Journal of the American Association for Laboratory Animal Science
Copyright 2006
by the American Association for Laboratory Animal Science

Vol 45, No 6
November 2006
Pages 27-34

Noninfectious Complications Due to Vascular Access Ports (VAPs) in Yucatan Minipigs (*Sus scrofa domestica*)

Christine A Ege,[1] Nannette C Parra,[1] and Thomas E Johnson[2,*]

Vascular access ports (VAPs) for studies requiring intermittent or continuous infusion and frequent sampling are well accepted and widely used in large animal species. However, the use of medical devices such as VAPs to facilitate sample collection can lead to complications. Noninfectious complications of VAP implantation can result from thrombotic or mechanical obstructions, other mechanical problems, and animal-associated complications. To facilitate our research, we surgically implanted VAPs in the right external jugular vein of 6 adult male and 3 female Yucatan miniswine (age, 12 mo) to enable collection of blood samples every 30 min for 8 h and then every 8 h for as long as 60 d. The VAPs were operational an average of 35.6 d (range, 29 to 56 d) and had an overall success rate of 77.8% with 7 of 9 VAPs functional. In these 7 animals, 53.1 samples on average (range, 28 to 95 samples) were collected from each VAP. Rates of noninfectious complications were 60% for thrombotic events and 40% for nonthrombotic events over the course of this study.

Abbreviation: VAP, vascular access port

Experimental procedures in swine frequently require chronic access to the vascular system for serial blood sampling. However, the use of medical devices, such as vascular access ports (VAPs), to facilitate collection of these samples can lead to complications. Although several sites are acceptable for routine venous access,[25,26] many are difficult to access[4] or do not provide sufficient volumes of blood for hematologic studies.[20] Furthermore, routine venipuncture can place undue stress on the experimental animal, and anesthetic or sedative drugs used to prevent pain and discomfort are potentially confounding variables in any experimental design.[6] The use of VAPs for studies requiring intermittent or continuous infusions and frequent sampling is well accepted and widely applied in large animal species.[26] A complete comparison of types of VAPs and selection criteria was published recently by Swindle and coworkers.[26]

Mueller and coworkers reported a 21% rate of infectious complications and an 8.5% rate of noninfectious complications associated with subcutaneous catheters in humans.[19] Noninfectious complications encountered in animal studies using VAPs can result from thrombotic or mechanical obstructions, other mechanical problems, and animal-associated complications. Although infections and catheter obstructions are the most common complications associated with VAP use,[14] few reports document the longevity and overall complication rate associated with VAP use in large animals.[26]

Thrombotic occlusion is a natural sequela of platelet aggregation and fibrin deposition, and thrombotic complications of indwelling catheters in swine are widespread because pigs are hypercoagulable.[6] The 4 types of thrombotic occlusions are fibrin sheath, fibrin tail, intraluminal thrombus, and mural thrombus.[13] A fibrin sheath (also known as an extraluminal thrombus or a fibrin sleeve) is the casing that develops when fibrin is deposited on the external surface of catheters, generally starting within 24 h of catheter placement,[2] whereas a fibrin tail occurs when fibrin, blood cells, and platelets adhere to only the end of a catheter. This deposition leads to persistent withdrawal occlusion,[13] which obstructs withdrawal but allows infused fluids to pass. An intraluminal thrombus occurs with a partial obstruction of the catheter lumen, resulting in slow flow during blood withdrawal or the need for high pressure to infuse fluids. Finally, a mural thrombus may occur if the catheter tip causes a vessel wall injury, resulting in fibrin from the injury attaching to the catheter surface and leading to catheter occlusion.[26] A nonthrombotic obstruction within the catheter lumen may be caused by precipitates, kinks, or inappropriate catheter tip location.

Other mechanical complications that may impinge on VAP use but not cause occlusion include unstable port hardware,[7] catheters that become disconnected from the ports,[8,24] migrating catheters,[17] leaky ports,[30,32] leaky catheters,[17,24] and incompatibility between the port placement location and the restraint device.[32] Finally, animal-associated noninfectious complications potentially affecting the use of the VAP include local necrosis,[3,8] erosion of the port through the skin,[3,21] vascular injury,[29] seroma formation,[25] and death.[8]

In the present study, we used VAPs in an attempt to avoid repeated venipuncture and associated problems (that is, infection and prolonged bleeding) in immunosuppressed animals experiencing platelet dysfunction. The experimental design required at least 3 blood samples daily over an extended period to analyze hematologic and blood chemical parameters; we therefore used VAPs for ease of collection. Ultimately in this study, noninfectious complications, including nonfunctional VAPs, were more problematic than infectious complications.

Materials and Methods

All procedures were performed under a protocol approved by the Armed Forces Radiobiology Research Institute Institutional

Received: 26 Apr 2006. Revision requested: 12 July 2006. Accepted: 12 July 2006.
[1]Uniformed University of the Health Sciences, Armed Forces Radiobiology Research Institute, Veterinary Sciences Department, Bethesda, Maryland; [2]Colorado State University, Department of Environmental and Radiological Health Sciences, Fort Collins, Colorado.
[*]Corresponding author. Email: Thomas.Johnson@colostate.edu

Animal Care and Use Committee. The facility is fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International.

Animals. For this study, 6 male and 3 female Yucatan miniswine (age, 12 mo; weight, 40 to 50 kg) were obtained from the Department of Defense nonnaïve animal pool. Animals were group-housed for 3 wk and then moved to individual stainless steel caging 1 wk prior to surgical implantation of VAPs. All animals participated in an environmental enrichment program consisting of provision of rooting and tug toys, positive reinforcement with fig bars after manipulations, and frequent positive interactions with humans. The room conditions were: temperature, 16 to 27 °C; relative humidity, 30% to 70%; and 12:12-h light:dark cycle. Mini-Swine Diet 8753 (Harlan Teklad Diets, Madison, WI) and water were provided ad libidum in stainless steel containers for all animals.

Surgical procedures. VAP catheters (model CP2 with a 7 French rounded tip silicone catheter; Access Technologies, Skokie, IL) were surgically implanted in the right external jugular veins of 9 animals under general anesthesia and according to the principles of aseptic surgery.[28] Pigs were sedated with intramuscular ketamine (20 mg/kg; Vetalar, 100 mg/ml, Fort Dodge Laboratories, IA) and xylazine (2 mg/kg; Rompum, Bayer, Shawnee Mission, KS). Atropine (0.05 mg/kg; atropine sulfate, Butler, Columbus, OH) was given to reduce mucosal secretions. After intubation, all animals were maintained under general anesthesia using isoflurane gas (Abbott Laboratories, North Chicago, IL) at a maintenance rate of 1% to 3% and oxygen flow rate of 1 to 2 l/min.

The catheter tip was positioned at the junction of the external jugular vein and vena cava. Prior to insertion of the VAP catheter, it was flushed with heparinized saline (3 IU/ml). To secure the VAP catheter within the vein, 1 preplaced silk 3-0 suture (Ethicon, Somerville, NJ) was used to ligate the cranial portion of the vessel. A second and third silk ligature were placed around the caudal portion of the vessel containing the VAP catheter and retention bead, with 1 ligature on either side of the bead. The port was secured within the scapular incision site to the underlying musculature by use of 0 prolene (Ethicon) at the 5 anchor holes on the port.

Catheter function was confirmed intraoperatively through aspiration of heparinized saline and withdrawal of a blood sample via the septum. The port reservoir and catheter were flushed again with 6 ml saline and locked with 3 ml of a heparinized saline (3 IU/ml) and gentamicin (0.2 mg/ml; Abbott Laboratories, North Chicago, IL) mixture. Gentamicin-containing lock solution was infused into the catheter once postoperatively; all subsequent lock solutions were heparinized saline.

During closure of the surgical sites, special attention was given to eliminating dead space around the port and around the catheter loop on the neck. The muscle and subcutaneous layers were closed with 3-0 PDS II (polydioxanone suture; Ethicon). Skin incisions were closed with 2-0 PDS II (Ethicon) in either a cruciate or horizontal mattress suture pattern. Tissue glue (VetBond, 3M, St Paul, MN) was used to seal sites to help prevent contamination. The procedure was completed in 1.5 to 2.5 h. Intraoperative intramuscular buprenorphine (0.01 to 0.02 mg/kg; Buprenex, Reckitt Benckiser, Richmond, VA) was provided for analgesia. Postoperative amoxicillin (500 mg orally once daily for 5 d) was administered to each animal. Postsurgical recovery and pain were monitored by daily visual examination of the incisions and overall conditions of the animals. Parameters monitored were food and water intake, activity, alertness, vocalization, guarding, and response to human contact. On the basis of thrice daily assessments, no animal required postoperative analgesia.

Irradiation. At 3 wk after VAP placement, each animal received 3.5 Gy (350 rads) whole-body gamma radiation from a ^{60}Co source at a dose rate of 0.4 to 0.6 Gy/min (40 to 60 rads/min). The dose was designed to induce severe immunologic and hematologic depression. All pigs were euthanized when they displayed predetermined clinical parameters of morbidity and moribundity. No supportive care in the form of fluids, antibiotics, or transfusions was provided.

Collection of blood samples. Baseline samples were collected at 4 wk (before VAP implantation surgery), 3 wk (at VAP implantation surgery), and 2 wk (after VAP implantation surgery) before irradiation. Each sample was approximately 6 ml in volume and was collected from the VAP if the device was available and functional. The project required additional blood sampling every 30 min for 8 h on the day of irradiation, commencing immediately after irradiation, and subsequent samples every 8 h for as long as 60 d. The frequency of sampling plus the potential for adverse effects on the samples precluded the use of anesthesia for each collection. During the first day of sampling postirradiation, animals were restrained in a humane restraint sling and given a 20-min unrestrained break every 2 to 3 h. After the first 8 h, collection of samples was performed cageside while the animal was distracted with food. However, if vascular access was compromised, the animal was restrained in a sling for each successive sample collection.

Two types of non-coring 1.9- to 3.9-cm (0.75- to 1.5-in.) Huber needles were used to access the port through the skin: straight or a right-angled (2.6 to 3.9 cm [1 to 1.5 in.]) with attached infusion set (Churchill Medical Systems, Horsham, PA). A right-angled butterfly needle was inserted initially and affixed to each animal.

Animals were sedated with xylazine (1.1 to 2.2 mg/kg), which also provided muscle relaxation and analgesia. During placement of a non-coring needle, port injection sites were scrubbed with povidone iodine and 70% isopropyl alcohol until all gross debris was removed (3 to 5 scrubs). The protrusion of the needle was padded with gauze to soften its edges, and a bandage (Tegaderm, 3M) was placed over the area to prevent debris from entering the needle puncture site. A right-angled non-coring butterfly needle then was inserted aseptically for chronic port access and sutured into place with 0 PDS II; the neck and shoulder were covered with a circumferential bandage consisting of gauze, elastic bandaging (Vetrap Bandage Tape, 3M), and elastic adhesive bandage material (Elastikon, Johnson & Johnson, New Brunswick, NJ) . The elastic bandaging covered the shoulder and neck of the animal, and the edges were secured with elastic adhesive bandage material. All needles were replaced at least once each week and when the bandage became soiled or the non-coring needle became dislodged from the port septum. Analgesia was provided only for needle replacement but not for routine use of the Huber needle.

To collect a sample, the injection cap was removed from the infusion set and a syringe was attached. Approximately 3 to 6 ml fluid was withdrawn from the catheter and port until blood no longer appeared to be mixed with saline. This fluid was discarded. The blood sample was collected into a new syringe and placed in appropriate vials for complete blood counts and serum chemical analysis. Next, 3 ml heparinized saline (3 IU/ml) was infused into the port and catheter as a locking solution. After each use, the female end of the infusion set was closed with an injection cap. An alternative procedure using a stopcock and 3 syringes was cumbersome to manipulate; needle insertion

Table 1. Summary of blood collections and complications encountered

Animal no.	Survival after surgery (d)	VAP operational period (d)	No. of samples collected via VAP	Total no. of samples required for study	Complications in light of clinical signs
21	32	7	1	37	Thrombotic
22	36	0	0	61	Thrombotic
23	63	56	95	102	Thrombotic
24	31	30	28	45	Nonthrombotic
25	30	30	42	42	Nonthrombotic
26	41	41	75	75	none
27	33	33	51	51	none
28	30	30	42	42	none
29	29	29	39	39	none

A VAP was defined as nonfunctional if no sample could be drawn beyond 7 d postoperatively. Therefore, the VAPs in animals 21 and 22 were considered to be nonfunctional.

could not be consistently and firmly maintained within the port septum when collecting samples using that method.

A standard protocol was followed for obtaining a sample from a problematic catheter. First, external pressure was applied to the non-coring needle where it entered the port to ensure the tip of the needle was all the way through the septum and into the reservoir. Second, high-pressure turbulent flushing was attempted with a change in the animal's position. A second person was needed to extend the neck of the animal by raising it or flexing it away from the side that contained the VAP. Third, the non-coring needle was replaced; at times the needle was clotted. Fourth, if the described series of interventions failed to return the VAP to functioning, the sample was collected from the jugular or ear vein. The next team would repeat the procedures at the next time point in hopes of restoring the VAP to use. Three sequential attempts over a 24 h period were made to rescue the VAP before it was considered nonfunctional.

Results

Of the 9 animals with surgically implanted VAPs, VAPs in 2 (animals 21 and 22) ultimately became nonfunctional (Table 1). Of the 7 minipigs with functional VAPs, 3 animals exhibited complications that interfered with sample collection (animals 23 to 25), whereas the VAPs functioned without difficulty in the remaining 4 animals (animals 26 to 29). The functional VAPs were operational an average of 35.6 d (range, 29 to 56 d), and an average of 53.1 samples (range, 28 to 95 samples) were collected through each VAP. All 9 animals had blood collected via the VAP during the 3-wk surgical recovery period after VAP implantation and at least twice more before irradiation and postirradiation bleeds.

Regarding the 2 miniswine with nonfunctional VAPs, animal 21 presented with a nonfunctional VAP on the day of irradiation, with the last pre-exposure sample drawn 14 d prior. At the time of this last baseline collection, the VAP could be flushed, but nothing could be withdrawn. During attempted withdrawal, the animal made a forceful movement within the sling and immediately a sample was easily collected. The withdrawal continued for 3 to 4 s and then stopped completely until the animal moved again. This sample could only be collected while the animal was moving. All subsequent samples were obtained by traditional venipuncture methods from the cranial vena cava. In addition, a voluminous hematoma was observed at this site of sampling. The hematoma was diagnosed 10 d postirradiation at the first sampling period of the day, and the animal was euthanized the same morning in light of predetermined clinical parameters.

The VAP was functional in animal 22 at 7 d postoperatively but nonfunctional 14 d later, at the last attempt for baseline collection. Although fluid could be flushed easily into the port, withdrawal of fluids was impossible; therefore blood was collected via traditional venipuncture techniques throughout the experiment. Repeated sampling from the ear vein and cranial vena cava eventually caused these vessels to become inaccessible. At 31 d into the experiment, the animal was sedated so that blood could be collected from the abdominal vein. In addition, this animal had an exaggerated thrombocytosis ($>1000 \times 10^3/\mu l$) relative to the other animals in the colony.

Among the 3 miniswine that displayed complications, the VAP in animal 23 exhibited sluggishness during the second day of blood collections postirradiation, after which the VAP functioned normally until 30 d postirradiation, when the VAP regularly exhibited positional difficulty upon withdrawal. The animal had begun to cough frequently 10 d prior to the onset of this complication.

In animal 24, a seroma developed within the port pocket. On the first day of blood collections postirradiation, the port hardware turned over within the subcutaneous space, preventing access to the port septum. Attempts to correct this problem by rotating the port within the space without surgical intervention were unsuccessful, so all samples were collected via the ear vein or cranial vena cava. By the next day, the port rotated again so that the septum was accessible, amid the continuous seroma formation and movement of the animal. Subsequently, the seroma was drained daily when the pocket was entered for blood sample collection, and each sample thereafter was collected via the port.

In animal 25, the port was loose but functional within the subcutaneous pocket. All blood samples were collected via the port, but light restraint requiring a second person was essential for sample collection because additional manipulations were necessary to stabilize the port underneath the skin during insertion of the non-coring needle.

The VAPs in animals 26 to 29 remained functional throughout the study.

Discussion

The use of VAPs in this study was cost-effective, efficacious, and humane when compared with conventional venipuncture. In addition, the use of VAPs circumvented expected problems seen in animals without functional VAPs. Despite several types of complications associated with VAP use, the overall success rate was 77.8%, with 7 of 9 VAPs remaining functional for the duration of the study. The functional VAPs allowed for collection of 373 of the 494 total blood samples drawn from all pigs.

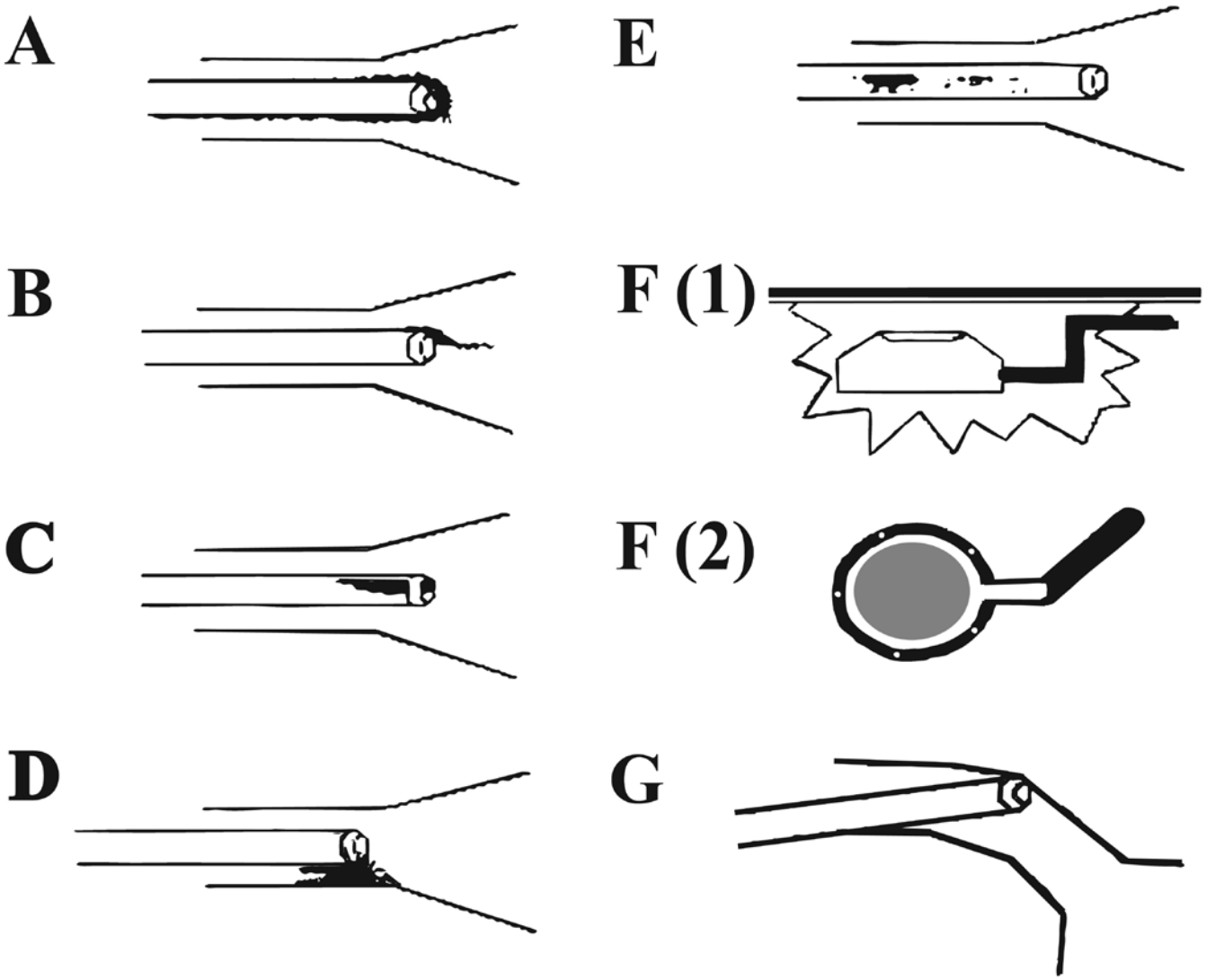

Figure 1. Schematic diagram of catheter occlusions. (A) Fibrin sheath—fibrin deposition completely occluding catheter tip. (B) Fibrin tail—occlusion occurs during negative pressure application, pulling tail into or over catheter lumen. (C) Intraluminal thrombus—fibrin deposition within catheter lumen causes slow infusion and withdrawal during catheter use. (D) Mural thrombus—fibrin deposition in response to vessel wall injury builds up an obstruction at the tip of the catheter. (E) Precipitated substance—within lumen of catheter causes slow infusion and withdrawal or complete obstruction. (F1) Kink—horizontal view of port hardware as it connects to kinked catheter. A kink in the catheter in the vertical plane as it enters the surgical site of the port location is due to inappropriate surgical placement of catheter too superficial to the skin thereby not entering catheter on the same tissue plane as the port. (F2) Kink—dorsal view of port hardware as it connects to the catheter. A kink in the catheter in the horizontal plane as it enters the surgical site of the port is due to inappropriate rotational fixation of the port. This can be prevented by securing the port to the catheter prior to securing the port to underlying facia and muscle. (G) Inappropriate tip location- tip of catheter occluded by vessel wall due to migration or inappropriate surgical placement. Tip should be placed in area of high turbulent flow.

Rates of noninfectious complications were 60% for thrombotic events and 40% for nonthrombotic events over the course of this study, comparable to rates reported in the literature. Stephens and colleagues reported 58% of malfunctions of central venous catheters were due to thrombotic causes and 42% were due to nonthrombotic or mechanical causes.[24] In light of the expected experimentally induced coagulapathies of these animals, we experienced fewer thrombotic complications than expected, despite our use of a low concentration of heparin in the lock solution (3 IU/ml). Heparinized saline concentrations used in swine typically range from 500 IU/ml[3,28] to 1000 IU/ml.[6,7,12,26,27,31] In a similar study in nonirradiated animals with normal platelet function, higher rates of suspected thrombotic complications occurred.[10] We did not consider fibrinolytic therapy to be a viable treatment option for these obstructive complications because of the expected experimentally induced platelet deficiencies in these animals. Further studies are necessary to determine whether thrombocytopenia decreases thrombotic complications associated with VAPs.

Although fewer than expected, thrombotic occlusions were common. Most of the 4 types of thrombotic occlusions (fibrin sheath, fibrin tail, intraluminal thrombus, and mural thrombus;[13] Figure 1) were exhibited in this study. Fibrin sheaths were identified covering the catheters post mortem, but not occluding the tips of catheters. Clinical signs suggesting the presence of fibrin tails and intraluminal thrombi disrupted sample collection. Mural thrombi could not be confirmed as cause of obstruction as post mortem examinations on most animals with thrombotic occlusions were not conducted until several weeks after discontinuation of catheter use.

Fibrin sheath and fibrin tail. A fibrin sheath (Figure 2) typically does not cause clinical problems unless it occludes the catheter

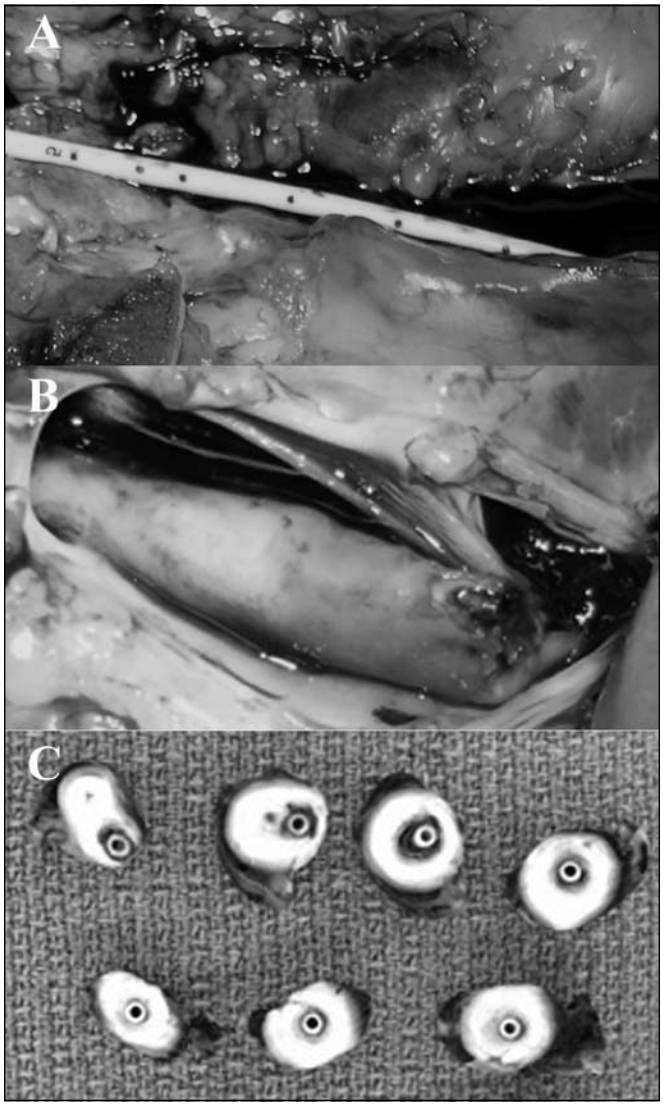

Figure 2. Vascular catheters (A) in situ without gross fibrin sheath and (B) in situ postmortem covered with fibrin sheath. A thick friable fibrin layer covers all but the tip of the catheter in the anterior vena cava. Fibrin layering could occlude the catheter tip prohibiting vascular access. (C) Multiple cross-sections of formalin-fixed catheter from animal in Figure 2 B. Fibrin deposition in concentric layers may be many times thicker than the diameter of the central to slightly eccentric white catheter.

tip (Figure 1 A),[5] in which case clinical symptoms of complete obstruction occur.[13] If obstruction occurs only while negative pressure is applied, it can be described as a "check valve" or "ball valve" effect caused by a fibrin tail (Figure 1 B).[12] In animal 21, a change in position that suddenly allowed withdrawal from the VAP suggests the development of a fibrin tail (Figure 1 B) or inappropriate catheter tip location (Figure 1 G) against a vessel wall or the heart wall. We suspect a fibrin tail and damage to the vessel wall further developed into a fibrin sheath or mural thrombus (Figure 1 D), causing a complete obstruction of the VAP by the time daily blood collections began. The hematoma in this animal likely arose due to subsequent repeated sampling from the cranial vena cava and experimentally induced thrombocytopenia. Animal 22 presented with signs of partial withdrawal occlusion with an exaggerated thrombocytosis. Because fluid could be flushed into the port but withdrawal of fluids was impossible, a fibrin tail was the most likely cause of thrombotic occlusion (Figure 1 B).

Clinical signs were the only tools available to us to diagnose thrombotic complications antemortem in the 3 animals with VAPs with suspected thrombotic complications (animals 21, 22, and 23). Thrombotic occlusions can be visualized with imaging techniques such as contrast radiology,[17,24,26] ultrasonography,[11,26] fluoroscopy, [2,7,17] and CT scan[7] to help determine the type of lesion causing problems. Diagnostic imaging would have been ideal for our purposes but was unavailable.

Intraluminal or mural thrombus. The sluggishness in withdrawal from the VAP in animal 23 was consistent with an intraluminal thrombus (Figure 1 E), which typically results from insufficient flushing techniques, inadequate flow through the lumen of the catheter, reflux from changes in intrathoracic pressure (such as coughing and/or vomiting), congestive heart failure, or frequent blood withdrawals via the catheter.[13]

The intraluminal thrombus in animal 23 was probably was dislodged from the lumen via aggressive flushing techniques because the problem of slow withdrawal was temporary. In the case of a suspected intraluminal thrombus, turbulent, [26] pulsating,[1] or alternating pressure[30] flushing typically corrects the problem but may release thrombotic emboli to organs downstream. Therefore, regular flushing (daily to weekly) and using a heparinized saline lock solution are the best courses of preventive maintenance.

Animal 23 showed clinical signs of illness (cough) 10 d prior to the positional difficulty in withdrawal, and at 7 d prior to the complication, the bleed frequency was decreased from thrice to once daily. The platelet levels had dipped and then returned to normal by this time. The combination of coughing, less frequent use, and return to a normal platelet level may have contributed to an intraluminal thrombus formation, catheter kinking, or a migrated catheter tip. The diagnosis of an intraluminal thrombus in animal 23 was confirmed at necropsy and histopathology, because the complication was active at the time of necropsy (Figure 3).

A mural thrombus (Figure 1 D) may be more likely to occur if a square-cut or bevel-tip intravascular catheter is used. The sharp edges can irritate the intimal lining, stimulating a thrombogenic response. Our study used a smooth rounded-tip catheter, which caused minimal intravascular trauma, thus prolonging patency.[26]

Nonthrombotic obstructions. Because injected substances can precipitate in the lumen of the catheter,[15,26] infused materials should be soluble and properly prepared before use. Some precipitate occlusions may be resolved with hydrochloric acid, sodium bicarbonate, or ethanol.[15] In addition, kinks are common causes of catheter obstructions,[16,21,24,26,32] and softer catheter materials (for example, silicone or polyurethane) are more prone to kinking problems than are stiffer materials (for example, polyethylene.) Finally, inappropriate catheter tip location may lead to catheter occlusion. Placement against a vessel wall or the heart wall can mechanically obstruct withdrawal, cause erosion of the vessel wall leading to inflammation and clot formation, irritate the endothelium, and cause arrhythmias.[26] The ideal location for the tip of the catheter is in the vessel lumen in an area of high or turbulent blood flow, with minimal contact with the vessel wall.[26] Because surgery is required to correct inappropriate catheter tip position, techniques used for proper tip placement include monitoring changes in the ECG during surgery,[18] conducting intraoperative fluoroscopy,[7] and presurgical planning using cadavers of the same size and species.[20]

Mechanical and animal associated complications often develop unexpectedly with VAP usage. In this study, a number of these conditions were detected.

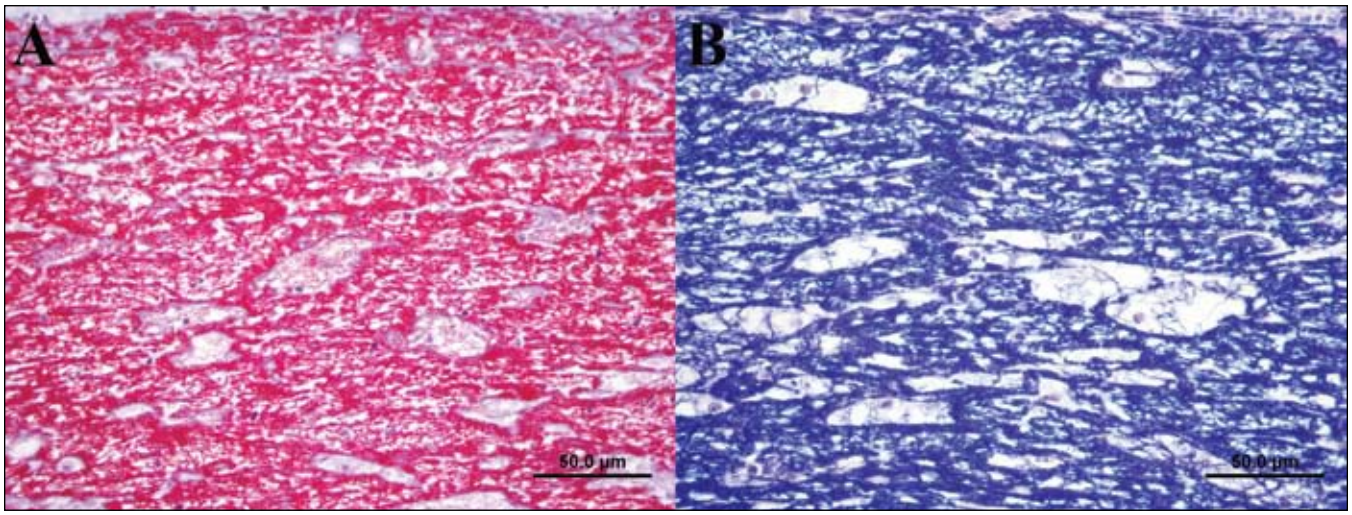

Figure 3. Photomicrographs demonstrating fibrin content of sheath in Figure 2 B. (A) Trichrome stain; magnification, ×600. Red identifies fibrin content. (B) Phosphotungstic Acid-Hematoxylin (PTAH) stain; magnification, ×600. Dark blue identifies fibrin content.

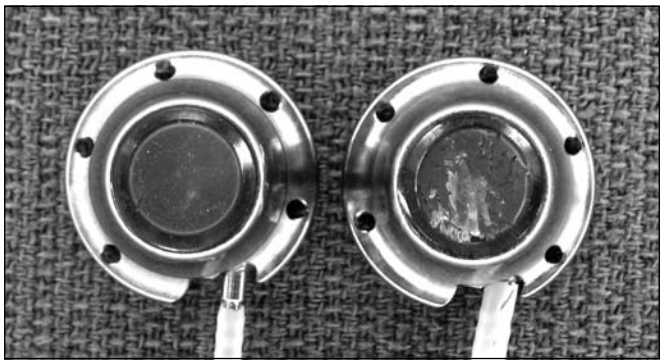

Figure 4. VAP port hardware. Normal use (left) and lacerated septum (right) removed from animals postmortem at completion of the study.

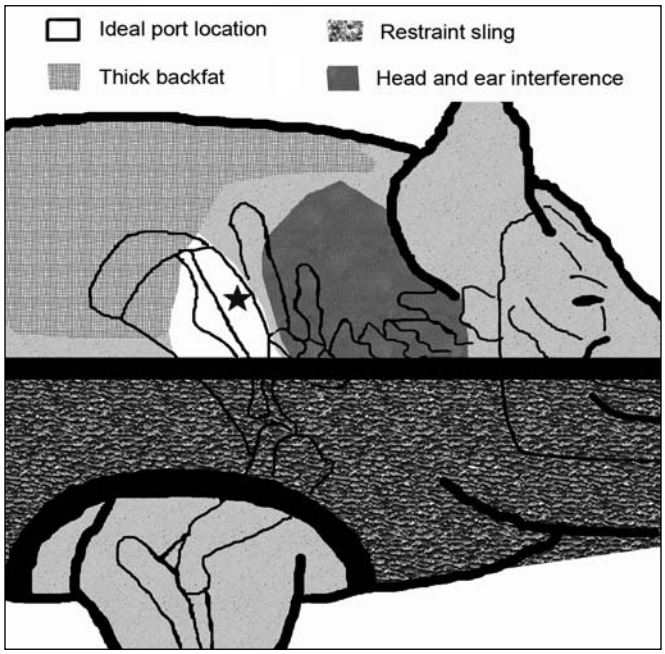

Figure 5. Schematic diagram of ideal placement of port hardware. The area identified by the star indicates the cranial edge of the scapula providing hard tissue support which is also low enough to avoid thick backfat, high enough to avoid restraint sling, and caudal enough to avoid interference from the head and ear for perpendicular entry into the skin.

Unstable port hardware. Mobility of the port hardware in animals 24 and 25 indicated inadequate fixture of hardware to underlying muscle or fascia. Because port inversion can make the septum inaccessible[1] or cause movement of the catheter, thus increasing the likelihood of kinking and catheter tip movement, surgical intervention is recommended where possible. The development of a seroma in animal 24 most likely was due to inadequate elimination of dead space within the subcutaneous port pocket during surgery.

Inappropriate needle usage. The use of a non-coring needle, which allows penetration of the port without coring of the port septum, is required to maintain septum integrity. The right-angle infusion set lies close to the skin, allowing a jacket to fit. The straight Huber stands perpendicular to the skin. Swine require various lengths of needles, depending on skin thickness and surgical technique. To select a needle of appropriate length, the combined thickness of the port septum, epidermis, and back fat should be considered. Too short a needle results in ineffective port access or premature needle dislodgement, as seen in animal 24; too long causes difficulty in securing the needle set components above the skin.[26] In our study, in cases in which the 2.6-cm (1 in.) needle was too short to access the port reservoir without external pressure to compress soft tissues overlying the port, the 3.8-cm (1.5 in.) needle was used. Furthermore, even though the right-angle infusion sets are designed for protracted use or continuous access,[26] their use should be limited to a period when the animal remains restrained without excess movement, because the skin over the port will move relative to the muscle to which the port is secured. If an indwelling needle remains in the skin, the movements of the animal could cause it to lacerate the underlying septum, as we saw in several ports in this study (Figure 4), potentially damaging the integrity and useful life of the port.

Disconnected or migrated catheter. Surgical error can lead to a catheter disconnecting from the port. This problem is identified when fluid other than blood (serosanguinous fluid or purulent material) are withdrawn from the port, yet fluid still can be infused. Another clinical sign is turbulence palpated through the skin during flushing. Imaging techniques using a contrast agent may help diagnose this problem, which can only be corrected by surgical replacement. Catheters manufactured with permanently attached, preplaced suture retention beads to help

prevent movement[23,26,27,30] can be secured within the vessel by 2 circumferential ligatures around the blood vessel proximal and distal to the bead within the vessel.[27]

Leaky port. Because ports can leak due to repeated localized needle insertion, manufacturers recommend rotation of needle insertion location throughout the port septum to prevent overuse of a narrow area of the port.[32] Although in vitro studies have shown that silicone rubber septa typically accept more than 1000 punctures with a 22-gauge Huber needle without leaking,[26] repeated injections at the same spot on a port can lead to premature deterioration of the silicone membrane. Ports occasionally sterilized and reused may be more susceptible to leaks.[30] If a port develops leaks, it can be surgically replaced without replacing the catheter.[32]

Inappropriate port site. For the successful operation of the VAP, appropriate site selection for the port is essential (Figure 5). Many factors should be considered to determine the accessibility of a VAP site selection: thickness of skin, obstacles to perpendicular entry through skin, compatibility with restraint device, and firm tissue support beneath port hardware. For this study, the ideal port placement location was directly over the scapula,[3] providing firm support to port hardware when the skin and septum were punctured. This location was low enough to avoid thick backfat on the dorsum of adult swine,[3] sufficiently caudal to the point of the shoulder so the ear and head did not interfere with the aseptic field and syringe apparatus needed for sample collection, and high enough to remain accessible while the animal was in a restraint device.[3,32]

Port dome size (especially height) should be small enough to fit in the animal's subcutaneous environment, but large enough for the researcher to easily palpate and stabilize during access. A port that is too tall can result in pressure necrosis and erosion through the skin[26] or may be susceptible to external traumatic injury.

Finally, several other animal-associated noninfectious complications that do not affect catheter use but may affect research results have been reported: painful phlebitis,[8,22,29] arrhythmias,[26] stress of capture and restraint,[31] traumatic skin lesions from group housing,[8] amyloidosis of the spleen and liver,[9] skin not tolerating multiple daily punctures over an extended period,[32] and difficulty in conducting multistep disinfection procedures with unrestrained animals.[6]

In our study, many benefits of using VAPs were immediately apparent. Their use reduced stress on the animals and staff, occupational injury, and labor requirements. In addition, the VAPs allowed cageside collection of samples without restraining devices. Most importantly, the use of VAPs decreased the handling of the animals, most of which were heavier than 45 kg. This labor reduction allowed 3 people to collect 12 samples in 15 min instead of 3 people collecting 1 sample in 15 min. VAPs provide an advantage to catheters with external components by allowing animals to be group-housed.

Disadvantages to using VAPs were the need for a major surgical procedure and cost of the VAP hardware and accessory supplies. VAPs cost more than external catheters and require relatively expensive non-coring Huber needles that are not used typically at most facilities.

An often desired advantage of using a VAP for serial collections is that it can be entirely enclosed subcutaneously without any external components. Maintaining the VAP and its components in a subcutaneous position was not a priority for this study. Because blood collections occurred 3 times daily, the gains obtained from prolonged Huber needle placement outweighed the infectious risks of maintaining a breach into the subcutis. The bandaging technique we used was designed to lessen the risk of infection. Although the external surfaces of the bandages became soiled, none were rubbed off or loosened by the animals, and the animals did not appear to interfere with them. Animals in this study did acquire bacterial infections and further studies are in progress to identify the sources of these infections. This information may indicate the role of the bandaging and handling techniques in preventing infection.

When confronting a partially or non-functional catheter, knowing how the complication occurs may help diagnose the problem and result in a more favorable outcome for the patient, equipment, and research results. The current practice of salvaging the dysfunctional catheter, in contrast to its removal and insertion of a replacement, is the preferred approach. Although thrombolytic therapy was not used in this study because of the experimental design, it would be appropriate to have a well-considered thrombolytic therapy plan to address thrombus-related obstructions. Particularly with large animals, replacing the device or removing the animal from the study may be more cost-effective than trying to correct the complication at hand. However, restoring catheter function helps to limit interruption of experimental manipulations, reduce risk of trauma to the patient, decrease risk of complications, decrease costs, and reduce the number of animals needed.[13] By addressing the noninfectious complications to restore catheter function, the use of VAPs in miniswine clearly leads to reduction and refinement.

Acknowledgments

The views expressed in this paper are those of the authors and do not necessarily reflect those of the Armed Forces Radiobiology Research Institute (AFRRI), Uniformed Services University, the Department of Defense, or Colorado State University. The authors thank Drs Terry Pellmar and Annette Hildabrand for their guidance and Dr Steven R Mog for his pathology work. Excellent comments from Aimee Buelow and Drs William Butler and Joseph Harre greatly improved this paper. An experiment of this magnitude could not have been conducted without the outstanding support of the AFRRI Veterinary Sciences Department animal care and husbandry staff, who worked tirelessly alongside Scott Johanson, Nicole McPherson, Don Randolph, Tridaugh Winston, and Golda Winston. Their 24/7 support was above and beyond our expectations.

References

1. **Access Technologies.** 1999. Vascular access ports technical bulletin no. PW011199. Skokie (IL): Access Technologies.
2. **Asch MR.** 2001. Venous access: options, approaches and issues. Can Assoc Radiol J **52:**153–164.
3. **Bailie MB, Wixson SK, Landi MS.** 1986. Vascular access port implantation for serial blood sampling in conscious swine. Lab Anim Sci **36:**4.
4. **Bain SAF, Ting J, Simeonovic CJ, Wilson JD.** 1991. Technique of venous catheterization for sequential blood sampling from the pig. J Invest Surg **4:**103–107.
5. **Bona RD.** 1999. Thrombotic complications of central venous catheters in cancer patients. Semin Thromb Hemost **25:**147–155.
6. **Chuang MS, Orvieto MA, Laven BA, Gerber GS, Wardrip C, Ritch C, Shalhav AL.** 2005. Comparison of external catheters with subcutaneous vascular access ports for chronic vascular access in a porcine model. Contemp Top Lab Anim Sci **44(2):**24–27.
7. **Clark TWI, Bilo JM, Beecroft JR.** 2002. Arterial port catheter system placement using a translumbar aortic route. Invest Radiol **37:**7–12.
8. **Cowart RPl, Payne JT, Turk JR, Tyler JW, Casteel SW.** 1999. Factors optimizing the use of subcutaneous vascular access ports in weaned pigs. Contemp Top Lab Anim Sci **38(3):**67–70.
9. **Doepel FM, Ringler DH, Petkus AR.** 1984. Secondary amyloidosis in rhesus monkeys with chronic indwelling venous catheters. Lab Anim Sci **34:**494–496.
10. **Ege CA.** 2005. Unpublished data.

11. **Freih M, Saba S.** 2005. Superior vena cava (SVC) thrombosis; diagnosis and follow up by transesophageal echocardiography (TEE). J Am Soc Echocardiogr **18:**280–281.
12. **Fudge M, Coleman RE, Parker SB.** 2002. A minimally invasive percutaneous technique for jugular vein catheterization in pigs. Contemp Top Lab Anim Sci **41(1):**38–42.
13. **Haire WD, Herbst LS.** 2000. Highlights bulletin: consensus conference on the use of alteplase (t-PA) for the management of thrombotic catheter dysfunction. J Vasc Access Devices **Summer:**28–36.
14. **Henderson KK, Mokelke EA, Turk JR, Rector RS, Laughlin MH, Sturek M.** 2003. Maintaining patency and asepsis of vascular access ports in Yucatan miniature swine. Contemp Top Lab Anim Sci **42(6):**28–32.
15. **Jacobson A.** 1998. Continuous infusion and chronic catheter access in laboratory animals. Lab Anim **27:**37–46.
16. **Landi M, Schantz J, Jenkins E, Warnick C, Kissinger J.** 1996. A survey of vascular access port infection in cynomolgus monkeys (*Maccaca fasicularis*). Scand J Lab Anim Sci **23:**441–448.
17. **Lokich JJ, Bothe A, Benotti P, Moore C.** 1985. Complications and management of implanted venous access catheters. J Clin Oncol **3:**710–717.
18. **Moritz MW, Dawe EJ, Holliday JF, Elliott S, Mattei JA, Thomas AL.** 1989. Chronic central vein catheterization for intraoperative and long-term venous access in swine. Lab Anim Sci **39:**153–155.
19. **Mueller BU, Skelton J, Callender DPE, Marchall D, Gress J, Longo D, Norton J, Rubin M, Venzon D, Pizzo PA.** 1992. A prospective randomized trial comparing the infectious and noninfectious complications of an externalized catheter versus a subcutaneously implanted device in cancer patients. J Clin Oncol **10:**1943–1948.
20. **Niiyama M, Yonemichi H, Harada E, Syuto B, Kitagawa H.** 1985. A simple catheterization from the ear vein into the jugular vein for sequential blood sampling from unrestrained pigs. Jpn J Vet Res **33:**1–9.
21. **Palmisano BW, Clifford PS, Coon RL.** 1989. Chronic vascular catheters in growing piglets. J Dev Physiol **12:**363–367.
22. **Pijpers A, Nordhuizen-Stassen EN, Goedegebuure SA, van Dobbenburgh OA**, **Roosendaal M**, **Cornelissen AH**, **Verheijden JH**. 1989. Intravenous catherization of conventional pigs without application of antimicrobial agents. Vet Quarterly **11:**216–221.
23. **Rodriguez H, Kunavongkrit A.** 1983. Chronic venous catheterization for frequent blood sampling in unrestrained pigs. Acta Vet Scand **24:**318–320.
24. **Stephens LC, Haire WD, and Kotulak GD.** 1995. Are clinical signs accurate indicators of the cause of central venous catheter occlusion. JPEN **19:**75–79.
25. **Swindle MM.** 1998. Surgery, anesthesia, and experimental techniques in swine. Ames (IA): Iowa State University Press.
26. **Swindle MM, Nolan T, Jacobson A, Wolf P, Dalton MJ, Smith AC.** 2005. Vascular access port (VAP) usage in large animal species. Contemp Top Lab Anim Sci **44(3):**7–17.
27. **Swindle MM, Smith AC, Goodrich JA.** 1998. Chronic cannulation and fistulization procedures in swine: a review and recommendations. J Invest Surg **11:**7–20.
28. **Swindle MM.** 1998. Surgery, anesthesia, and experimental techniques in swine. Ames (IA): Iowa State University Press.
29. **Takken A, and Williams KC.** 1981. A simplified procedure for long-term catherization of the anterior vena cava in adult pigs. Aust Vet J **57:**17–20.
30. **Van Leengoed LA, de Vrey P, Verheijden JH.** 1987. Intravenous catheterization in pigs: an evaluation of two methods. Zentralbl Veterinarmed A **34:**649–656.
31. **Webb AI, Bliss JM, and Herbst LH.** 1995. Use of vascular access ports in the cat. Lab Anim Sci **45:**110–114.
32. **Weirich WE, Will JA, Crumpton CW.** 1970. A technique for placing chronic indwelling catheters in swine. J Appl Physiol **28:**117–119.
33. **Wojnicki F, Bacher J, Glowa J.** 1994. Use of subcutaneous vascular access ports in rhesus monkeys. Lab Anim Sci **44:**491–494.