, and a 12:12-h light:dark cycle. Barley straw bedding and enrichment through rubber toys was provided. Upon arrival, swine were bathed and received a single dose of ivermectin (0.3 mg/kg SC; Vetrimec 1%, MWI Animal Health, Boise ID) and a single dose of fenbendazole (5 mg/kg PO; Panacur, Merck, Madison, NJ). During their acclimation period, swine were fed a commercial swine diet (7037 Teklad Miniswine Diet, Envigo, Madison, WI) and received municipal water (filtered and chlorinated, 2 ppm) ad libitum via an automatic watering system (Edstrom Industries, Waterford, WI). Food enrichment items (e.g., fresh fruits and vegetables) were provided daily, along with enrichment devices. A veterinarian performed a full physical exam on all animals before approving their use in the study; no animals were excluded on the basis of physical exam findings.

Table 1. Demographics and baseline hemodynamic parameters ($n = 15$ pigs)

	Mean (1 SD)
Initial weight (kg)	45.3 (5.9)
Hemodynamics before neuromuscular blocking drug	
Heart rate (bpm)	87.8 (11.1)
Mean arterial pressure (mm Hg)	69.1 (11.5)
Respiratory rate (breaths/min)	11.6 (2.0)
End-tidal CO_2 (mm Hg)	38.1 (4.0)

Anesthesia and monitoring. On the day of the procedure, swine were fasted for at least 6 h and allowed free access to water until sedation. Swine were anesthetized with tiletamine–zolazepam (6.0 mg/kg IM or SC; Tiletamine–zolazepam, Zoetis, Kalamazoo, MI) and butorphanol (0.2 mg/kg IM or SC; Dolorex, Intervet, Madison, NJ) and transported to the operating room. Peripheral intravenous access was achieved through catheterization of the auricular vein, anesthesia was induced by using 3% to 5% isoflurane delivered in 100% oxygen via face mask (Moduflex Optimax, Dispomed, Quebec, Canada), and the airway was secured via endotracheal intubation with a 7.0- to 8.0-Fr cuffed tube (Teleflex Medical, Research Triangle Park, NC). Anesthesia and vital signs were monitored continuously (Intellivue MP50 monitor, Philips Healthcare, Amsterdam, Netherlands) and recorded every 5 min via electrocardiography, pulse oximetry, esophageal temperature probe, capnography, noninvasive blood pressure monitoring (until invasive arterial blood pressure monitoring was obtained), and bispectral index monitoring (BIS Quatro, Covidien, Mansfield, MA). A transvaginal 10- to 12-Fr silicone Foley urinary catheter (Surgivet, Smiths Medical, St Paul, MN) was placed to monitor urine output. Anesthesia was maintained via 1% to 3% isoflurane (titrated to maintain a surgical plane of anesthesia) in 100% oxygen, and animals were placed on mechanical ventilation (EMC model 2000, Hallowell, Pittsfield, MA). Normocapnia was achieved by continuous monitoring of end-tidal carbon dioxide, adjusting parameters to maintain at 38.0 ± 4.0 mm Hg.

Vascular access and monitoring. An ultrasound-guided percutaneous or surgical cutdown technique was used to place a 7.5- or 9-Fr introducer and catheter (Fast-Cath, Abbott, St Jude Medical, Plymouth, MN; Avanti+, Cordis, Miami Lakes, FL) in each of the 2 femoral arteries for continuous monitoring of blood pressure, including MAP, and to allow controlled hemorrhage. A 9-Fr central catheter introducer was similarly placed in the femoral vein or external jugular vein. A pulmonary artery catheter (Continuous Cardiac Output Swan-Ganz, Edwards Lifesciences, Irvine, CA) was advanced into the pulmonary artery to measure central venous pressure and cardiac output and to calculate SVR. To maintain synchrony with the ventilator, a neuromuscular blocking agent (Rocuronium, X-Gen Pharmaceuticals, Big Flats, NY) was administered as a bolus (1 to 1.5 mg/kg IV), followed by constant rate infusion at 2.0 to 2.5 mg/kg/h for the remainder of the procedure. A peripheral nerve stimulator (Ministim, Avanos Medical, Alpharetta, GA) was placed on a distal hindlimb, and neuromuscular measurements were performed via acceleromyography using train-of-four.[23] Adequate depth of anesthesia was assessed by monitoring blood pressure and HR, and bispectral index monitoring was available as a supplement. A Rad-57 pulse oximeter (Massmio, Irvine, CA) was used to measure the noninvasive pulse variability index. A Vigilance II monitor (Edwards Lifesciences, Irvine, CA) was connected to the pulmonary artery catheter, and cardiac output and SVR measurements were collected continuously. All data were stored on a local networked computer system.

Attaining initial normovolemia. Normovolemia was defined as a starting central venous pressure greater than 5 mm Hg and a plethysmography variability index (as assessed by the Rad-57) of less than 13. This index is a validated measure of intravascular volume status that relies on changes in cardiac output that

occur with oscillations in intrathoracic pressure throughout the respiratory cycle.[14] Swine that did not meet those criteria were given a 10-mL/kg IV bolus of intravenous Lactated Ringers (Baxter, Deerfield, IL) over 5 min. A repeat bolus of 10 mL/kg IV was given if the normovolemic hemodynamic parameters were not met after the initial bolus. Regardless of central venous pressure or plethysmography variability index measurements, the study protocol began once 20 mL/kg lactated Ringers had been given.

Cardiovascular medications. We used several previously described cardiovascular medications to induce hemodynamic disturbances, investigate the hemodynamic response to each individual drug, and compare noninvasive assessments of oxygenation, blood flow, and perfusion. Medications were administered and responses measured during both euvolemia and hypovolemia, with each animal serving as its own control. Each of the 5 medications was administered sequentially to each pig, followed by induction of volume-controlled hemorrhage, and then repeated administration of the 5 medications while the pig was in a state of hypovolemic shock.

Administration of medications and induction of hemorrhage. All hemodynamic agents were administered into the central venous circulation via the infusion port of the pulmonary artery catheter. All drug infusions were administered by using a Medfusion 3500 syringe pump (Smiths Medical). Bolus doses of medications were administered manually as an intravenous push dose of the medication. Time 0 was defined as the start time of administration of the first medication. HR, cardiac output, SVR, central venous pressure, MAP, mean pulmonary artery pressure, and the plethysmography variability index were all monitored directly according to the described protocol throughout the dosing of the various study medications.

At 0 min, a bolus of 1 µg/kg IV phenylephrine (West-ward Pharmaceuticals, Eatontown, NJ) was administered. Nicardipine infusion (4 mg/h; Exela Pharma Sciences, Lenoir, NC) was started at 15 min and continued until 25 min. Dobutamine (10 µg/kg/min IV; Hospira, Lake Forest, IL) was started at 30 min and continued until 40 min. At 45 min, esmolol (Baxter, Deerfield, IL) was given as a single bolus of 0.5 mg/kg IV. Nitroglycerin (American Regent, Shirley NY) was administered at 2 µg/kg/min from 60 until 70 min.

At 80 min, acute hemorrhage was induced by manually removing 30 mL/kg (approximately 50% of the estimated total blood volume) from the femoral artery over a 10 min interval. At 100 min, the same sequence of drug administrations was repeated in the same order with the same relative timing. The drug dosing sequence is illustrated in Figure 1. At 180 min, after all study medications had been administered, pigs were euthanized while under a surgical plane of anesthesia by using a pentobarbital-based euthanasia solution (>87 mg/kg IV or intracardiac; Euthanasia Solution, VetOne, MWI, Boise, ID).

Statistical analysis. During the administration of each drug, all hemodynamic variables were normalized to the value observed when the administration of the drug was initiated. Thus, the hemodynamic data were analyzed in 10 segments: one for each of the 5 study drugs both before and after controlled hemorrhage. This design allowed us to compare the effects of the drugs between subjects by measuring the relative change of each parameter after the administration of each study drug.

All statistics were performed by using the data analysis extension of Excel (Microsoft, Redmond, WA). The maximal amount of change relative to initial value was determined for each hemodynamic parameter for each drug before and after controlled hemorrhage. The normal distribution of the maximal change in each parameter in both phases was tested by using the Shapiro–Wilk test. The average maximal change for each hemodynamic parameter after administration of each drug was then compared between the normovolemic and hypovolemic states by using paired Student *t* tests and reporting with a 95% CI. A *P* value of 0.05 was considered significant. Descriptive values are show as the mean ± SD. Given the descriptive nature of this study, no effort was made to control for multiple comparisons.

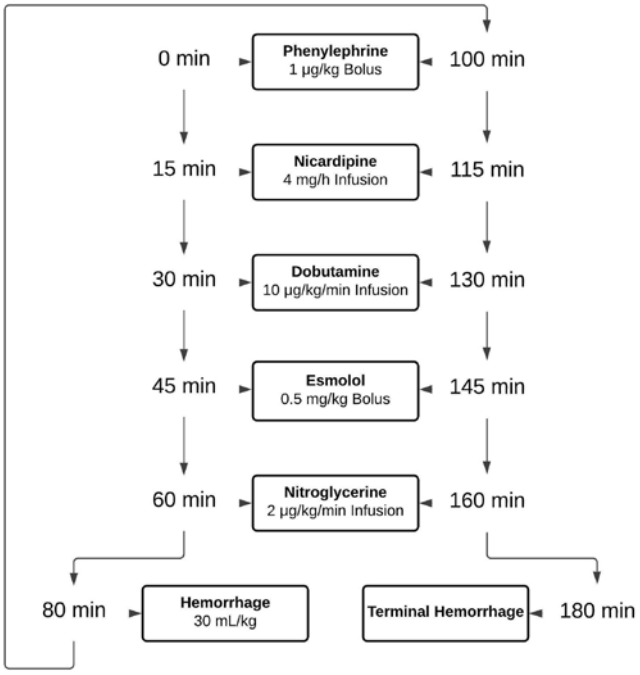

Figure 1. Timing of study interventions.

Results

All pigs that were enrolled completed the study protocol. All data analysis was completed as intended. The baseline demographic information and hemodynamic variables for all study animals can be found in Table 1. The maximal degrees of change seen for each study medication in both the normovolemic period and after hemorrhage are listed in Table 2. Hemorrhage had the greatest effect on the hemodynamic response to medications that primarily stimulate adrenergic receptors (phenylephrine, dobutamine, esmolol), with each drug respectively having significantly different responses in 5, 5, and 4 of the measured hemodynamic responses respectively when administered during either a hemorrhagic or normovolemic state. For the other 2 drugs, the volemic status of the pig significantly affected fewer measures, with nicardipine and nitroglycerine respectively affecting only 1 and 3 variables differently after hemorrhage. Hemorrhage was round to not only attenuate, but reverse the effect of esmolol on both mean arterial blood pressure and systemic vascular resistance.

Hemorrhage independently was found to have a significant impact on multiple of the hemodynamic variables that were studied (Figure 2). Heart rate significantly increased, while cardiac output, stroke volume, and mean arterial pressure significantly decreased. The measured systemic vascular resistance demonstrated an initial decline during the period of the hemorrhage, but eventually was found to significantly increase following the hemorrhage itself.

Table 2. Maximal relative increases in hemodynamic parameters after drug administration

Drug	Before bleed	After bleed	*P*
Phenylephrine			
Heart rate	**−5.21%**	**3.30%**	**0.012**
MAP	**−14.98%**	**19.62%**	**0.002**
Cardiac output	**−7.53%**	**17.00%**	**0.011**
SVR	**−20.29%**	**26.70%**	**0.013**
mPAP	**−16.68%**	**31.57%**	**<0.001**
CVP	−15.50%	−14.24%	0.828
Stroke volume	13.12%	20.15%	0.809
PVI	−13.09%	−9.93%	0.619
Nicardipine			
Heart rate	3.19%	6.44%	0.246
MAP	**−6.40%**	**7.74%**	**0.014**
Cardiac output	6.48%	15.36%	0.067
SVR	−6.85%	−6.10%	0.596
mPAP	11.24%	−5.11%	0.199
CVP	−18.62%	13.84%	0.262
Stroke volume	3.72%	6.86%	0.084
PVI	10.71%	−9.63%	0.549
Dobutamine			
Heart rate	**59.55%**	**28.14%**	**0.015**
MAP	**25.25%**	**8.07%**	**0.016**
Cardiac output	**46.09%**	**9.84%**	**0.001**
SVR	**−49.18%**	**−9.88%**	**0.014**
mPAP	6.41%	8.85%	0.679
CVP	−12.82%	24.66%	0.832
Stroke volume	16.85%	4.71%	0.249
PVI	**87.83%**	**−6.31%**	**0.049**
Esmolol			
Heart rate	−17.26%	−10.29%	0.397
MAP	**−14.10%**	**11.83%**	**0.031**
Cardiac output	**−36.96%**	**−10.90%**	**0.002**
SVR	77.23%	31.68%	0.165
mPAP	**−16.10%**	**7.30%**	**0.027**
CVP	−6.88%	−8.40%	0.371
Stroke volume	**−13.77%**	**11.20%**	**0.001**
PVI	−26.64%	8.70%	0.051
Nitroglycerin			
Heart rate	**-3.62%**	**9.69%**	**0.003**
MAP	−9.10%	7.71%	0.305
Cardiac output	5.40%	7.30%	0.988
SVR	−15.16%	6.34%	0.926
mPAP	**-10.49%**	**10.35%**	**0.010**
CVP	−15.50%	9.18%	0.215
Stroke volume	**2.94%**	**−5.52%**	**0.033**
PVI	18.06%	16.41%	0.889

CVP, central venous pressure; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PVI, plethysmography variability index; SVR, systemic vascular resistance

Bold text indicates values that differ significantly ($P < 0.05$) before compared with after bleeding.

Discussion

This study provides a comprehensive examination of the effect of vasoactive medications in swine after hemorrhage, thereby describing the complex hemodynamic behavior that is induced by hemorrhagic shock. Through extensive hemodynamic monitoring, we quantified the various effects of vasoactive medications before and after severe hemorrhage. The results reported here prior to hemorrhage are consistent with those published previously.[1,2,11,33,34] However, responses after hemorrhage were often attenuated or sometimes even opposite to those in the normovolemic animal; these findings are previously unreported and have profound implications regarding both the scientific study of the hemorrhage in swine and the veterinary care of these animals when they are on study.

The pathophysiologic state of hemorrhage induces a complex interplay of hemodynamic derangements to any physiologic model. Our findings in this study demonstrate the highly variable effects of hemorrhage on these commonly used medications, which otherwise are very predictable. For example, the effect of an equivalent dose of dobutamine on subjects that had undergone hemorrhage is markedly attenuated as compared with that of the same subjects in a euvolemic state. Increases in HR, MAP, and CO were all attenuated when this drug was administered after hemorrhage. These differences in drug effect were all statistically significant and should be considered when administering vasoactive medications in swine subjected to hemorrhage.

The effect of equivalent doses of phenylephrine under conditions of euvolemia and hemorrhage underscores this point. Whereas euvolemic subjects tended to have decreases in HR, MAP, cardiac output, SVR, and mean pulmonary artery pressure after the administration of a phenylephrine bolus, hemorrhaged swine had the opposite response to this medication: each of these hemodynamic parameters increased after the administration of an equivalent phenylephrine bolus after the same swine had undergone hemorrhage.

These alterations in hemodynamic response to various medications after hemorrhage warrant additional investigation. Derangements in the autonomic and adrenal axes that accompany the physiologic shock of hemorrhage may be implicated in changing the responses to the study medications. As demonstrated by the results of this study, hemorrhage itself induces various changes in the hemodynamics of a subject, and the interactions between hemorrhagic physiology and vasoactive medications warrant consideration when using hemorrhagic models. Our study demonstrates the need to account for the complex and dynamic physiologic effects of hemorrhage when planning the use of vasoactive drugs in study protocols. The effects of some agents apparently are attenuated, whereas others are enhanced after hemorrhage, and this variability must be addressed to ensure that the desired clinical effect is realized if these drugs are used.

In conclusion, this study presents a robust analysis of the *Sus scrofa* translational model and the effects of common cardiovascular medications on the circulatory system of these animals. The information we collected and presented here can inform veterinarians and others of unexpected effects of vasoactive medications studies of hemorrhage in swine. These findings provide the basis for future studies of hemorrhage and drug effects in swine.

Acknowledgments

The views expressed in this article reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of the Army, Department of Defense, or the United States Government. We thank

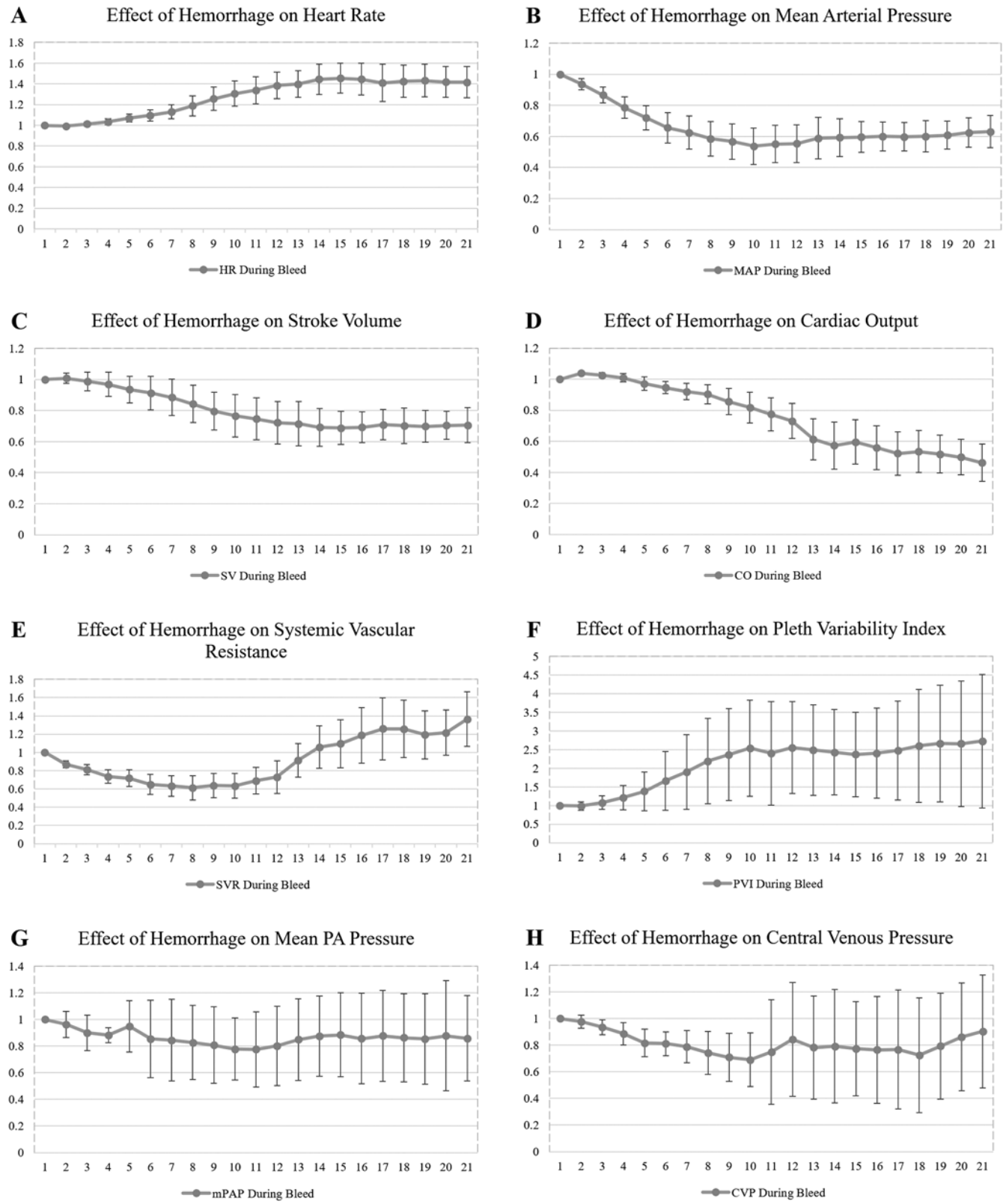

Figure 2. The effects of hemorrhage (30 mL/kg over 10 min) on investigated hemodynamic parameters. The values of these parameters were normalized to the value that was measured at the start of the hemorrhage, and these normalized values were then averaged over the 15 subject animals. The error bars represent 95% CI for each data point. (A) Heart rate. (B) Mean arterial pressure. (C) Stroke volume. (D) Cardiac output. (E) Systemic vascular resistance. (F) Plethysmography variability index. (G) Mean pulmonary artery pressure. (H) Central venous pressure.

the staff of the Naval Medical Center Portsmouth Animal Resources Division for their tireless assistance in providing the animal care that made this study possible.

References

1. **Baines CP, Szwarc RS, Ball HA.** 1994. Parallel tolerance between platelet cyclic GMP and preload effects of nitroglycerin in anesthetized minipigs. Br J Pharmacol **113:**334–335. https://doi.org/10.1111/j.1476-5381.1994.tb16900.x.
2. **Bilello JF, O'Hair KC, Kirby WC, Moore JW.** 1991. Intraosseous infusion of dobutamine and isoproterenol. Am J Dis Child **145:**165–167.
3. **Britz GW, Tomas J, Lumsden A.** 2020. Feasibility of robotic-assisted neurovascular interventions: initial experience in flow model and porcine model. Neurosurgery **86:**309–314.
4. **Carrara M, Babini G, Baselli G, Ristagno G, Pastorelli R, Brunelli L, Ferrario M.** 2018. Blood pressure variability, heart functionality, and left ventricular tissue alterations in a protocol of severe hemorrhagic shock and resuscitation. J Appl Physiol **125:**1011–1020. https://doi.org/10.1152/japplphysiol.00348.2018.
5. **Chalkias A, Koutsovasilis A, Laou E, Papalois A, Xanthos T.** 2020. Measurement of mean systemic filling pressure after severe hemorrhagic shock in swine anesthetized with propofol-based total intravenous anesthesia: implications for vasopressor-free resuscitation. Acute Crit Care **35:**93–101. https://doi.org/10.4266/acc.2019.00773.
6. **Cole JB, Corcoran JN, Engebretsen KM, Stellpflug SJ.** 2020. Use of a porcine model to evaluate the risks and benefits of vasopressors in propranolol poisoning. J Med Toxicol **16:**212–221. https://doi.org/10.1007/s13181-020-00758-8.
7. **Eastridge BJ, Hardin M, Cantrell J, Oetjen-Gerdes L, Zubko T, Mallak C, Wade CE, Simmons J, Mace J, Mabry R, Bolenbaucher R, Blackbourne LH.** 2011. Died of wounds on the battlefield: causation and implications for improving combat casualty care. J Trauma **71:**S4–S8. https://doi.org/10.1097/TA.0b013e318221147b.
8. **Eastridge BJ, Holcomb JB, Shackelford S.** 2019. Outcomes of traumatic hemorrhagic shock and the epidemiology of preventable death from injury. Transfusion **59 S2:**1423–1428. https://doi.org/10.1111/trf.15161.
9. **Evans JA, van Wessem KJ, McDougall D, Lee KA, Lyons T, Balogh ZJ.** 2009. Epidemiology of traumatic deaths: comprehensive population-based assessment. World J Surg **34:**158–163. https://doi.org/10.1007/s00268-009-0266-1.
10. **Glaser JJ, Cardin S.** 2020. Prehospital adenosine, lidocaine, and magnesium has inferior survival compared with tactical combat casualty care resuscitation in a porcine model of prolonged hemorrhagic shock. J Trauma Acute Care Surg **88:**e105–e106. https://doi.org/10.1097/TA.0000000000002540.
11. **Herity NA, Allen JD, Silke B, Adgey AA.** 1994. Comparison of the ability of nicardipine, theophylline, and zaprinast to restore cardiovascular haemodynamics following inhibition of nitric oxide synthesis. Br J Pharmacol **112:**423–428. https://doi.org/10.1111/j.1476-5381.1994.tb13089.x.
12. **Hildebrand F, Andruszkow H, Huber-Lang M, Pape HC, van Griensven M.** 2013. Combined hemorrhage–trauma models in pigs: current state and future perspectives. Shock **40:**247–273. https://doi.org/10.1097/SHK.0b013e3182a3cd74.
13. **Institute for Laboratory Animal Research.** 2011. Guide for the care and use of laboratory animals, 8th ed. Washington (DC): National Academies Press.
14. **Jung YS, Cho WS, Suh GJ, Lee JC, Kwon WY, Kim KS, Kim T, Shin SM, Kang MW, Lee MS, Lee B.** 2020. Pulse oximeter plethysmograph variation during hemorrhage in β-blocker–treated swine. J Surg Res **256:**468–475. https://doi.org/10.1016/j.jss.2020.07.004.
15. **Katzung KG, Leroy JM, Boley SP, Stellpflug SJ, Holger JS, Engebretsen KM.** 2019. A randomized controlled study comparing high-dose insulin to vasopressors or combination therapy in a porcine model of refractory propranolol-induced cardiogenic shock. Clin Toxicol (Phila) **57:**1073–1079. https://doi.org/10.1080/15563650.2019.1580372.
16. **Kelly JF, Ritenour AE, McLaughlin DF, Bagg KA, Apodaca AN, Mallak CT, Pearse L, Lawnick MM, Champion HR, Wade CE, Holcomb, JB.** 2008. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003–2004 versus 2006. J Trauma **64 Suppl:**S21–S27. https://doi.org/10.1097/TA.0b013e318160b9fb.
17. **Kuckelman J, Barron M, Moe D, Lallemand M, McClellan J, Marko S, Eckert M, Martin MJ.** 2018. Plasma coadministration improves resuscitation with tranexamic acid or prothrombin complex in a porcine hemorrhagic shock model. J Trauma Acute Care Surg **85:**91–100. https://doi.org/10.1097/TA.0000000000001942.
18. **Kumar R, Chung WY, Dennison AR, Garcea G.** 2017. Ex vivo porcine organ perfusion models as a suitable platform for translational transplant research. Artif Organs **41:**E69–E79. https://doi.org/10.1111/aor.12865.
19. **Lallemand MS, Moe DM, McClellan JM, Smith JP, Daab L, Marko S, Tran N, Starnes B, Martin MJ.** 2017. Resuscitative endovascular balloon occlusion of the aorta for major abdominal venous injury in a porcine hemorrhagic shock model. J Trauma Acute Care Surg **83:**230–236. https://doi.org/10.1097/TA.0000000000001548.
20. **Längin M, Mayr T, Reichart B, Michel S, Buchholz S, Guethoff S, Dashkevich A, Baehr A, Egerer S, Bauer A, Mihalj M, Panelli A, Issl L, Ying J, Fresch AK, Buttgereit I, Mokelke M, Radan J, Werner F, Lutzmann I, Steen S, Sjoberg T, Paskevicius A, Qiuming L, Sfriso R, Rieben R, Dahlhoff M, Kessler B, Kemter E, Kurome M, Zakhartchenko V, Klett K, Hinkel R, Kupatt C, Falkenau A, Reu S, Ellgass R, Herzog R, Binder U, Wich G, Skerra A, Ayares D, Kind A, Schonmann U, Kaup F, Hagl C, Wolf E, Klymiuk N, Brenner P, Abicht J.** 2018. Consistent success in life-supporting porcine cardiac xenotransplantation. Nature **564:**430–433. https://doi.org/10.1038/s41586-018-0765-z.
21. **Lee JM, Kim HK, Lim KS, Park J-K, Choi KH, Park J, et al.** 2018. Influence of local myocardial damage on index of microcirculatory resistance and fractional flow reserve in target and nontarget vascular territories in a porcine microvascular injury model. JACC Cardiovasc Interv **11:**717–724. https://doi.org/10.1016/j.jcin.2017.11.028.
22. **Libert N, Chenegros G, Harrois A, Baudry N, Decante B, Cordurie G, Benosman R, Mercier O, Vicaut E, Duranteau J.** 2021. Performance of closed-loop resuscitation in a pig model of haemorrhagic shock with fluid alone or in combination with norepinephrine: a pilot study. J Clin Monit Comput **35:**835–847. https://doi.org/10.1007/s10877-020-00542-7.
23. **Madsen MV, Donatsky AM, Jensen BR, Rosenberg J, Hammelev KP, Gatke MR.** 2013. Monitoring of intense neuromuscular blockade in a pig model. J Clin Monit Comput **28:**351–355. https://doi.org/10.1007/s10877-013-9539-1.
24. **Magliocca A, Olivari D, De Giorgio D, Zani D, Manfredi M, Boccardo A, Cucino A, Sala G, Babini G, Ruggeri L, Novelli D, Skrifvars MB, Hardig BM, Pravettoni D, Staszewsky L, Latini R, Belloli A, Ristagno G.** 2019. LUCAS versus manual chest compression during ambulance transport: a hemodynamic study in a porcine model of cardiac arrest. J Am Heart Assoc **8:**e011189. https://doi.org/10.1161/JAHA.118.011189.
25. **Maïga S, Allain G, Hauet T, Roumy J, Baulier E, Scepi M, Dierick M, Van Hoorebeke L, Hannaert P, Guy F, Favreau F.** 2017. Renal autotransplantation promotes cortical microvascular network remodeling in a preclinical porcine model. PLoS One **12:**e0181067. https://doi.org/10.1371/journal.pone.0181067.
26. **Møller-Helgestad OK, Ravn HB, Møller JE.** 2018. Large porcine model of profound acute ischemic cardiogenic shock. Methods Mol Biol **1816:**343–352. https://doi.org/10.1007/978-1-4939-8597-5_27.
27. **Moore JC, Holley J, Segal N, Lick MC, Labarère J, Frascone RJ, Dodd KW, Robinson AE, Lick C, Klein L, Ashton A, McArthur A, Tsangaris A, Makaretz A, Makaretz M, Debaty G, Pepe PE, Lurie KG.** 2018. Consistent head up cardiopulmonary resuscitation haemodynamics are observed across porcine and human cadaver translational models. Resuscitation **132:**133–139. https://doi.org/10.1016/j.resuscitation.2018.04.009.
28. **Nouira S, Elatrous S, Dimassi S, Besbes L, Boukef R, Mohamed B, Abroug F.** 2005. Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic

shock. Crit Care Med **33:**2339–2343. https://doi.org/10.1097/01.CCM.0000182801.48137.13.

29. **Oates A, Nubani R, Smiley J, Eiferman D, Lonchyna V, Higgins RS.** 2009. Myocardial protection of insulin and potassium in a porcine ischemia–reperfusion model. Surgery **146:**23–30. https://doi.org/10.1016/j.surg.2009.03.028.
30. **Ostadal P, Mlcek M, Gorhan H, Simundic I, Strunina S, Hrachovina M, Kruger A, Vondrakova D, Janotka M, Hala P, Mates M, Ostadal M, Leiter JC, Kittnar O, Neuzil P.** 2018. Electrocardiogram-synchronized pulsatile extracorporeal life support preserves left ventricular function and coronary flow in a porcine model of cardiogenic shock. PLoS One **13:**e0196321. https://doi.org/10.1371/journal.pone.0196321.
31. **Rutherford RB, Balis JV, Trow RS, Graves GM.** 1976. Comparison of hemodynamic and regional blood flow changes at equivalent stages of endotoxin and hemorrhagic shock. J Trauma **16:**886–897. https://doi.org/10.1097/00005373-197611000-00007.
32. **Suzuki Y, Yeung AC, Ikeno F.** 2011. The representative porcine model for human cardiovascular disease. J Biomed Biotechnol **2011:**1. https://doi.org/10.1155/2011/195483.
33. **Tisdale JE, Sun H, Zhao H, Fan CD, Colucci RD, Kluger J, Chow M.** 1996. Antifibrillatory effect of esmolol alone and in combination with lidocaine. J Cardiovasc Pharmacol **27:**376–382. https://doi.org/10.1097/00005344-199603000-00010.
34. **Troncy E, Francoeur M, Salazkin I, Yang F, Charbonneau M, Leclerc G, Vinay P, Blaise G.** 1997. Extrapulmonary effects of inhaled nitric oxide in swine with and without phenylephrine. Br J Anaesth **79:**631–640. https://doi.org/10.1093/bja/79.5.631.
35. **Udesen NLJ, Helgestad OKL, Banke ABS, Frederiksen PH, Josiassen J, Jensen LO, Schmidt H, Edelman ER, Chang BY, Ravn HB, Moller JE.** 2020. Impact of concomitant vasoactive treatment and mechanical left ventricular unloading in a porcine model of profound cardiogenic shock. Crit Care **24**95–105. https://doi.org/10.1186/9513054-020-2816-8.
36. **Zhu W, Zhang E, Zhao M, Chong Z, Fan C, Tang Y, Hunter JD, Borovjagin AV, Walcott GP, Chen JY, Qin G, Zhang J.** 2018. Regenerative potential of neonatal porcine hearts. Circulation **138:**2809–2816. https://doi.org/10.1161/CIRCULATIONAHA.118.034886.