

Experimental Models in Interventional Neuroradiology

K. G. TerBrugge,¹ P. Lasjaunias,² and P. Hallacq¹

Various experimental models have been developed to test interventional neuroradiologic techniques. Most have been used to test various devices and embolic materials, and a small number of models have been designed for teaching or training purposes. Experimental models in endovascular techniques have seldom been used to simulate disease processes in order to facilitate their understanding.

Endovascular treatment methods that pertain to the nervous system are natural outgrowths of improved techniques of cerebral and spinal angiography. Serbinenko [1] and subsequently Djindjian et al. [2] and Debrun et al. [3] were among the first to apply interventional techniques to clinical conditions, often with good outcomes. As the techniques spread from Europe to North America and Japan, a wide variety of approaches were developed. The outcomes of such treatments were unpredictable and often associated with significant complications. This fact, coupled with lack of access to reliable embolization products, led to the collaboration of interventional neuroradiologists and manufacturers to develop improvements in techniques and to standardize the various products. This collaboration led to significant research efforts to assess the in vitro characteristics of embolic materials and devices prior to their use in humans. As a result, the quality and reliability of products released for treatment purposes have greatly improved over the past decade.

While most research efforts were directed toward the tools of the trade, a few experimental models were created to facilitate training in interventional techniques. A limited number

of interventional experimental models has been developed to improve understanding of the disease processes that are amenable to endovascular therapy. Following is a review of the literature pertaining to the various models available to the interventional neuroradiologist.

Experimental Models Related to Delivery Devices and Their Effects on Biological Tissues

Subsequent to the description of the clinical application of certain balloon catheters by Serbinenko [1], Kerber [4], and Pevsner and Doppman [5], Debrun et al. [6] described an experimental model and carried out animal experiments (in mongrel dogs) in which they verified the characteristics of a new calibrated-leak balloon device. A latex, nondetachable flow-directed calibrated-leak balloon catheter was used to selectively embolize branches of the renal, external carotid, and vertebral arteries. Embolization was carried out with isobutyl 2-cyanoacrylate (IBCA), and the vertebral artery was identified as the vessel of choice to assess the solidification time of the glue. Partington et al. (Partington CR et al., presented at the annual meeting of the American Society of Neuroradiology, March 1989) used rats to assess the biocompatibility and thrombogenicity of polyethylene catheters. A 1-French polyethylene catheter was well tolerated when left for up to 6 months in the aorta and the iliac arteries of the rat. Histologic examination showed no change in the appearance of the large-sized vessels over a 6-month interval and no evidence of thrombotic, thromboembolic, or inflammatory

Received March 19, 1991; revision requested March 21, 1991; revision received May 28, 1991; accepted May 29, 1991.

This work was supported in part by Mallinckrodt Canada Inc.

¹ Division of Interventional Neuroradiology, The Toronto Hospital, 399 Bathurst St., Toronto, Ontario M5T 2S8, Canada. Address reprint requests to K. G. TerBrugge.

² Division of Diagnostic and Therapeutic Endovascular Neuroradiology, Hopital Bicetre, 78 Rue de General Leclerc, 94275 Le Kremlin, Bicetre Cedex, France.

complications. In small to medium-sized vessels, myointimal hypertrophy was noted, apparently not associated with significant decrease in the diameter of the vessel lumen. The histopathologic effect of balloon angioplasty on canine cerebral vessels was described by Pile-Spellman et al. (Pile-Spellman J et al., ASNR, May 1987). Cerebral arteries were isolated and mounted in a chamber with control of intra- and extraluminal fluid pressures, and angioplasty was carried out with latex balloons with inflation diameters of 8.5×4.5 mm and 5×2.5 mm for periods of 20–40 sec. Preconstriction of vessels was achieved after infusion with a 20-mol/l solution of potassium chloride. Mild histologic damage to the endothelium was noted after angioplasty returned precontracted vessels to their original size, while disruption of vessel wall layers occurred when vessels underwent angioplasty to more than 150% of their normal size.

Various types of vascular occlusive agents have been tested with experimental and animal models. To assess the clinical problem of balloon deflation, Hawkins and Szaz [7] described an experimental model that evaluated the behavior of latex balloons filled with different metrizamide solutions. When balloons were immersed in a plasma solution, tritiated water passed bidirectionally through the wall at a rate unrelated to the concentration or the volume of contrast medium in the balloon. There was no exchange of sodium ions across the wall, and the osmolality of the metrizamide did not change over a period of up to 6 weeks. The authors concluded that deflation of rubber latex balloons was not due to osmosis, but rather to damage of the balloon during manipulation, the use of time-expired balloons, or the escape of contrast medium through an insecurely tied neck. Goto et al. [8] described the inflation characteristics of a new low-viscosity hydrophilic polymerizing substance to be used in detachable silicone balloon systems that would facilitate permanent inflation of detachable balloons and avoid long-term reliance on the integrity of balloon shells or valve mechanisms. This substance combines 2-hydroxyethyl methacrylate (HEMA) with a cross-linking agent (polyethylene glycol dimethacrylate) and a water-soluble curing system (hydrogen peroxide and ferrous ammonium sulfate) and polymerizes in 40–60 min at body temperature. Detachable silicone balloons were filled with a mixture of activated HEMA and metrizamide and kept in normal saline for up to 30 days while plain radiographs were obtained. The balloons remained radiopaque as long as the balloon shell and valve mechanisms were competent. The histopathologic effect of detachable latex balloons was described by Quisling et al. [9], who used a high-flow aortocaval fistula model in the rat. Closure of the fistula site required the balloon to remain inflated for at least 7 days. Thrombus formation and acute inflammation were noted in the acute phase, while diminishing inflammation and progressive fibrosis of the fistula sites occurred in the chronic phase.

Experimental Models for Evaluating Thrombotic and Embolic Materials

Deposition of platinum *coils* through a microcatheter system was assessed by Graves et al. (Graves VB et al., ASNR,

March 1989) by using a dog model in which aneurysms were surgically created in the common carotid artery with a vein graft. Platinum coils with simple curves, complex curves, and complex curves with silk fibers were then placed through a microcatheter into the aneurysms with varying degrees of ease, stability, and thrombogenicity.

In order to explain certain rare complications associated with particle embolization in the external carotid artery territory, Jack et al. [10] examined particles of polyvinyl alcohol sponge (PVA, Ivalon) prepared with the blender technique. Light and scanning electron microscopy were used to evaluate the characteristics of these particles. It was demonstrated that, when PVA was prepared with the blender technique, smaller particles (2–50 μm) outnumbered larger particles (over 50 μm) by a ratio of 15:1, possibly explaining why particle embolization may lead to deep penetration of the vascular tree and ischemic cranial nerve palsies. Histopathologic analysis of PVA deposition in the rat cerebral cortex was reported by Quisling et al. [11]. They showed that PVA elicited no significant inflammatory response in embolized vessels or in their surrounding tissues. The possible synergistic effect of PVA and Gelfoam was tested in mongrel dogs by Horton et al. [12]. The feeding artery to the upper pole of one kidney was embolized with Gelfoam powder, and the artery to the lower pole was embolized with a mixture of PVA and Gelfoam powder. The animals were sacrificed 6–8 weeks after embolization, and microscopic examination of the kidneys revealed more complete obliteration of the renal cortex when a mixture of PVA and Gelfoam powder, rather than powder alone, was used for embolotherapy. The feasibility of *dextran microspheres* as an embolic material was described by Dion et al. [13] with the use of mongrel dogs. The renal arteries were selectively catheterized, and dextran microspheres of different sizes were injected. Follow-up angiograms were obtained for up to 6 weeks, and histologic examination revealed a doubling in the size of the dextran particles on reaching their destination and permanent vessel occlusion and infarction, without perivascular hemorrhage, in the territory embolized. Strother et al. [14] described an animal model in which a new embolic agent, *glutaraldehyde cross-linked collagen* (GAX), was tested. GAX was injected into the internal iliac artery of the mongrel dogs, and the material persisted within the embolized tissue for as long as 2 months without producing a cellular response, as evidenced by microscopic examination. Lee et al. [15] chose the pig rete as the site to evaluate three embolic materials, GAX, Angiostat, and microfibrillar collagen hemostat (MCH) in 33% ethanol. Since no other animal model exists that resembles an arteriovenous malformation, the pig rete was chosen as it somewhat simulates such a malformation. Fed by and draining into the internal carotid artery, the network consists of vessels measuring between 70 and 275 μm , thereby resembling the nidus of an arteriovenous malformation. Slow flow is noted into the draining arteries, which in turn reconstitute the distal internal carotid artery. The three embolic agents were injected through a 4- or a 5-French catheter placed in the internal carotid artery. GAX passed readily through the rete, making it less than an ideal embolic agent, while Tisseel (Immuno, Vienna, Austria), a fibrin sealant, was difficult to inject through the small-sized catheters.

MCH with ethanol was considered to be an effective embolic agent, although long-term occlusive effects (longer than 6 weeks) were not tested. Following a surgically created side-to-side anastomosis, the carotid artery of the mongrel dog was catheterized by Mawad et al. (Mawad ME et al., ASNR, March 1989) to assess injection of embolic materials. This experiment showed that human fibrinogen and bovine thrombin injected separately through a double-lumen 2.4-French catheter will form a solid adhesive mixture that can be used as an embolic agent in a high-flow vascular malformation model.

The pathologic effect of ethanol as an embolic agent following selective embolization of renal arteries in dogs was evaluated by Dion et al. (Dion J et al., ASNR, June 1984). This agent caused full-thickness necrosis of the walls of vessels at the site of injection and distally when 98% and 75% solutions of alcohol were used. Only intimal and medial necrosis were noted when a 50% solution of alcohol was injected.

The histologic response to transarterial bucrylate deposition was assessed in dogs by Kish et al. [16] and Cromwell et al. [17]. Kish et al. injected bucrylate directly into the surgically exposed normal cortical arteries of mongrel dogs, while Cromwell et al. injected a 50% mixture of Pantopaque and bucrylate into the renal arteries of the mongrel dog. Both experiments revealed endothelial damage on electron microscopy in the acute phase, with chronic inflammatory response to the foreign body on 5-month follow-up. The pig rete was used by Brothers et al. [18] to evaluate the histopathologic response difference between *n*-butyl 2-cyanoacrylate (NBCA) and IBCA. Acute vasculitis becoming chronic and granulomatous after 1 month was observed with both NBCA and IBCA. Both glues showed frequent foci of extravascular extrusion through the embolized rete and the recanalization of previously occluded embolized vessels.

Centeno et al. [19], Philips et al. [20], and Klimek et al. [21] used a rabbit model for assessment of clot lysis after acute occlusion of the carotid artery circulation. Klimek et al. performed selective internal carotid catheterization via the femoral approach by using 2.2-French microcatheters, while Centeno et al. used 4-French catheters positioned into the common carotid arteries of the rabbits. Autologous blood clots were prepared by adding thrombin to a venous blood sample; after 1 hr, 0.75 ml of that clot was deposited into the distal common carotid artery [19]. After another hour, streptokinase infusion through the catheter into the common carotid artery was started with a dose of 3000–5000 U/min for a total of 1–2 hr. Serial angiograms were carried out for up to 6 hr, and after 24 hr the animals were sacrificed and the brains examined microscopically [19]. Philips et al. placed a 3-French catheter via the femoral approach into the proximal internal carotid artery, and 0.035 ml of autologous blood clot was injected and noted to lodge in the distal internal carotid artery system. An IV bolus of tissue plasminogen activator, representing 20% of the total dose (1 mg/kg body weight of the rabbit), was given 15 min after embolization, while the remainder was infused intravenously over a 30-min interval. Serial angiograms were obtained for up to 3 hr, after which time the animals were sacrificed. While partial or complete thrombus dissolution was noted in almost 90% of the animals

evaluated by Philips et al. [20], the results of streptokinase infusion for the purpose of clot lysis have so far been ambiguous, not indicating a definite benefit vs no treatment [19].

Experimental Models That Facilitate Testing of Devices

The production of experimental aneurysms at a surgically created arterial bifurcation was described by Forrest et al. [22]. In this model the carotid arteries of a rabbit were joined and a vein pouch was used at the junction to create the aneurysm. Geremia et al. [23] described an animal model in which multiple vein pouches were used to create multiple aneurysms along the common carotid artery in mongrel dogs for the purpose of balloon occlusion via the femoral artery approach. These are variations to the technique originally described by German and Black [24] in 1954. Cervical carotid aneurysms were surgically created by using an end-to-side vein pouch technique in the rabbit by O'Reilly et al. [25] for the purpose of intravascular laser coagulation of these aneurysms.

Experimental Models Developed for Teaching and Training

A teaching simulator for therapeutic embolization was described by Kerber and Flaherty [26] in which a submersible pump drives fluid through a circuit of tubing into which a catheter can be placed for the purpose of deposition of embolic material. This model was modified by Bartynski et al. [27] to contain a wire mesh sieve in order to more closely resemble a human arteriovenous malformation and to allow tissue adhesive to be used as an embolic agent. Recently, Jungreis and Kerber [28] proposed a solution that could simulate whole blood in a mechanical model of the cerebral circulation. This transparent solution has nonnewtonian viscosity characteristics approximating those of whole blood.

A primate model for training in the various aspects of interventional techniques was described by TerBrugge et al. [29]. This model allows the trainee to progress through the various stages of embolization techniques from superselective angiography to glue deposition. Geremia et al. [23] described an animal training model in which balloon detachment into experimentally created aneurysms could be practiced in the mongrel dogs. Superselective catheterization and embolization of arterioarterial malformations in swine was described by Lylyk et al. (Lylyk P et al., ASNR, May 1987). This animal model is meant to resemble a human arteriovenous malformation and allows training in the transcatheter deposition of various liquid and particulate embolic materials.

Experimental Models That Facilitate Understanding of Disease

Roach et al. [30] and Stehbens [31] described various glass models of arterial bifurcations that have been created to study the flow patterns and hemodynamic characteristics that might influence the development of berry aneurysms. Kerber and Heilman [32] used a similar glass model to assess whether better understanding of the flow characteristics might

predict the feasibility of deposition of adhesive material within an aneurysm. The role of hemodynamic stress on experimentally created saccular aneurysms in rabbits was demonstrated by Stehbens [33]. Following side-to-side anastomosis of the common carotid artery and the adjoining external jugular vein, ligation of the vein was performed proximal and distal to the anastomosis, creating a saccular aneurysm. The animals were put on a stock rabbit-pellet diet. All aneurysms older than 2 weeks exhibited phlebosclerosis, which can be regarded as an early stage of arteriosclerosis, indicating hemodynamic stress in the vein grafts.

A primate model in which a fistula was created between the circle of Willis and the jugular vein was used by Scott et al. [34] to assess autoregulation in response to changes in blood pressure and carbon dioxide. Morgan et al. [35] created carotid-jugular fistulas in the rat to assess the phenomenon of a noninfarctional hypoperfusion caused by an arteriovenous malformation. They were able to force the intracranial arterial circulation to communicate retrogradely with the intracranial venous system via the carotid jugular fistula following ligation of the jugular system distally at the lower cervical level.

Intravascular microcatheter pressure monitoring has been carried out both in the experimental and clinical settings in an attempt to better understand the physiology of vascular malformations (Duckwiler GR et al. and Jungreis CA et al., ASNR, March 1989).

Summary

Models in interventional neuroradiology should be used to answer precise questions raised by interventional neuroradiologists with a thorough knowledge of the available literature. A model will not facilitate the decision-making process at the time of embolization procedures, and it cannot replace experience or intellectual maturation. Thorough knowledge of the comparative anatomy and biology is mandatory before embarking on an animal experiment. Experimental or animal models should be designed to teach dexterity and simulate the clinical decision-making process. Treatment decisions are based on a thorough knowledge of the clinical situation and understanding of the natural history of the disease. As the speciality of interventional neuroradiology has become more clearly established [36], a wealth of information has been made available through publications in the international scientific literature and through standard textbooks in the field [37]. Experimental models in interventional neuroradiology will continue to represent an essential component of further growth in the specialty. The new models will probably not only be directed toward the development of embolic materials and devices but also be geared toward improved understanding of the many disease processes that the specialty is asked to treat.

ACKNOWLEDGMENT

We thank Sharon Whynot-Hay for clerical assistance.

REFERENCES

- Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels. *J Neurosurg* 1974; 41:125-145
- Djindjian R, Cophignon J, Rey A, Theron J, Merland JJ, Horidart R. Superselective arteriographic embolization of the femoral route in neuro-radiology. *Neuroradiology* 1973; 6:143-152
- Debrun G, Lacour P, Caion JP, Hurth M, Conroy J, Keravel Y. Detachable balloon and calibrated-leak balloon techniques in the treatment of cerebral vascular lesions. *J Neurosurg* 1978; 49:635-649
- Kerber C. Use of balloon catheters in the treatment of cranial arterial abnormalities. *Stroke* 1980; 11:210-216
- Pevsner PH, Doppman JL. Therapeutic embolization with a microballoon catheter. *AJNR* 1980; 1:171-181
- Debrun GM, Vinuela FV, Fox AJ, Kan S. Two different calibrated leak balloons: experimental work and application in humans. *AJNR* 1982; 3:407-414
- Hawkins TD, Szaz KF. The permeability of detachable latex rubber balloons: an in vitro study. *Invest Radiol* 1987; 22:969-972
- Goto K, Halbach VV, Hardin CW, Higashida RT, Hieshima GB. Permanent inflation of detachable balloons with a low-viscosity, hydrophilic polymerizing system. *Radiology* 1988; 169:787-790
- Quisling RG, Mickle JP, Ballinger W Jr. Latex vascular occlusion balloons: histopathologic evaluation in a high-flow aortocaval fistula model. *AJNR* 1985; 6:583-587
- Jack CR Jr, Forbes G, Dewanjee MK, Brown ML, Earnest F IV. Polyvinyl alcohol sponge for embolotherapy: particle size and morphology. *AJNR* 1985; 6:595-597
- Quisling RG, Mickle JP, Ballinger WB, Carver CC, Kaplan B. Histopathologic analysis of intra-arterial polyvinyl alcohol microemboli in rat cerebral cortex. *AJNR* 1984; 5:101-104
- Horton JA, Marano GD, Kerber CW, Jenkins JJ, Davis S. Polyvinyl alcohol foam-Gelfoam for therapeutic embolization: a synergistic mixture. *AJNR* 1983; 4:143-147
- Dion JE, Rankin RN, Vinuela F, Fox AJ, Wallace AC, Mervart M. Dextran microsphere embolization: experimental and clinical experience with radiologic-pathologic correlation. *Radiology* 1986; 160:717-721
- Strother CM, Laravuso R, Rappe A, Su SL, Northern K. Glutaraldehyde cross-linked collagen (GAX): a new material for therapeutic embolization. *AJNR* 1987; 8:509-515
- Lee DH, Wriedt CH, Kaufmann JCE, Pelz DM, Fox AJ, Vinuela F. Evaluation of three embolic agents in pig rete. *AJNR* 1989; 10:773-776
- Kish KK, Rapp SM, Wilner HI, Wolfe D, Thomas LM, Barr J. Histopathologic effects of transarterial bucrylate occlusion of intracerebral arteries in mongrel dogs. *AJNR* 1983; 4:385-387
- Cromwell LD, Freeny PC, Kerber CW, Kunz LL, Harris AB, Shaw CM. Histologic analysis of tissue response to bucrylate-Pantopaque mixture. *AJR* 1986; 147:627-631
- Brothers MF, Kaufmann JCE, Fox AJ, Deveikis JP. *n*-Butyl 2-cyanoacrylate—substitute for IBCA in interventional neuroradiology: histopathologic and polymerization time studies. *AJNR* 1989; 10:777-786
- Centeno RS, Hackney DB, Rothrock JR. Streptokinase clot lysis in acute occlusions of the cranial circulation: study in rabbits. *AJNR* 1985; 6:589-594
- Philips DA, Davis MA, Fisher M. Selective embolization and clot dissolution with tPA in the internal carotid artery circulation of the rabbit. *AJNR* 1988; 9:899-902
- Klimek E, Fournier D, Montanera W, Glen J, Sharma R, Terbrugge K. Selective transfemoral cerebral angiography of the rabbit. *J Neuroradiol* 1990; 17:20-25
- Forrest MD, O'Reilly GV. Production of experimental aneurysms at a surgically created arterial bifurcation. *AJNR* 1989; 10:400-402
- Geremia GK, Hoile RD, Haklin MF, Charletta DA. Balloon embolization of experimentally created aneurysms: an animal training model. *AJNR* 1990; 11:659-662
- German WJ, Black SP. Experimental production of carotid aneurysms. *N Engl J Med* 1954; 250:104-106
- O'Reilly GV, Forrest MD, Clarke RH, Schoene WC. Intravascular laser coagulation of experimental aneurysms. *Acta Radiol* 1986; 369:586-590
- Kerber CW, Flaherty LW. A teaching research simulator for therapeutic embolization. *AJNR* 1980; 1:167-169
- Bartynski WS, O'Reilly GB, Forrest MD. High-flow-rate arteriovenous

- malformation model for simulated therapeutic embolization. *Radiology* **1988**; 167:419-421
28. Jungreis CA, Kerber CW. A solution that simulates whole blood in a model of the cerebral circulation. *AJNR* **1991**; 12:329-330
 29. TerBrugge K, Lasjaunias P, Chiu MC, Marotta TR, Tatton W, Glen J. The rhesus monkey as an animal model for training in neuroradiology. *AJNR* **1989**; 10:1203-1208
 30. Roach MR, Scott S, Ferguson GG. The hemodynamic importance of the geometry of bifurcations in the circle of Willis (glass model studies). *Stroke* **1972**; 3:255-267
 31. Stehbens WE. Flow in glass models of arterial bifurcations and berry aneurysms at low Reynolds numbers. *Q J Exp Physiol* **1975**; 60:181-192
 32. Kerber CW, Heilman CB. Flow in experimental berry aneurysms: method and model. *AJNR* **1983**; 4:374-377
 33. Stehbens WE. Chronic changes in experimental saccular and fusiform aneurysms in rabbits. *Arch Pathol Lab Med* **1981**; 105:603-607
 34. Scott BB, McGillicuddy JE, Seeger JF, Kindt GW, Giannotta SL. Vascular dynamics of an experimental cerebral arteriovenous shunt in the primate. *Surg Neurol* **1978**; 10:34-38
 35. Morgan MK, Anderson RE, Sundt TM Jr. A model of the pathophysiology of cerebral arteriovenous malformations by a carotid-jugular fistula in the rat. *Brain Res* **1989**; 496:241-250
 36. Lasjaunias P. Surgical neuroangiography: search for a specialty. *AJNR* **1987**; 8:581-582
 37. Lasjaunias P, Berenstein A. *Surgical neuroangiography*, vols. 1-3. Berlin: Springer-Verlag, **1990**

RELATED ARTICLES

1. Black SPW. Experimental saccular aneurysms by an arteriovenous fistula method. *Missouri Med* **1963**; 60:340-343
2. Hashimoto N, Handa H, Hazama F. Experimentally induced cerebral aneurysms in rats. *Surg Neurol* **1978**; 10:3-8
3. Hashimoto N, Kim C, Kikuchi H, Kojima M, Kang Y, Hazama F. Experimental induction of cerebral aneurysms in monkeys. *J Neurosurg* **1987**; 67:903-905
4. Hecht ST, Horton JA, Kerber CW. Hemodynamics of the central nervous system arteriovenous malformation nidus during particulate embolization. *Neuroradiology* **1991**; 33:62-64
5. Kim C, Kikuchi H, Hashimoto N, Hazama F. Histopathological study of induced cerebral aneurysms in primates. *Surg Neurol* **1989**; 32:45-50
6. Kim C, Kikuchi H, Hashimoto N, Hazama F. Angiographic study of induced cerebral aneurysms in primates. *Neurosurgery* **1990**; 27:715-720
7. McCune WS, Samadi A, Blades B. Experimental aneurysms. *Ann Surg* **1953**; 138:2:216-218
8. Nishikawa M, Yonekawa Y, Matsuda I. Experimental aneurysms. *Surg Neurol* **1976**; 5:15-18
9. Stehbens WE. Chronic changes in the walls of experimentally produced aneurysms in sheep. *Surg Gynecol Obstet* **1979**; 149:43-48
10. Zanetti PH, Sherman FE. Experimental evaluation of a tissue adhesive as an agent for the treatment of aneurysms and arteriovenous anomalies. *J Neurosurg* **1972**; 36:72-79