Introduction

Vascular surgical procedures and implantation of catheters and devices are common experimental procedures. Swine and especially miniature breeds are commonly used in experimental and preclinical trials for devices and procedures. This includes such procedures as creating aneurysms and treating them with medicated stents. Other manuscripts on this website describe the surgical and non-surgical implantation of catheters for infusion and blood collection as well as venipuncture techniques. This manuscript reviews common surgical procedures and experimental studies involving the blood vessels of swine. Complete descriptions of many of these techniques have been described.

Vascular Anatomy

The size and morphology of many of the blood vessels makes them useful for interventional catheter and surgical procedures. The basic anatomy of the porcine blood vessels and their major distribution regions are similar to humans. The aorta has a true vaso vasorum which provides the blood supply to the aortic wall which is more similar to humans than many other species (Figure 1). Histologically the same layers and structures exist in the vasculature as seen in other mammalian species. The growth of the porcine cardiovascular system has been described as being analogous to the growth of that of the human. This is particularly true when you compare the growth of the blood vessels from birth to sexual maturity of the pig which is analogous to the growth of the system from birth to sexual maturity in humans. Pigs have been described as a translational model for arteriogenesis since they react to stimuli for induction of collateral growth of arteries in a similar manner to humans. A significant difference in the vasculature is the presence of a rete mirabile in swine (Figure 2). This structure at the base of the brain inhibits passage of catheters through the carotid vessels into the cerebral vessels. The vessel size is 70-2x75 µm (mean 154 µm).

In studies with in vitro porcine coronary arteries several physiologic characteristics shared with humans have been observed. The have similar responses to stimulators and neurotransmitters such as calcium, serotonin, norepinephrine, nitric oxide, endothelins and matrix metalloproteinase. They have similarities in baroreceptors and responses to cardioactive drugs. There is heterogeneity within regions of the same vessel and between the various blood vessels as there are in humans. This heterogeneity includes differences in endothelial layers, number of periarterial nerves in the adventitia, density of adrenergic innervation and thickness of the vessel walls. The pig has similar alpha and beta receptors with heterogeneity between large and small vessels.

The venous system parallels the arterial system in a similar manner as all mammals. There are valves in the peripheral veins similar to humans. The regional angiography of the major vascular distribution of the porcine has been published.
Peripheral blood vessels of swine are prone to vasospasm and are relatively easy to rupture during catheterization techniques. Good surgical technique and gentle handling of tissues cannot be replaced by use of topical antispasmodic agents such as lidocaine or papaverine. When performing vascular access surgery, the division of muscular tissues should be performed in fascial planes between muscle bodies and not by dividing musculature. Blood vessels should be handled gently and suture material used around the blood vessels should not be abrasive; for example, silk should not be used. The use of elastic vessel loops, especially the rounded types, is the preferred method of isolating and occluding blood vessels during catheterizations (Figure 3). Experience has shown that they do not have the sawing action that braided suture materials have on vessels, which frequently leads to vasospasm. When using gauze, it should be wetted with warm saline to prevent hypothermic vasoconstriction. Gauze should be pressed and held on a bleeding site, never rubbed. The use of electrocautery for hemostasis and ablation of collateral branches works well, as long as the power settings are not high enough to cause collateral cauterization and vasoconstriction.2

Anastomosis of blood vessels is a routine procedure required for experimental procedures, such as organ transplantation, creation of vascular defects or implantation of vascular grafts. The basic techniques of suturing are the same as for other species. Two characteristics of the porcine vascular system are important considerations. These are the tendency to vasospasm and the pig’s rapid clotting time, which necessitates frequent administration of heparin intraoperatively for some procedures. If blood vessels are totally occluded during a surgical procedure systemic heparinization is essential. The iv dosage of heparin is 100-300 units/kg as a priming dose with maintenance doses of 100-200 units/kg given approximately every 45 minutes and monitored by prolongation of activated clotting time (ACT) to a range of 180-300 seconds. 2 Protamine (1 mg/kg IV for every 100 units of heparin) does not need to be used routinely to reverse the anticoagulation. There can be allergic reactions to the agent and it can also have a delayed rebound effect with anticoagulation occurring hours following its use. Protamine would be indicated if the ACT is substantially >300 seconds postoperatively.

If blood vessels are cross clamped for a procedure such as anastomosis or suturing of a graft, then atraumatic vascular forceps, such as bulldog clamps for small vessels and Satinsky or DeBakey clamps for larger vessels should be utilized. Cross clamping resulting in total occlusion of blood flow is problematic in some regions, notably the aorta. When cross clamping the aorta or other major vessel without substantial collateral circulation, heparin should always be administered. The total cross-clamp time of the prerenal descending aorta that is tolerated without ischemic damage to the spinal cord is approximately

### Table 1. Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage mg/kg</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Heparin</td>
<td>100-300 IU/kg, iv</td>
<td>Anticoagulant, thrombin inhibition</td>
</tr>
<tr>
<td>Hirudin (Lepirudin)</td>
<td>1 mg/kg sc, sid</td>
<td>Thrombin inhibitor</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>50-75 µg/kg sc, sid or bid</td>
<td>Low molecular weight heparin, antithrombotic</td>
</tr>
<tr>
<td>Dabigatran etexilate (Pradaxa)</td>
<td>20 mg/kg po, bid</td>
<td>Competitive thrombin inhibitor</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox, Clexane)</td>
<td>2 mg/kg sc, bid</td>
<td>Low molecular weight heparin, Inhibits prothrombin to thrombin formation</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10 mg/kg po, sid</td>
<td>Platelet inhibition</td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>75 mg/kg po, sid</td>
<td>Inhibition of platelet activation and aggregation</td>
</tr>
<tr>
<td>Warfarin (Coumadin)</td>
<td>0.04 - 0.08 mg/kg po, sid</td>
<td>Anticoagulation, vitamin K inhibition</td>
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15 minutes. Cross clamping results in the same syndromes of decreased cardiac index and increased arterial pressure that occur in humans.2

The number of branches to the psoas musculature that are ligated during isolation of the aorta should be limited to the minimal number required for the procedure. Ligation of substantial numbers of these branches, i.e., four to six continuous pairs in most regions, can also result in spinal cord ischemia. Consequently, it is preferential to perform vascular surgery using tangential clamps that only partially occlude the aorta. Peripheral vessels are less of a problem when cross clamped, but heparinization should be used if the goal of the procedure is to provide a patent vessel.2

Blood vessels may have to be ligated for certain procedures. Except for the carotid artery, these vessels may be ligated and sacrificed bilaterally instead of being surgically repaired, without significant postoperative complications. Both carotid arteries can be sacrificed with staged surgeries to allow collateral circulation to develop. Collateral circulation is sufficient with one intact carotid artery. One of either the external or internal jugular veins on each side of the neck should also be left intact, but this is not essential.2

Synthetic nonabsorbable 5/0-6/0 cardiovascular suture is indicated for most vascular anastomoses in swine. Larger vessels, such as the aorta, are sutured in a continuous pattern and smaller vessels are sutured using simple interrupted sutures. For large vessels, the wall of the aorta most distal from the surgeon is the starting point. The technique of using double-armed cardiovascular suture for such an anastomosis is described in detail. If substantial leakage occurs, then the leaks can be repaired with simple interrupted sutures. If leakage is minor, then the anastomotic incision may be packed with gauze for 3-5 minutes. This is usually sufficient for clotting to occur at the needle puncture sites. Longitudinal incisions in blood vessels, such as the aorta, may also be utilized. They may be closed in a similar fashion or, if extra security is required, a continuous mattress suture with buffering tags at the knots may be used. This suture pattern is oversewn with simple continuous or continuous Lembert sutures.2

When smaller vessels are repaired with simple interrupted patterns, the basic procedure is the same. The wall of the vessel distal from the surgeon is sutured first and the sides are sutured alternatively until the portion of the wall most proximal to the surgeon is closed last. A triangular pattern may also be used for appropriately sized vessels with the first sutures placed distal to the surgeon as for the other patterns. Vascular picks are helpful in positioning the walls of the smaller vessels for proper alignment during suturing.2

Veins may be sutured in the same manner as arteries; however, they are much more friable and easily torn with sutures. Closure of the surgical incision is routine for the area in which the vessel is located.2

Postoperative anticoagulant therapy may be indicated for procedures such as implantation of grafts or placement of stents. Anticoagulant agents are listed in Table 1. It should be emphasized that there is individual variation in the reaction to the various agents and some variation between breeds of pigs. Pigs must be monitored for bleeding post administration of the low molecular weight heparins and thrombin inhibitors. There are minimal complications with the administration of aspirin. If gastric upset occurs use enteric coated tablets or aspirin with Maalox. The titration of warfarin products also requires close monitoring. In our laboratories aspirin is used for long term postoperative therapy when stents or grafts are implanted. A combination of low molecular weight heparin (Hirudin or Dalteparin) sc plus Clopidogrel (Plavix) for the first 7-10 days is used in addition. If implanted devices require long term anticoagulant therapy for months, warfarin is used. Other laboratories have reported success with other combinations of agents.2
Surgical and Interventional Catheterization Models

Swine are a favored model for both interventional catheterization and device implantation within the cardiovascular system. This is due to the similarity of their wound healing characteristics to humans and the ability to evaluate development of collateral circulation and neointimal proliferation. As a general rule miniature breeds should be utilized for projects which are scheduled for more than three weeks. This is due to the continued growth of the blood vessels which is much greater in domestic breeds. A domestic farm pig can be expected to increase the diameter 35-40% and length 25-30% over a six month growth period. This can cause the intravascular device to become dislodged or change the architecture of the blood vessel. Sexually mature minipigs are the preferred model for the long term studies necessary in preclinical trials.

Common Surgical Models: Graft implantation (Figure 4) and the creation of aneurysms are some of the most common types of manual surgical procedures performed in swine. Other procedures such as constrictive banding of major blood vessels and arteriovenous fistulas are performed in order to create models of heart failure due to volume or pressure overload and are beyond the scope of this manuscript. Detailed descriptions of these various procedures have been published and illustrated.

Graft implants made of various biomaterials and tissue engineered products are the most common types of implants requiring an anastomosis. Depending upon the size of the graft the most common vessels used are the aorta, carotid or femoral artery. Porcine graft implants have been shown to have a smooth fibrin surface and be relatively resistant to experimental infection; these characteristics may make them useful for some preclinical studies. Endothelialization of implanted biomaterials usually occurs.

Many different types of aneurysms have been created in swine mainly to develop a model for testing of interventional catheter devices to close the defect. Turjman and Massoud published classical works for creation many types of aneurysms in the neck vessels. Using a combination of procedures on unilateral external jugular veins, carotid arteries, and ascending cervical arteries, three types of bifurcation aneurysms, two types of terminal aneurysms, wide-necked aneurysms, and fusiform aneurysms were created. Aortic aneurysms have generally been created by making an incision in the vessel and creating a ballooned window with a material such as bovine pericardium or PTFE. Intervventional Catheter Models: Interventional catheter models are one of the primary areas of experimentation in swine. The various types of procedures include intravascular stents, balloon angioplasty, implantation of devices for measuring cardiovascular function, and anti-thromboembolic devices. Generally the research associated with these procedures is related to testing of a new device design or a medication which eludes from the implanted stent. Most of the time the interventional catheter techniques utilize the Seldinger procedure for vascular access which is described in another manuscript on this website. Interventional catheterization techniques have also been described in depth.

Summary

Swine have been widely used in vascular surgery and interventional catheterization protocols in research. This is due to their anatomic and physiologic similarities to humans. Miniature breeds are preferable to the use of domestic farm breeds for chronic studies due to the continued and significant growth of the blood vessels in farm pigs. This manuscript offers surgical and perioperative care advice based upon extensive experience in porcine vascular models.
Selected References


