Dilated cardiomyopathy and ischemic heart failure models in pigs

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A previous manuscript on this website1, Surgically produced volume and pressure overload heart failure models in swine, discussed heart failure models that could be produced in swine using selected surgical techniques. Pressure overload hypertrophy is produced by surgical banding of the great vessels of the heart and leads to concentric hypertrophy of the heart. Volume overload hypertrophy of the heart is produced by surgically creating valvular regurgitation or an arteriovenous fistula leading to eccentric hypertrophy of the heart. These conditions lead to different types of heart failure which are reviewed in the previous manuscript. The manuscript also describes the anatomy and physiology of the porcine heart. 1

This manuscript describes two other common forms of heart failure and the methods used to create them in swine. Dilated cardiomyopathy is created by rapid epicardial pacing leading to congestive heart failure. Myocardial infarction is produced by occlusion or partial occlusion of one or more coronary arteries leading to ischemic heart disease and a variety of cardiac dysfunctions. These conditions have unique differences from the cardiac hypertrophy models described above. 2

Dilated cardiomyopathy
Dilated cardiomyopathy is one of the most common types of heart failure.2-5 It is the end result of many different initiating causes including coronary artery disease, infectious myocarditis, substance abuse, chronic tachycardia and hypertension. In humans it is generally a slowly progressing condition characterized by increases in the end systolic and diastolic volumes as well as a progressive decrease in ejection fraction. The ventricles dilate and the walls do not respond with compensatory hypertrophy as they do with volume and pressure overload. The symptoms are those of congestive heart failure usually predominately affecting the lungs and liver.

The model has been produced in swine by inducing supraventricular tachycardia with an implanted pacemaker.2-5 In order for the ventricles to become dilated the pacing rate should be set between 180-240 beats per minute. The pacemaker leads can either be screw in or sutured types and are placed epicardially onto the left atrium. The surgical approach is through the left 3rd intercostal space following the techniques described for thoracic surgery. After selecting a suitable site for the pacemaker lead implantation, the lead is attached and sutured in place with Ethibond. The lead is tunneled out of the thoracic cavity to a site on the dorsum of the rib cage distal from the thoracotomy incision. The pacemaker is connected and placed into a subcutaneous pocket. The incisions are closed in the usual manner for thoracotomies and the pig allowed to
recover prior to stimulating the pacemaker to produce tachycardia. (Figure 1)

The model progresses rapidly to biventricular dilation and heart failure within three weeks displaying morphologic and physiologic alterations in the myocardium.\textsuperscript{3-5} Because of the rapid deterioration of cardiac function, these pigs have to be monitored closely for signs of hypoperfusion, pulmonary congestion and cyanosis. If the pigs develop cyanosis it can be readily identified in the snout and nipples of non-pigmented pigs. Careful monitoring should include auscultation as well as observation for deviations from normal pig behavior. Furosemide (2-6 mg/kg IV or PO) can be administered orally to ameliorate the signs of pulmonary edema. Catastrophic heart failure can occur more rapidly in some individuals and turning the pacing rate down or turning the pacemaker off can provide more immediate relieve from distress.

**Ischemic Heart Disease**

Ischemic heart disease is generally caused by blockage of one or more coronary arteries and a resulting myocardial infarction. This condition is a leading cause of death in western society as well as a cause of significant morbidity and debility in persons who survive an acute attack. Angina pectoris, fatigue and congestion are frequently the first signs of a decrease in coronary arterial perfusion. Dysfunction of the myocardium results in a decrease in ejection fraction and arrhythmias. Survivors of an acute episode can develop significant changes in the myocardium including such conditions as aneurysms of the ventricular wall. When scar tissue replaces the damaged myocytes the heart contracts stiffen as restrictive cardiomyopathy develops.\textsuperscript{2, 6-10}

Models of myocardial infarction have been produced in a variety of ways in swine due to their analogous distribution of the coronary arterial circulation which is right side dominant and congruent with 90% of the human population. Swine do not have existing collateral coronary circulation which makes them uniquely susceptible to acute myocardial infarction when compared to other animal models. Any of the coronary arteries can be accessed either surgically or via an interventional catheter. The approach and extent of the coronary arterial...
occlusion which is survivable for a chronic model will depend upon which vessel and occlusal method is used.

The model which would be most analogous to humans would be the creation of occlusion by inducing atherosclerosis, which has been discussed in another manuscript on this website. (Figure 2) This method requires that the vessel of interest be damaged using an angioplasty catheter while the animal is being fed an atherosclerotic diet. The atherosclerotic plaque develops over 4-6 months and results in a gradual occlusion and infarct in a similar manner as the condition which occurs in humans over >4 decades of life. However useful information can also be gained from other methods of creating the models depending upon the goals of the study.

Acute infarcts can be created by ligation or applying clips to the vessel of interest and this method is commonly used when studying non survival models. (Figure 3) Mortality and incidence of arrhythmias is decreased by limiting the time of the occlusion or the percent of the vessel which is occluded. For significant survival the left anterior descending artery should be occlude below the first main lateral branch of the vessel. The circumflex can be ligated closer to its origin for survival procedures. The incidence of arrhythmias is also decreased by limiting the length of time of the occlusion. After 30 minutes the incidence approaches 100%. Myocardial stunning can be produced by occlusions of less than 15 minutes. If total occlusions are performed and then released after a prolonged period of time reperefusion will immediately result in an arrhythmia unless antiarrhythmics such as amiodarone (0.5-3.5 mg/kg/hr) or lidocaine drips (50 µg/kg/min) are administered.

Closed chest techniques using interventional catheter methods can be performed to create total occlusions and avoid any complicating factors that may arise from open chest surgical techniques. Intravenous drips of lidocaine (50 µg/kg/min) as an antispasmodic and slow infusion of nitroglycerine (100-200 µg diluted in saline) at the aortic root to act as a vessel dilator make the access to the vessel of interest easier to accomplish. Various foreign materials such as microspheres or coils can be injected at the site.
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of interest. These methodologies are used to create chronic models of complete occlusion.

Interventional angioplasty catheters can be advanced into a coronary artery and inflated for a limited period of time to produce myocardial stunning or a reversible infarct. Many of the original coronary stent designs led to restenosis by neointimal growth at the site of implantation. These flawed stents can be implanted in pigs to produce an infarction in 4-6 weeks. This infarction when healed has been demonstrated to produce an aneurysm of the ventricular wall.

All of the vessels can be accessed using a median sternotomy. The left circumflex and proximal portion of the left anterior descending arteries can be approached via a lateral thoracotomy in the 4th intercostal space. The right circumflex and posterior interventricular arteries can be approached via the right 4th intercostal space. The surgical techniques have been described in detail.¹ ²

Perioperative Care Procedures
Heart failure models are complex especially when they are maintained for a prolonged period of weeks to months. Successful production and maintenance of these models starts with the protocol planning and the selection of the anesthetic and analgesic regimens. ²

Postoperatively it is best to minimize the handling of animals with infarction for the first week. Significant increases in survival have been observed if the animals have minimal physical contact with humans and other animals,
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especially in the first three days. Noninvasive monitoring techniques, such as telemetry units or jacket monitoring devices, can also be used. (Figure 4)

![Figure 4. Lifejacket for monitoring ECG.](image)

Anesthetic selection is vital when producing heart failure models. The use of Telazol® (tiletamine/zolazepam) especially when combined with xylazine has been associated with major depression of cardiovascular function in these models. Preanesthetic agents considered to be safe for the initial surgery include ketamine, diazepam, and acepromazine. In our laboratories we induce the pigs with ketamine 33 mg/kg and acepromazine 1.1 mg/kg SC. Diazepam 2mg/kg can also be used with the ketamine 20 mg/kg SC. The inhalant anesthetics with the least cardiodepression are isoflurane and sevoflurane for providing general anesthesia.

If the animals have to be sedated following the induction of heart failure then even more diligence should be used in the selection of sedatives and anesthetics. Midazolam 100-500 µg SC can be used as a sedative for procedures such as performing echocardiography. Diazepam 0.5-10 mg/kg PO is also safe as a sedative for handling of compromised animals. Etomidate 4-8 mg/kg IV can be used to induce an anesthetic state with minimal cardiovascular compromise. If severe cardiovascular compromise is involved then high dose opioid infusion techniques using sufentanil (10-15 µg/kg/hr), remifentanil or alfentanil provide protection against myocardial dysfunction and arrhythmias by improving coronary arterial blood flow. The inhalant anesthetics mentioned above are also safe to use and sevoflurane offers a slight advantage over isoflurane for safety in these animals.

The antiarrhythmic techniques of lidocaine and/or amiodarone IV infusions described above should be instituted whenever there is going to be stimulation of the cardiac conduction system; as would happen with ventricular catheterization.

Analgesia should be administered preemptively. For lateral thoracotomies a dorsal nerve root block should be performed in the intercostal space being incised as well as the adjacent
spaces cranial and caudal to the incision site. Median sternotomies should have local anesthetic infiltration of the incision line. Lidocaine and bupivacaine can be used for these procedures. Preemptive injections of carprofen 1-2 mg/kg and/or buprenorphine .01-.05 mg/kg sc or IV should also be used. If the protocol involves the use of high dose opioid infusions then that will serve as the preemptive analgesic without separate administration of bupivicaine. Fentanyl patches are too variable in their activity to be reliable. If they are used then blood levels should be established in advance for the specific sized pig used in the study.

Selection of Breed
Minipigs should be utilized for chronic projects involving keeping the animals for more than a few weeks. There are advantages and disadvantages to the various breeds depending upon the particular project. In general the Yucatan mini or micro is the most common breed used for atherosclerosis or heart failure models. Sexually mature Hanfords are used if there is a need for a heart size analogous to humans. The Sinclair breed has also been used in many of these projects. Consultation with a veterinarian to determine the best breed should be sought in advance of performing the project.

Selected References


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