Homeostasis Models

Hemorrhagic Shock Models in Swine

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Introduction

Swine have long been used as models for the study of hemorrhagic shock.[1, 2] In recent years there has been a resurgence of interest in the pathogenesis and treatment of hemorrhagic shock due to the ongoing conflicts associated with combating terrorism. Hemorrhage associated with trauma is a complex issue in humans because of the usual multiple system injuries that accompany it. This manuscript will discuss hemorrhagic shock as a primary issue and trauma models will be addressed in a separate manuscript.

Hemorrhagic shock leads to decreased cardiac output, stroke volume, and increased heart rate. These decreases lead to the reduced tissue perfusion that will result in multiple organ failure over time at fatal hemorrhage levels. Complete reviews of the effects of various hemorrhagic shock models on physiologic function have been published.[2, 3]

Complete physiologic parameters of the various pigs used for these types of studies have been published.[1, 2, 4] These values may vary considerably between breeds and ages of pigs within the same breed. For example the circulating blood volume ranges from 58.1-73.9 ml/kg. It is best to calculate the baseline values for the pigs used in the study at the time they are entered into the protocol.

Hemorrhage Models[2, 3]

The fixed pressure model (Wiggers Model) is developed by rapidly withdrawing blood until a predetermined arterial pressure is attained. Following experimental techniques the collected blood is sometimes reinfused to another predetermined level. For example decreases by 50 mmHg in 15 minutes or 40 mmHg in 10 minutes have been used.3 This type of fixed pressure model is most attractive because it can be reproduced by multiple labs. However, this type of situation is not analogous to the human clinical situation. It may have its most utility as a model of prolonged hypotension.

The fixed volume model is developed by removing a fixed volume of blood over a predetermined period of time. There are differences in rate and amount of blood removed. Some may use a model that changes the rate of blood loss during the process of removal.[2, 3] This simulates the rapid loss initially that may occur with major vascular trauma with lesser loss as blood pressure decreases. Examples of this model would be 40-60% of the total blood volume in 15, 30, 100 or 120 minutes. 3 Some authors use an exponential pattern of blood withdrawal in 7.5 ml/kg aliquots until 37.5 ml/kg has been withdrawn in five intervals over 60 minutes.[2]

Another model to be considered is uncontrolled hemorrhage. This model is induced by aortic laceration of a given size such as a 5 mm puncture. With this model a compensatory increase in blood pressure follows an initial 5-10 minute decrease.[3]

An additional model based upon oxygen debt as the target endpoint has been proposed.[3] This model is based upon decreasing blood flow until a predetermined oxygen debt is achieved in 60 minutes independent from blood pressure or volume of hemorrhage. Oxygen debt occurs when there is a decrease in blood flow and tissue perfusion. The brain, liver, kidney, heart and immunologic tissues are most susceptible to this damage. Arterial oxygen delivery in 20-25 kg swine is 14-26 ml/min/kg. An oxygen debt of 95 ml/kg approximates the LD50 in swine.[2-4] Base excess and lactate are blood parameters that are good indicators of the severity of hemorrhagic shock. For example in swine a base excess of -15.3 mmol/l compares well to the value of -14.5 mmol/l in humans for lethal hemorrhagic shock.[3]

Most of the time animals are anesthetized during these procedures. Commonly instrumentation is implanted during the procedure. Blood may be withdrawn from either an artery or a vein. In the pig the most common sites are the carotid or femoral artery if arterial bleeding is being studied. The most common veins for catheterization are the external jugular, internal jugular or femoral. In some cases splenectomy may be performed to eliminate the reserve volume that can result from compensatory splenic contraction.[1] The administration of anesthetics is also a complicating factor in the outcome but ethical standards as regulated by an IACUC may preclude creating these models without anesthesia. If an awake animal is to be studied then the instrumentation and catheterization will have to be done in advance of the blood removal. Models of trauma combined with hemorrhagic shock would be the most clinically relevant but standardization and ethical issues are both a problem. Comparison of human and porcine shock models are detailed in Table 1. Table 2 provides the various formulas used for calculation of body surface area from body weight (BW) in swine.

Anesthetic Selection[1]

Anesthetics and sedatives will be a confounding variable for any hemorrhagic shock model. Anesthetics will enhance the effects of hemorrhage as well as dampening the normal compensatory responses to loss of blood.[2] However, the effects may be minimized by selection of agents which have minimal physiologic effects for the goals of the research project.[1] Any model utilized is most likely going to have instrumentation

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	American College of Surgeons Hemorrhage Definitions (70Kg Human)				Defense Advanced Research Projects Agency (DARPA) Texas A&M University (TAMU)
	Class I	Class II	Class III	Class IV	Swine Model (40Kg)
Blood Loss (ml)	Up to 750	750-1500	1500-2000	>2000	> 1500
Blood Loss (% Blood Volume)	Up to 15 %	15-30 %	30-40 %	>40 %	60%
Pulse Rate	<100	>100	>120	>140	>150
Blood Pressure	Normal	Normal	Decreased	Decreased	Decreased
Pulse Pressure (mmHg)	Normal or Increased	Decreased	Decreased	Decreased	Decreased
Respiratory Rate	14-20	20-30	30-40	> 35	> 35
Urine Output (mL/hr)	>30	20-30	5-15	Negligible	Negligible
CNS/Mental status	Slightly anxious	Mildly anx-ious	Anxious, Confused	Confused, lethargy	NA
Fluid Replacement (3:1 rule)	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood	Crystalloid
Survival without resuscitation	Good	Guarded	Moderate	Lethal	Lethal < 3 hours
Survival with resuscitation	NA	Good	Good	Moderate	High > 80%

Table 1. Comparison of Porcine Model to Human Hemorrhagic Shock

American College of Surgeons, Selected Readings in General Surgery Volume 35, Numbers 5-6, Trauma, Part I & II: Care of the Injured, http://www.facs.org/srgs/index.html
Texas A&M Institute for Preclinical Studies, http://tips.tamu.edu/

and/or vascular catheters implanted. The techniques of implanting catheters and devices have been detailed.[1]

Some basic principles of selecting anesthetic regimens can be followed. If injectable agents are utilized then they should not be given as repeated bolus injections by any route. If they are used as the sole agent for sedation or anesthesia then they should be administered as a continuous iv infusion. If inhalant anesthetics are used then isoflurane or sevoflurane will have the shortest recovery time and the least metabolites. If combined with nitrous oxide in a 50:50 combination with oxygen then the MAC value of the inhalant agent can be greatly reduced. Use of inhalants is contraindicated when the study precludes ventilation and requires that the animals breathe room air.

For implantation of catheters and devices deep surgical anesthesia and analgesia will be required. Once the surgery is completed and the incisions are closed then the anesthetic level can be lightened to a sedative level if the experiment is to be performed in an anesthetized animal. This is readily accomplished if an inhalant anesthetic is used as the sole anesthetic. In this case the pig can be restrained in a sling and induced under anesthesia using a face mask.

The selection of injectable anesthetics for these procedures is more complex. Agents which are most likely to have lasting cardiovascular depression are the barbiturates, tiletamine/zolazepam, alpha adrenergic agonists, and propofol. Opioid and benzodiazepine infusions would likely have the least effects at a sedative level. Ketamine has minimal cardiovascular effects after 30-45 minutes and can be used for induction. If analgesics are used in the protocol the NSAIDs have minimal effects on cardiovascular function. The best one to use in swine is carprofen because it does not affect bleeding time and others such as meloxicam can increase activated clotting time significantly. Buprenorphine would be the systemic opioid with the most efficacy and least side effects in swine. Use of local anesthetics and epidural morphine may also be considered. Guidelines on anesthesia and perioperative care are located in other manuscripts on this website.[5]

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0.0734 x Bwkg0.656 (m2)	Farm Pigs
0.121 BWkg 0.575 (m2)	Miniature Pigs
(70 X BW0.75)/1000 (m2)	Miniature Pigs
337.2 + 0.553 BWgm (cm2)	Pigs <2 kg

Table 2. Formulas for Body Surface Area in Swine

Formulas from: Swindle MM. 2007. Swine in the Laboratory: Surgery, Anesthesia, Imaging and Experimental Techniques, 2nd Ed[1]

Use of Miniature Swine

Most acute studies have been performed in immature farm breeds of pigs. The relevance of this model to adult human hemorrhagic shock has been questioned.[2] Miniature breeds reach sexual maturity at 4-6 months of age and breeds such as the Hanford attain the weight of adult humans as well.[1] In addition most of the male domestic pigs have been castrated which may also be a complicating factor in the results. It may be indicated to use sexually mature minipigs for preclinical studies in which therapeutics are intended for adult humans. This would assure maturity of the cardiovascular system and the circulatory responses. If the studies are related to Department of Defense initiatives then most of their therapy would be related to young adults.

Conclusions

Swine are important models in the study of hemorrhagic shock. That field of study has renewed interest due to the ongoing worldwide conflicts related to terrorism. Because of the similarities of the cardiovascular physiology and blood clotting mechanisms in swine they are an appropriate species for the study of therapies related to the syndrome.[1]

Selected References

1. Swindle MM. 2007. Swine in the Laboratory: Surgery, Anesthesia, Imaging and Experimental Techniques, 2nd Ed, Boca Raton: CRC Press (Taylor and Francis).
2. Hannon JP. 1992. Hemorrhage and hemorrhagic shock in swine: a review, in Swindle MM (ed), Swine as Models in Biomedical Research, Ames, IA: Iowa State University Press, pp 197-245.
3. Rixen D, Neugebauer EAM. 2004. Changing paradigms in animal models of traumatic/ hemorrhagic shock, Eur J Trauma 5: 279-288.
4. Hannon JP, Bossone CA, Wade CE. 1990. Normal physiologic values for conscious pigs used in biomedical research. Lab Anim Sci 40(3): 293-298.
5. Sinclair website: http://www.sinclairbioresources.com/Literature/TechnicalBulletins.aspx

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