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Swine as Surgical Models in Biomedical Research

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Swine are considered to be one of the major animal species utilized in preclinical trials for translational research. Over the last 20 years they have also replaced dogs as the general surgical model in the international arena for both training and research. This presentation will provide anatomic and physiologic justification for the use of porcine models in surgical protocols as well as the description of the methodologies used to produce the models.

Anatomic and Physiologic Considerations

Swine share a number of anatomic and physiologic characteristics with humans that make them potentially a better model for some procedures as compared to other large animal species. Systems that are most commonly cited as being suitable models include the cardiovascular, urinary, integumentary and digestive systems. These characteristics and models have been reviewed in the literature.1,2

The differences between domestic farm breeds and miniature breeds are related to their growth rate and size at sexual maturity rather than actual anatomic differences in organs and structures. Thus, when different breeds are age matched the organ sizes will reflect the increased size of domestic breeds as compared to miniature breeds; however, the physiologic function should be the same. Conversely when animals are weight matched the sizes will be similar for organs and structures; however, the physiologic function will be related to the relative maturity of the animals. As an example most domestic breeds would be expected to grow from 1-2 kg at birth to >100 kg at four months of age. The most common miniature breeds available in the US are the Hanford, Yucatan, Yucatan micro, Sinclair and Göttingen from largest to smallest. These miniature breeds weigh 0.5-1 kg at birth and grow to 17-20 kg for the Hanford and 7-9 kg for the Göttingen in four months. Sexual maturity for all breeds occurs between 4-6 months of age. As a general rule farm pigs are only used in protocols lasting a maximum of 3-6 weeks depending upon the age at the start of the protocol unless growth is part of the study. For example using domestic breeds for implantation of cardiovascular devices for six month studies can result in dislodgement of the device due to the increased length and diameter of the cardiovascular structures. As a general rule the Hanford miniature pig develops adult human sized organs and structures between 6-8 months of age while the other breeds never develop an equivalent size for most organs and structures.

Cardiovascular and Pulmonary: The heart and blood vessels are uniquely similar in anatomy and function to the same structures in humans. Studies involving the cardiovascular system are the most commonly performed research studies in swine. The heart and great vessels of 80 kg pigs are comparable in size to those of adult humans. Coronary arterial circulation is right side dominant without preexisting collateral circulation like 90% of the human population. The conduction system differs in that it is more neural than humans and has prominent Purkinje fibers. Humans are more myogenic in their conduction and do not have as prominent a neural circulation. The left hemiazygous vein drains the intercostals vessels directly into the coronary sinus unlike humans and most other animal species. Thus, the coronary sinus is large and contains both coronary and systemic blood in its outflow. The blood vessels contain a true vaso vasorum like humans which is important in vascular healing. Swine have been established as a growing heart model for surgical procedures. The growth of the heart and cardiovascular system from birth to four months of age is analogous to the growth of the same system in humans into the mid teens. Swine are also uniquely susceptible to the induction of atherosclerosis with atherogenic diets.

The lungs have the typical seven lobes of quadruped animals. The mediastinum is friable as is the pulmonary tissue and must be handled gently during surgery.

Digestive: The digestive system of the pig includes the gastrointestinal tract (GI), liver, pancreas and the various secretory glands associated with digestion. The stomach is like that of humans with the exception of the torus pyloricus which is a muscular outpouching in the pyloric region. The small intestine is approximately 10% duodenum, 80% jejunum and 10% ileum and is approximately 30-40 times the length of the pig’s body. The mesentery is friable and the vascular arcades of the mesenteric vessels form in the subserosa of the small intestine. The spiral colon consists of the cecum and 2/3 of the large intestine arranged in a series of centripetal and centrifugal coils tightly adhered to each other in the upper left quadrant of the abdomen. Tenia and haustra are present. In spite of the anatomical variations from the human the physiology of digestion is similar because swine are true omnivores.

The liver has the same gross anatomy as humans except that it has five lobes and is more prominent on the left side and proportionately larger as are the livers of most quadruped animals. Histologically the porcine liver has fibrous interlobular septae separating the...
hepatic lobules. There are both similarities and differences in hepatic metabolism and hepatic enzymes of the cytochrome P 450 system.

The pancreas is large and encircles the cranial mesenteric vessels. The function of the islet cells is very similar to human and pork insulin from slaughterhouse collections was the standard for treatment of human diabetics for the decades preceding the development of laboratory produced varieties.

**Urinary:** The kidneys of the pig are multirenunculate and multipapillate with a true calyceal system. In adult swine they are approximately the size of human kidneys and have an internal renal anatomy more similar to humans than even other primates. The left kidney is more cranial than the right. The most significant difference from the human is the separation of the blood supply to the poles of the kidney. The blood supply divides the kidney along a transverse avascular plane rather than a longitudinal one.

**Integumentary:** The skin of the pig is relatively hairless and it has a fixed subcutaneous layer like humans. There are a few eccrine sweat glands which are located in the snout and carpal glands. Swine have apocrine sweat glands and sebaceous glands throughout the skin but these have minimal function in thermoregulation compared to humans. The cutaneous blood supply and sequence of events in wound healing has made them a standard model of wound healing and reconstructive surgical treatments.

**Neurologic and Ophthalmic:** The central nervous system and specifically the brain of the pig has been rapidly evolving as a model system for humans due to both its size and its anatomic characteristics. Swine have a gyrencephalic brain which is white matter predominant with similar developmental peaks to that of humans. Blood flow characteristics are also similar; however, swine have a rete mirabile. The spinal cord terminates with the conus medullaris at S2-3 unlike the human. The eye of the pig is similar in size to the human and it is most similar in its retinal anatomy and function. Swine also have a vitreous humor with characteristics similar to humans.

**Other Organs and Systems:** Other systems and organs used less frequently include the reproductive system, the endocrine system and the musculoskeletal system. The female reproductive system is composed of a typical bicornuate uterus with elongated fallopian tubes and an elongated cervix. The placenta is a diffuse epitheliochorial type with placentation transport characteristics similar to humans. The male reproductive system has all of the accessory sex glands associated with humans except that the prostate is not a predominant gland. The bulbourethral and vesicular glands are the most prominent. The penis has a corkscrew tip and a sigmoid flexure. The musculoskeletal system is seldom utilized because of the massive structure of the bones and the musculature. There are similarities in cartilage metabolism and the stifle joint is utilized for those types of studies.

There are unique anatomic aspects to some portions of the endocrine system. The thyroid gland is unilobular and located on the ventral surface of the trachea at the level of the thoracic inlet. The thymus has a significant portion of its mass in the neck which shrinks closer to the thorax with maturity. The parathyroid glands are a single pair 1-3 mm in diameter and are located on the surface of the thymus at its cranial aspect.

For a more detailed description of the anatomy and physiology reference textbooks are available.\(^{1,3}\)

**Surgical Models and Procedures**

Virtually any surgical procedure that can be performed on other large animal biomedical models can be performed in swine. It is beyond the scope of this manuscript to describe all the surgically induced models and procedures that can be performed. Development of these models has been described in depth.\(^1\) Principles involved with the production of the surgical models will be described.

Swine are the default model for non survival surgical training classes. This would include developing expertise in performing general procedures as well as specialized techniques such as endoscopic and laparoscopic procedures. Some specialty associated societies require that their members be trained in procedures on the porcine model. An example is the acute trauma and life support (ATLS) training given to paramedics who perform procedures such as tracheotomy, placement of chest tubes and vascular cutdowns.

The most common survival surgical procedures performed in lab animals involve the implantation of catheters and devices; and this is true in swine as well.\(^{1,4}\) The most common devices implanted include exteriorized catheters for blood collection and administration; vascular access ports (VAP); telemetry systems and implantation of devices and materials for preclinical files.

When implanting catheters and devices, asepsis is one of the most important aspects. Besides aseptic skin prep the use of iodine impregnated adhesive drapes prevents any contact with the skin and can eliminate many problems. Numerous studies in humans and animals have shown that the dosage of antibiotic that prevents infection is the dose that is in the blood at the time the skin incision is made. Routine use of antibiotics for prolonged periods postsurgically should not be necessary unless there was a known contamination during the procedure. Other precautions to be made include...
avoiding inflammatory sutures to which swine have a known sensitivity. Those sutures are silk, surgical gut and antimicrobial coated absorbable sutures. The general principles of surgery should include secure closure of dead space and secure attachments at every entry and exit site in structures and body cavities. Skin closure in swine should be performed as a subcuticular suture using absorbable suture material. Catheter maintenance should be performed aseptically and IV catheters should be locked with heparin or taurolidine citrate solution (TCS). TCS is also antimicrobial and is preferable to the use of antibiotics. Using appropriate perioperative care procedures will allow the maintenance of implanted devices for months to years. If a biomaterial becomes infected post implantation then it will be resistant to antibiotic therapy and it should be surgically removed.

Cardiovascular models (CV) include the following: myocardial infarction (MI), transplantation, pressure overload hypertrophy, volume overload hypertrophy, dilated cardiomyopathy, valvular replacement, stent implantation, aneurysm repair, stent implantation, balloon angioplasty, graft implantation, pacemaker testing, and atherosclerosis related therapy. The Seldinger technique can be used for interventional catheter related procedures either in the femoral, carotid or jugular vessels. Large devices such as telemetry or pacemaker units are best implanted in the jugular furrow. Smaller devices such as VAPs can be implanted subcutaneously and they should be placed on the dorsum of the body to prevent the pig from rubbing and irritating the incisions. The thoracic cavity can be entered either via a lateral thoracotomy or a median sternotomy.

Digestive system models include: endoscopic surgery, laparoscopic surgery, natural orifice transluminal endoscopic surgery (NOTES), liver transplantation, islet cell transplantation, pancreatitis, cholecystectomy, biliary stents, intestinal fistulation, intestinal transplant, endotoxic shock production, and peritoneal dialysis. Abdominal incisions and closure are similar to other species. The intestinal tract requires 2-3 days to empty until after 48 hours. Hyperosmotic purgatives can be used to accelerate the cleansing. Swine will readily consume liquid diets such as Ensure© or Gatorade©. Oral medications and test substances can be hidden and consumed in foods such as cat food meatballs, flavored syrups, fruits and pastries.

Urinary system models include: renal transplantation, renal hypertension, intrarenal surgery, hydroureteronephrosis, intrarenal reflux, vesicoureteral reflux, artificial bladders, and ureteral stents. The kidneys can be surgically approached using a retroperitoneal flank approach which avoids having to retract the intestinal mass. Retrograde passage of catheters through the penis is not possible but that approach is easily performed in the female.

Dermatologic models include: wound healing, plastic surgical techniques, reconstructive techniques, burn models, and artificial skin grafts. The techniques for closure of skin incisions and preparation of skin for surgery are discussed in the sections above.

Neurologic models include: neurotrauma, stroke, cerebrospinal fluid (CSF) catheters, cranial reconstruction, epidural catheters, and spinal cord trauma. The main issue with neurosurgery in the pig is the thickness of the skull and the massive bone structure of the vertebrae. These approaches require power tools and skillful surgical approaches.

Another specialized model involves fetal surgical techniques for implantation of catheters and fetal wound healing studies. These techniques are highly specialized and require intense efforts to maintain fetal normothermia and homeostasis.

Summary
Not covered in this manuscript are the perioperative care techniques that are required to successfully produce chronic surgical models. This includes caging, husbandry and handling techniques. Likewise many failures of chronic models involve the inappropriate design of the anesthetic and analgesic protocols. A series of DVD training modules has been developed to cover these aspects of the porcine surgical models as well as videos of some of the actual surgical techniques.

Selected References