Gross and Histopathological Observations of Long-term Catheterized Vessels in Experimental Sheep

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With 10 figures and 2 tables

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Summary

Chronic indwelling central vessel catheters provide vascular access for compartmental infusion or sampling. However, complications with catheter patency during the postoperative and/or experimental period often arise. In order to identify physiological occurrences common with such complications, 10 multicatheterized sheep (61.8 ± 7.8 kg BW), obtained from a previous nutrient flux study were used for gross and histopathological investigation. Catheters had been surgically placed in a hepatic portal vein (PVC), a hepatic vein (HVC), a distal mesenteric vein (MVC) and a mesenteric artery (MAC). In the previous study, catheters (PVC, HVC and MAC) were used to collect blood samples or infuse (MVC) p-aminohippurate. Catheters were maintained for a total of 58 days prior to necropsy. Histopathological findings indicated that catheter failures were associated with the following tissue responses: (i) thromboses with frequent focal vasculitis; (ii) euplastic tissues associated with extensive fibrosis; (iii) granulomas; (iv) neovascularization of the media; (v) calcification processes; and (vi) micro-abscesses. Additional studies are needed that address and incorporate improvement of catheter design and placement to minimize irritation of endothelium, improvement of catheter treatments and therapeutic regimes, and development and use of alternative anti-coagulants. A greater understanding of the mechanisms leading to failure will help researchers improve catheter performance and patency.

Introduction

Central vessel catheterization (CVC) has been utilized in various livestock models to study the effects of diet, natural products, growth and development, nutrient metabolism, and health (Naylor et al., 1985; Krehbiel et al., 1992; Oliver et al., 1995; Nappert et al., 1998; Caston-Bladerrama et al., 2001; Ferrell et al., 2001). Ideally, catheters provide access for infusion of compounds into an experimental animal or patient, and provide sampling access to a specific compartment. However, complications often arise with catheter performance during the postoperative/experimental period. Catheter failures increase the number of animals necessary to complete a study, and subsequently, make studies more costly and difficult. Furthermore, failures during medical treatments lead to decreased efficiency and increased cost of treatment. Catheter-related thrombosis is a major complication affecting CVC and can result in an impaired ability to collect blood or to infuse experimental agents through the catheter (Aitken and Tonelli, 2000; Monreal and Davant, 2001). The incidence of catheter-related thrombosis reportedly can be as high as 66% in humans (Timsit et al., 1998). Use of thrombolytic agents to clear a catheter and gain catheter function is a practice commonly accepted in sheep and pigs (Leuvenik and Dierx, 1997). In addition, filling catheters with heparin solutions to avoid intracatheter clotting and prolong patency is a common practice (De-Neef et al., 2002). However, there are no reports regarding catheters losses and/or complications due to this practice in animals. In humans, the advantage gained in patency of the catheter by repeated use of such treatments is not known (Little and Walsh, 2002). Although advances have been made in the functionality of CVC, problems still remain to be solved. Thrombosis continues its prevalence in most intravenous devices utilized for chemotherapy in humans (Freytes, 2000; Arenas-Marquez et al., 2001; Sterba, 2001). Further, inflammatory processes lead to thrombophlebitis and/or septicemia that produce micro and metastatic abscesses in all intravascular catheterizations of humans and experimental animals. Biofilm-associated infections persist as difficult and critical issues (Khordori and Yasien, 1995; Schmid, 2000) for catheter performance. For example, *Staphylococcus epidermidis* has become the most frequently isolated pathogen in catheter-related infections (28%) of all nosocomial blood stream infections reported from 1986 to 1989 (Banerjee et al., 1991; Schaeberg et al., 1991).

Huntington et al. (1989) discussed problems that can arise from CVC in cattle and potential remedies, but few other reports are encountered in the literature regarding the pathological findings of post-traumatic processes caused by indwelling catheters in experimental animals. Our own experience indicates that surgical complications and catheter patency problems are major impediments to conducting studies using this technique. Therefore, the objective of this research was to define postmortem and histopathological characteristics associated with dysfunctional long-term blood vessel catheters in experimental sheep.

Materials and Methods

Ten multicatheterized sheep (61 ± 7.8 kg BW, c. 14 months old) used for gross and histopathological studies were
obtained following a nutrient flux study (data not shown). Catheters were placed in the hepatic-portal vein (PVC), a hepatic vein (HVC), a distal mesenteric vein (MVC) and a mesenteric artery (MAC). All animal experimentation was approved by the New Mexico State University Institutional Animal Care and Use Committee (nos 97-0001 and 99-0001).

Catheters were made of Polyvinyl Acetate-Tygon® microbore tubing (1.27 mm inner × 2.29 mm outer diameter; formula S-54-HL; Cole Palmer, Vernon Hills, IL, USA). Overall lengths were 130, 130, 150, and 160 cm for PVC, HVC, MAC, and MVC, respectively, whereas lengths of the catheter tips were 9, 6, 38 and 25 cm for PVC, HVC, MAC and MVC respectively. For anchoring and vessel placement proximity, two cuffs (length = 0.5 cm; 2.4 mm inner × 4 mm outer diameter; ethyl vinyl acetate; Cole Palmer) were fixed with cyclohexanone approximately 1 cm apart beginning 6, 9, 38 and 25 cm from the insertion end for PVC, HVC, MAC and MVC respectively. Subsequently, 2% tri-dodecylmethylammonium (TDMAC)-Heparin (Polysciences, Inc., Warrington, PA, USA) was aspirated into the full length of the catheter while insertion ends below anchor cuffs were submersed for 2.5 min. Catheters were flushed with CO₂ and allowed to air dry overnight.

Surgical placement of catheters followed procedures reported by Ferrell et al. (1992). Briefly, surgical procedures involved induction of anaesthesia with intravenous administration of 0.1 mg xylazine and 100 mg ketamine per 50 kg of body weight. Wethers were placed in left lateral recumbency and general anaesthesia was maintained throughout the surgical procedures using a continuous mixture of 1.5–2.5 l oxygen and 1–2.5% halothane. A paracostal incision of approximately 6 cm was made from the first rib and proceeding to the last rib, and approximately 10 cm below the lumbar transverse process. The portal (caudal to liver) and hepatic veins (cranial to the gall bladder) were located and catheterized by passing the catheter through a puncture hole created with a 14 G needle. Likewise, the mesenteric artery and vein were located (mid-jejunum or at the caecae), isolated, and catheterized. All catheters were sutured in place with silk. Following catheterization, intestines were rinsed with sterile saline, blood clots and other detached tissue were removed, and intestines were returned to the body cavity taking care to reposition the omentum in the correct orientation. All catheters were routed through the abdominal muscles, then subcutaneously to the midpoint of the back, and exteriorized. Catheters were swabbed with Nolvasan (Fort Dodge, Overland Park, KS, USA) to minimize the possibility of infection, and stored in a cloth pouch fixed to the wool for protection. The incision was closed, and the sheep were moved to a recovery area.

Banamine (50 mg/ml, Flunixin meglumine; Schering Plough, Union, NJ, USA) was administered intramuscularly (2 ml/day) for 3 days as an anti-inflammatory agent. Three millilitres of penicillin G procaine (300 000 U/ml; Vetco, St Joseph, MO, USA) was administered subcutaneously for 5 days. On day 6, a single intramuscular dose of 4 ml per sheep of a 1000 IU/ml vitamin B complex (American Livestock Supply, Madison, WI, USA) was administered.

After surgery, catheters were maintained for 58 days before necropsy. The MVC was used to introduce a continuous infusion of a 5% p-aminohippuric acid (Sigma Chemical Co., St Louis, MO, USA) solution for measurement of blood flow by downstream dilution (Katz and Bergman, 1969), with remaining catheters used to collect blood samples during the previous nutrient flux study (data not shown). Briefly, the previous study was conducted as follows. Sheep were adapted to maintenance diets for 2 weeks. Subsequently, animals were exposed orally to a locoweed extract containing 1.6 mg swainsonine/kg BW. A 24-h sampling period followed, whereby samples were collected every 3 h from the mesenteric artery and portal and hepatic veins to study nutrient and swainsonine flux through splanchnic tissues. During this period p-aminohippuric acid was infused via the MVC to measure blood flow. Sheep were then fed their respective treatment diets containing locoweed (to deliver swainsonine) during the next 21 days. At the end of the 21 days, a second 24-h sampling period was conducted using the same protocol as mentioned above. Sterile heparinized (100 U/ml; Sigma Chemical Co.) 0.9% saline (Abbot Laboratories, North Chicago, IL, USA) solution was used to maintain catheter patency between sampling periods. During the sampling periods, catheter patency was maintained between collections using heparinized saline as above, but at 10 U/ml.

A total of eight functional tests per catheter were performed at 3- to 6-day intervals. An extra test of catheter function occurred 1 day after each sampling period of the companion study with the last evaluation performed the day of necropsy. The functional evaluation of catheters consisted of attempting to aspirate at least 5 ml of blood using a 5 ml disposable syringe in <1 min. If these criteria were met the catheter received a score of ‘ok’; if it took more than 1 min but less than 3 min then the catheter received a score of ‘slow’; and when it took more than 3 min to obtain some blood or none at all, the catheter received an score of ‘fail’. After each evaluation, the catheter void volume was filled with a 0.9% saline solution containing 100 U/ml heparin.

For postmortem observations, sheep were killed via intracardiac administration of Euthasol (Delmarva Laboratories Inc., Midlothian, VA, USA) at a dose of 1 ml/3.73 kg BW. After killing, the animal was immediately placed in a left recumbent position. The necropsy was performed by cutting the skin and muscle walls following a line approximately 5 cm below the apophysis of the dorsal and lumbar vertebrae beginning at the first rib and proceeding to the last rib, and continuing through the abdominal area to the iliac bone in the hip. Maintaining an approximate 45° angle, a cut downward to the median ventral line was made. The skin and muscle walls were removed to expose all abdominal organs. The right scapula was exposed and separated from the ribs so that the front right limb could be rotated entirely forward to facilitate exposure of the ribs. Ribs were cut close to the vertebrae and sternum to expose all thoracic organs. After initial exploration, the trachea, oesophagus and main vessels were tied together at the level of the neck and separated from the head and neck. A similar procedure was used with the caudal side of the abdominal viscera at the rectum level. The diaphragm muscle was cut around its attachment to the ribs to facilitate removal of all internal organs for examination of organ morphology. To inspect catheter placement, condition, and integrity, blood vessels were first opened at the catheter terminus and the tip was examined. Dissection of the vessels along the length of the catheter was performed. The surrounding tissue was left intact with the vessel in order to observe the pathology with a microscope. Once dissected, the entire catheter and vessel were...
placed into a 10% zinc–formalin solution (pH = 7.0; Anatech, Battle Creek, MI, USA) for preservation. Small longitudinal and transversal pieces of tissue surrounding the catheters were prepared for histopathological analysis.

Histological preparations of tissue samples were accomplished using haematoxylin–eosin staining procedures described by Allen (1992). Briefly, fixed tissues were dehydrated through a series of alcohols of increasing concentrations. Tissues were then placed in xylene for removal of alcohol in preparation for embedding in paraffin. The sections were floated onto glass slides and placed on a warming table to dry and increase adherence. The specimens were treated with xylene and stained with haematoxylin and eosin. Histopathological observations were conducted using a light microscope to permit identification of tissue and cell structures.

Results and Discussion

Catheter failures

Observations of catheter patency by vessel during the nutrient flux study period are shown in Table 1. MAC presented the

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<th>Animal</th>
<th>Catheter position</th>
<th>Days relative to surgery</th>
<th>Necropsy observations</th>
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Table 1. Summary of catheter patency

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<th>Description</th>
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<th>Number of catheters checked</th>
<th>Portal vein catheter failure</th>
<th>Hepatic vein catheter failure</th>
<th>Mesenteric vein catheter failure</th>
<th>Mesenteric artery catheter failure</th>
<th>Total failures</th>
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Table 2. Individual catheter performance relative to surgical implantation and corresponding necropsy findings

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<th>Animal</th>
<th>Catheter position</th>
<th>Days relative to surgery</th>
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highest frequency of failures, with seven of 10 fails by the conclusion of the study; PVC, HVC and MVC failed in 3, 4 and 3 of 10 sheep respectively. There was a tendency for increased number of catheter failures immediately after the 24-h sampling period as evidenced by higher failure rates at 38 and 58 days postoperative (Table 1). Intense sampling would increase the physical forces within the blood vessel resulting in potential endothelial cell damage and smooth muscle fatigue. This could lead to increased blood clot formation locally thus, interfering with catheter function. Interestingly, the number of increased fails following a sampling period was numerically higher on day 38, after heparin was used, than on the day 58 catheter check when it was not (Table 1). This may suggest a role of heparin in these failures. In support of this postulation, Barrett and Lester (1990) revealed that heparin caused more phlebitis than saline in catheterized humans. It has also been reported that injected heparin, by forming immune complexes, induces platelet activation on the surface of endothelial cells, heightening the risk of thrombosis (Aster, 1995). This would be compounded if physical forces of catheter use also induced endothelial cell damage. On the final day (64 and 65 days postoperative) of the trial (day of necropsy), total failures amounted to more than 40% of the catheters (Table 1).

Observations of catheter performance and necropsy results by individual sheep are summarized in Table 2. Of the 320 functional tests performed during the overall experiment, 8.7% of catheters classified as slow and 21.8% were classified as failures. Intensive sampling dates for the nutrient flux study were 36 and 57 days postoperative, during which samples were collected every 3 h for a 24-h collection period. To salvage failing catheters, 0.9% saline containing 20 U/ml heparin was liberally flushed through the catheters. Patency was regained in the MAC of sheep 8 and 123, and HVC of sheep 92 on both sampling dates. In general, these failures decreased the power and efficiency of the nutrient flux study because of reduced treatment replicates.

Necropsy findings

Thrombosis is reportedly one of the major causes for dysfunctional catheters (Tagalakis et al., 2002). During necr-
opsy of the experimental animals, thrombi were identified as being among the most frequent findings related to catheter failure (e.g. Figs 1a and b). Size of the thrombi varied from 0.1 to 1.2 cm. In addition, morphology of the thrombi included: papulae (Fig. 2a), sessile polyps (Fig. 3a), pediculated polyps (Fig. 4a), stranded fibrinosis (Fig. 5a) and sacciform encapsulations (Fig. 6a). Tissues which strongly adhered to these catheters presented with fibrinoid sacciform encapsulations (Fig. 6), fibrinoid strands (Fig. 5) and obtrusive clots into the orifice of the catheter tips (Figs 1a and b).

During gross examination, a loop in the catheter of the mesenteric artery of sheep 0002 (Table 2; Fig. 7) was discovered. Other gross observations included flaccid vessel walls in portal, hepatic and mesenteric vessels of sheep 0020 (Table 2; Fig. 8) that appeared to block the catheter’s orifice during aspiration. Further atypical findings were found with the mesenteric artery and vein catheters of sheep 0123 and 0071 respectively (Table 2). In these animals, the catheter tip diverged from the main targeted mesenteric vessel into a smaller branch. Similarly, the MACs in sheep 0008 and 0092 diverged towards the renal arteries causing the tips to reside very close to the kidneys (Table 2, data not shown). The source of failures for these catheters with such atypical locations was difficult to discern. The cause of failure for the mesenteric artery catheters of sheep 0005 and 0095 was not identifiable. Dysfunctions of other catheters that had been slow or that failed only temporarily were attributed to transient clots.

Histopathology

Injury to the intima of a blood vessel typically leads to inflammation and thrombosis that may be intense or incipient and slow (Tagalakis et al., 2002). Two markers of incipient inflammation have been identified, the C-reactive protein and interleukin 6 (Pradhan et al., 2001). Low-grade inflammation has gained attention in relationship to metabolic disorders since high blood levels of those proteins have been associated with type 2 diabetes mellitus (Barzilay et al., 2001; Christensen, 2001) and atherosclerosis (Fackelman, 1997). These studies indicated that inflammation plays a central role in the thickening of the interior surface of the arterial walls. Inflammation processes elicit a cascade of reactions that include: platelet aggregation, coagulation and the onset of euplastic tissues.
In the catheterized vessels of sheep used in the current experiment, histopathological observations demonstrated different levels of inflammatory processes and tissue reactions that are typical against injuries caused by foreign materials. Mechanical actions like the positive pressure from saline infusion or negative pressure from blood extraction may have irritated and inflamed the intimae and/or the vessel’s tunica even in the absence of bacterial infection. Blood vessel tissues where catheters functioned well and appeared normal, still exhibited mild responses to their presence (Fig. 9). Moreover, in tissues where catheters had failed, more critical histopathological changes were noted. In particular, vessel endothelium exhibited a number of pathologies including thrombi with frequent focal vasculitis (Fig. 10), euplastic tissues associated with extensive fibrosis (Fig. 6), granulomas signalling chronic inflammations (Figs 2 and 4), neo-vascularization of median layers (Fig. 9), calcification processes (Figs 3 and 5), and micro-abscesses (Fig. 3). In most cases, the reactive tissues suggested the presence of physical or mechanical trauma due to the presence of catheters (Figs 6 and 7). Microscopic observations of intravascular thrombi strongly suggest that they might develop from tiny structures (Figs 2 and 3) into highly organized tissues (Figs 4 and 10). These thrombi were actively producing focal vasculitis as well as some micro-abscesses in surrounding tissues. Granulomas, representative of inflammation, were present in almost all altered tissues particularly at the tunica intima and the tunica adventitia of the vessels. Often, granulomas were associated with early stages of hyperplasia of the tunica and with unexpected processes of neo-vascularization and calcification (Figs 3 and 5).

Although this study was not designed for bacterial identification, bacterial presence was suggested by observation of apparent septic thrombi and granulomas in several histopathological findings (Figs 2c, 3c and 5c). Reportedly, major complications with indwelling vascular catheters in humans are caused by *S. epidermidis*, *Staphyloccocus aureus* and *Candida* species (Raad and Bodey, 1992). Similar associated bacteria may have contributed to the observed responses of some tissues in these sheep. In spite of the fact that sheep were treated with antibiotics during and after
surgery and catheters were sterile, it appeared infection was still a problem for some sheep. It has been reported that biofilm formation on indwelling synthetic materials (Khardori and Yasien, 1995) and generation of protective enzyme shields surrounding biofilms (Netting, 2001) are bacterial strategies used to counter antimicrobial agents and host defence mechanisms. Furthermore, bacteria in a biofilm occupy a spectrum of physiological states, from rapidly growing to dormant. This diversity works to the advantage of the bacteria by having only a certain number of microbes in a particular state where the antimicrobial agent may be effective, but not effecting the remainder of the population (Costerton et al., 1999). Thus, traditional antimicrobial therapy is of limited effectiveness in eradicating these infections. Costerton et al. (1999) reported a number of typical biofilm bacterial species, like *Streptococcus* in teeth, *Pseudomonas* in contact lenses, and *S. epidermidis* in central venous catheters and sutures. *Pseudomonas putida* is a
and reduce the number of animals needed for studies requiring central vein catheterization.

Acknowledgements

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References


Conclusions

In conclusion, central vein catheterization in experimental animals remains an informative, but challenging technique. Several aspects of the methodology must be addressed. First catheter design and placement to limit physical irritation of vessel endothelium needs further investigation. Further, improved catheter treatments and antibiotic therapeutic regimes would aid in the reduction of persistent bacterial infections and biofilms associated with intravascular devices. Likewise, development and use of effective anti-coagulants to replace heparin, given its potential to form immune complexes and subsequent platelet activation, for catheter patency maintenance may improve catheter performance. A better understanding of the causes of catheter dysfunction following surgery will allow improved success rates with catheter patency. Such improvements will improve collection of data and reduce the number of animals needed for studies requiring central vein catheterization.

bacteria that is a plant saprophyte that normally lives in the soil and uses a strategy in biofilms by changing its phenotype (Sauer et al., 2002). This bacteria was reported by the Center for Disease Control and Prevention (1986) to be isolated from contaminated closed vials containing heparin sodium without preservatives. Another very common bacteria is Pseudomonas aeruginosa that has been shown to use its antibiotic-resistance genes to produce more defensive proteins in biofilms than in solitary cells (Costerton et al., 1999; Sauer and Camper, 2001).

Fig. 10. (a) Postmortem photograph (bar = 20 mm) of the mesenteric artery of sheep no. 21 opened longitudinally. A polypoid thrombus with a broad attachment to the intimae located at the tip of the catheter is shown in the circle. (b) Photomicrograph (bar with a broad attachment to the intimae located at the tip of the artery of sheep no. 21 opened longitudinally. A polypoid thrombus and its attachment to the vessel’s intimae showed the pathological processes involved: thrombus organization (1), necrosis (2), and focal vasculitis (3).


