Thrombogenicity of hydrophilic and nonhydrophilic microcatheters and guiding catheters.


http://www.ajnr.org/content/18/7/1243
Thrombogenicity of Hydrophilic and Nonhydrophilic Microcatheters and Guiding Catheters

David F. Kallmes, J. Kevin McGraw, Avery J. Evans, John M. Mathis, Robert W. Hergenrother, Mary E. Jensen, Harry J. Cloft, Maria Beatriz Lopes, and Jacques E. Dion

PURPOSE: To assess in a swine model the in vivo thrombogenicity of various microcatheters and guiding catheters as a function of catheter material, catheter coating, and duration of implantation.

METHODS: Microcatheters (Tracker 18 and Fastracker 18, Target Therapeutics, Fremont, Calif; Magic 1.8, Balt, Montmorency, France; and Transit, Cordis Endovascular Systems, Miami Lakes, Fla) were placed through 6F guiding catheters (Fasguide, Target Therapeutics, and Envoy, Cordis Endovascular Systems) into the common carotid arteries of swine for 30 minutes (short term), 90 minutes (medium term), and 35 days (long term). Guiding catheters were implanted for 5 hours. At the end of the implantation periods the catheters were retracted and fixed for scanning electron microscopy.

RESULTS: The surface of the Fastracker microcatheter was devoid of debris after both short- and medium-term implantation. The Tracker microcatheter had minimal accumulation of cellular elements whereas the Transit microcatheter showed moderate accumulation of nondeformed red blood cells. Neither the Tracker nor the Transit microcatheter showed evidence of increasing debris accumulation after medium-term implantation as compared with short-term implantation. The Magic microcatheter was coated with gross thrombus after both short- and medium-term implantation. The Fasguide guiding catheter was nearly devoid of debris, while the Envoy guiding catheter had moderate thrombus formation. Long-term implantation of the Fastracker microcatheter was well tolerated whereas that of the Transit catheter resulted in vessel occlusion.

CONCLUSIONS: Hydrophilic microcatheters and guiding catheters are less thrombogenic than their nonhydrophilic counterparts, but not all hydrophilic coatings are equally hypothrombogenic. Degree of thrombogenicity depends on catheter material rather than surface morphology. Medium-term implantation did not yield increasing thrombus formation relative to short-term implantation.

Index terms: Catheters and catheterization, instruments; Animal studies


Thromboembolic events are the most feared complication of cerebral angiography. The inherent thrombogenicity of angiographic catheters and guidewires has been the focus of numerous animal and clinical studies. Early reports detailed the relative thrombogenicity of various catheters, implicating surface irregularities (1–3), construction material (4–6), and duration of procedure (7) as risk factors for thrombus formation. Other reports showed that heparin bound to catheter surfaces yielded reduced thrombogenicity (8–12).

Hydrophilic coatings are a relatively recent advance in catheter and guidewire technology. Hydrophilic catheters and guidewires may facilitate difficult catheterizations, especially for neuroendovascular therapeutic procedures in which extremely distal access is required. Because the duration of many of these interventional procedures is relatively long, nonthrombogenic catheter materials are critical.
The thrombogenicity of hydrophilic surfaces has been previously investigated, with variable results. Hydrophilic coatings have been shown to diminish the thrombogenicity of polyurethane catheters (13). Furthermore, a recent in vitro study found that hydrophilic surfaces bound less fibrinogen and fewer platelets than did either nonhydrophilic or heparin-coated catheters (14). However, Leach et al (15) concluded that hydrophilic catheters were at least as thrombogenic as nonhydrophilic catheters but that adding heparin coating to the hydrophilic catheters yielded a highly nonthrombogenic surface.

We report the results of an in vivo experiment using a swine model in which scanning electron microscopy (SEM) was used to compare the thrombogenicity of various microcatheters after short-, medium-, and long-term implantation. The samples evaluated included both hydrophilic (Fastracker 18, Target Therapeutics, Fremont, Calif, and Transit, Cordis Endovascular Systems, Miami Lakes, Fla) and nonhydrophilic (Tracker 18, Target Therapeutics, and Magic 1.8, Balt, Montmorency, France) microcatheters. The Tracker and Fastracker catheters are constructed of polyethylene and polyetherurethane, respectively; the Tracker catheter has a nonhydrophilic silicone coating while the Fastracker catheter is coated with hydrophilic Hydrolene (Target Therapeutics), which consists of a combination of polyvinylpyrrolidone and polyacrylamide. The distal portion of the Transit catheter is constructed of polyetherurethane and coated with a polyvinylpyrrolidone-based hydrophilic coating. The Magic catheter is constructed of uncoated, plasticized, radiopaque polyvinylchlo- ride. The guiding catheter materials included polyethylene coated with Hydrolene (Fasguide, Target Therapeutics) and polyetherurethane coated with silicone (Envoy, Cordis Endovascular Systems).

Materials and Methods

Short- and Medium-Term Implantation

A 30-kg swine was anesthetized and maintained under general anesthesia with halothane. Eight French arterial sheaths were placed bilaterally in the common femoral arteries. The sheaths were connected to a continuous flush of heparinized saline (4000 U/1000 mL, 10 drops/min). An intravenous bolus of 3000 U of heparin was administered. Systemic anticoagulation was maintained throughout the procedure using 1000-U intravenous boluses of heparin each hour. Through the right-sided sheath, a custom-steamed 6F Fasguide guiding catheter was placed in the right common carotid artery (CCA). The Fasguide was connected via a rotating hemostatic valve to a continuous flush of heparinized saline (4000 U/1000 mL, 10 drops/min). Via coaxial technique, a Fastracker 18 microcatheter was placed through the Fasguide catheter into the right CCA. The tip of the microcatheter protruded approximately 10 cm beyond the tip of the guiding catheter. The lumen of the microcatheter was continuously flushed with heparinized saline (4000 U/1000 mL). After 30 minutes, the rotating hemostatic valve was removed from the guiding catheter and, while allowing free back-bleeding, the microcatheter was rapidly retracted. Its tip was placed immediately in SEM fixative solution (4.0% paraformaldehyde with 2.5% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4). Via the left-sided arterial sheath, a custom-steamed 6F Envoy guiding catheter was placed in the left CCA. A similar technique as that described above was used to place a Transit microcatheter into the left CCA for 30 minutes before harvesting its catheter tip. Subsequently, similar procedures were followed in placing a Tracker 18 microcatheter and a Magic 1.8 microcatheter for 30 minutes into the right and left CCAs, respectively. All catheters were examined for evidence of gross thrombus formation at the time of immersion into the fixative solution. These four catheter samples constituted the short-term implantation sample cohort.

Subsequently, again using the coaxial technique, Fastracker 18 and Tracker 18 microcatheters were placed serially through the respective guiding catheters in the right CCA for 90 minutes and then harvested as described above. Transit and Magic 1.8 microcatheters were placed serially in the left CCA for 90 minutes and also harvested as described above. These four catheter samples, constituting the medium-term sample cohort, were also examined for evidence of gross thrombus formation at the time of immersion in the fixative solution.

Upon retrieving the final medium-term microcatheter implantation sample, both guiding catheters were retracted until their tips were within the lumens of the 8F sheaths. At this point, the guiding catheter–sheath systems were retracted together and removed from the animal, so that debris would not be inadvertently removed by retracting the guiding catheters through the diaphragms of the sheaths. Once removed from the animal, the guiding catheters were pushed out of the ends of the sheaths and fixed for SEM. Total implantation time of the guiding catheters was 5 hours.

In addition to the samples described above, clean samples of each microcatheter and guiding catheter type were examined by SEM. Both nonsteamed and steamed samples of the guiding catheters were included to assess possible surface changes induced by steam-shaping the catheter tip.

Sample Preparation.—The samples were fixed overnight in the SEM fixative solution. After fixation, a 1.0-cm segment was removed from the distal end of each catheter and placed in phosphate buffer at 24°C. Catheter seg-
ments were washed in phosphate buffer, postfixed for 1 hour in 2.0% osmium tetroxide in distilled water, washed in distilled water, and dehydrated in ethanol. They were then dried in a Tousimis Samdri-780 critical-point dryer, using liquid carbon dioxide as the transitional fluid. Following critical-point drying, the segments were affixed to specimen mounts with double-faced cello tape, coated with approximately 20 nm of a gold/palladium alloy in a Technics Hummer V sputter coater, and examined in a JEOL 6400 scanning electron microscope.

**Long-Term Implantation Samples**

**Day 1.**—At the termination of the short- and medium-term experiments, long-term implantation samples of each of the four microcatheters were prepared on the bench. The distal 15 cm of each type of microcatheter was used. To diminish the risk of distal embolization of the implanted catheter segments, stiffeners were inserted into the samples. These stiffeners included segments of coil pushers for the Fastracker, Tracker, and Transit microcatheters and a mandril for the Magic microcatheter. After placing the stiffeners in the lumens of the microcatheters, the ends of the catheters were heat-sealed with a flame. A 6F nontapered guiding catheter was placed over a wire into the right CCA. The wire was then removed. The Fastracker long-term implantation sample was back-loaded into the guiding catheter and pushed out into the CCA. A similar technique was used in placing the Transit, Tracker, and Magic microcatheter long-term implantation samples into the left CCA and the right and left subclavian arteries, respectively. The heparinization was reversed with protamine. The arterial sheaths were removed and hemostasis was obtained without difficulty.

**Day 35.**—The same swine was reanesthetized. Fluoroscopic examination showed the Fastracker and Transit microcatheter segments unchanged in position in the right and left CCA, respectively. The Tracker microcatheter segment had embolized from the right subclavian artery retrograde to the right femoral artery. The Magic microcatheter had embolized to a distal subclavian muscular branch.

Using a 5F diagnostic catheter from a left common femoral artery approach, we performed selective catheterization and digital subtraction angiography (DSA) of the right CCA, left CCA, left subclavian artery, and right iliac artery. Subsequently, the swine was anticoagulated with 10 000 U of heparin bolus and then killed using standard...
euthanasia solution. The implanted microcatheter samples as well as the adjacent vessels were harvested and placed in formalin for histologic analysis.

Results

Short- and Medium-Term Implantation Samples

SEM reproductions of the short- and medium-term implantation catheter samples are shown in Figures 1 through 4.

Tracker Microcatheter (Fig 1).—SEM of the clean catheter sample revealed the presence of shallow grooves (Fig 1A). Gross examination of the short- and medium-term implantation samples revealed no evidence of macroscopic thrombus formation. SEM revealed that the short-term implantation sample contained scattered cellular elements, including red blood cells (RBCs), white blood cells, and platelets (Fig 1B and C). There was little, if any, fibrillary component present. There was no increase in debris noted on the medium-term sample relative to the short-term sample (Fig 1D).

Fastracker Microcatheter (Fig 2).—SEM of the clean catheter sample revealed multiple, regularly spaced, small, round elevations (Fig 2A). Gross examination of the short- and medium-term implantation samples revealed no evidence of macroscopic thrombus formation. The surfaces of the short- and medium-term implantation samples of the Fastracker microcatheter were devoid of debris (Fig 2B–D).

Transit Microcatheter (Fig 3).—SEM of the clean catheter sample showed mild, diffuse irregularities (Fig 3A). Gross examination of the short- and medium-term implantation samples revealed no evidence of macroscopic thrombus formation. The surface of the Transit microcatheter samples contained nondeformed RBCs after both short- and medium-term implantation (Fig 3B–D). There was no increase in density of RBC accumulation after medium-term implantation relative to short-term implantation. There

Fig 2. Fastracker microcatheter.
A, High-magnification view of a clean Fastracker microcatheter shows multiple shallow elevations on the surface of the catheter.

Low- (B) and high- (C) magnification views of the short-term implantation sample shows minimal, if any, particulate debris deposition. A single crenated RBC (curved arrow) was found along with possible small platelet aggregates (open arrow). However, the remainder of the surface of this catheter was essentially clean.

D, High-magnification view of medium-term implantation sample appears similar to the clean catheter shown in A, with multiple shallow elevations.

Note 10- and 100-μm bars on the high- and low-magnification images, respectively.
Fig 3. Transit microcatheter.
A. High-magnification view of clean catheter sample shows multiple shallow irregularities.
Low- (B) and high- (C) magnification views of short-term implantation sample show bandlike deposition of particulate debris. The bandlike deposition may be related to mild undulation of the catheter surface related to metal braids. Multiple crenated RBCs are present (arrows).
D. High-magnification view of the medium-term implantation sample shows multiple noncrenated RBCs of approximately equal deposition density to that noted on the short-term implantation sample.
Note 10- and 100-μm bars on the high- and low-magnification images, respectively.

Fig 4. Magic microcatheter.
A. High-magnification view of clean catheter sample shows an essentially smooth surface.
Low- (B) and high- (C) magnification views of the short-term implantation sample show gross thrombus adherent to microcatheter surface. Large platelet aggregates (arrow) as well as areas of fibrin deposition (arrowheads) are noted.
Note 10-μm and 1-mm bars on the high- and low-magnification images, respectively.
was no fibrillary component noted on the catheter surfaces.

**Magic Microcatheter (Fig 4)**.—SEM of the clean surface of this catheter showed a smooth surface (Fig 4A). Visual inspection at the time of sample harvesting revealed gross thrombus formation on both the short- and medium-term implantation samples. The gross thrombus is shown in Fig 4B and C.

**Fasguide Guiding Catheter (Fig 5)**.—SEM of both the nonsteamed and steamed samples showed a smooth surface (Fig 5A). The surface of the implanted Fasguide had minimal, scattered RBCs without other debris (Fig 5B and C).

**Envoy Guiding Catheter (Fig 6)**.—SEM of the nonsteamed and steamed samples revealed mild irregularities (Fig 6A). The surface of the implanted Envoy had widespread accumulation of RBCs enmeshed in a fibrous network, representing either fibrin or other plasma proteins (Fig 6B and C).

**Long-Term Implantation (Fig 7)**

DSA of the right CCA, containing the Fas-tracker long-term implantation sample, revealed no evidence of stenosis within the parent vessel (Fig 7A). DSA of the left CCA, containing
the Transit microcatheter long-term implantation sample, showed that the CCA was occluded at the level of the proximal portion of the implanted catheter, with distal reconstitution of flow (Fig 7B). DSA of the right common femoral artery, containing the Tracker microcatheter long-term implantation sample, revealed an angiographically normal vessel. Because the Magic microcatheter had embolized to a distal, muscular branch of the left subclavian territory, DSA was of little value.

Histologic examination showed that the carotid artery that contained the Fastracker microcatheter was essentially normal, without evidence of intimal or medial injury (Fig 8A). Conversely, the carotid artery that contained the Transit microcatheter had marked intimal hyperplasia (Fig 8B).

Discussion

This study addressed the in vivo thrombogenicity of microcatheters as a function of catheter material, catheter coating, and duration of implantation. Our results show that some hydrophilic coatings diminish thrombogenicity: the hydrophilic Fastracker microcatheter accumulated less debris than its nonhydrophilic counterpart, the Tracker microcatheter. Also, the hydrophilic Fasguide guiding catheter was remarkably free of debris, even after 5 hours of implantation. However, the Transit microcatheter, also hydrophilically coated, appeared more thrombogenic than the hydrophilic Fastracker microcatheter. The hydrophilic coatings of these catheters differ: the distal portion of the Transit catheter is coated with a polyvinylpyrrolidone-based coating, while the Fastracker and Fasguide catheters are coated with Hydrolene, a combination of polyvinylpyrrolidone and polyacrylamide. This difference in hydrophilic coating material may not only account for the differences in thrombogenicity noted in our study but also for the apparent disparities in the literature, in which Nagoaka et al (13) reported...
a benefit with hydrophilic catheters while Leach et al (15) did not. However, Nagoaka et al (13) used polyvinylpyrrolidone-coated catheters, similar to that of the Transit catheter. These latter investigators used a rabbit model rather than a swine model, and interspecies variability may account for some of these observed differences.

We also determined that, among the nonhydrophilic materials evaluated, silicone-coated polyethylene microcatheters were much less thrombogenic than polyvinylchloride microcatheters. The relative hypothrombogenicity of polyethylene has been shown by several authors (5–7, 16). However, in contradistinction to prior reports (1–3), we found that a smooth catheter surface was not necessarily protective against thrombus formation. For instance, the Magic microcatheter had the smoothest surface but the highest degree of thrombus formation. This suggests that catheter material rather than surface morphology is the prime determinant of thrombogenicity.

The Transit, Tracker, and Fastracker microcatheters showed no evidence of increasing thrombus formation over time. This may be related to the pathophysiology of thrombus formation at polymer surfaces. Most investigators believe that the initial event in the evolution of clot on the surface of a catheter is the adsorption of plasma proteins, including fibrinogen, albumin, and gamma globulin (17–21). The rate of plasma protein adsorption is rapid, often seen within minutes of catheter implantation. Subsequently, via mechanisms that are poorly understood (22), the adsorbed plasma proteins incite platelet adhesion and activation, with resultant formation of thrombus. The microcatheter samples evaluated in our experiment, with the exception of the Magic catheter, showed no evidence of fibrillary debris deposition. This may indicate that the catheters were resistant to plasma protein deposition, the absence of which precluded significant thrombus formation, regardless of implantation duration.

The surface of the Magic catheter was covered by macroscopic thrombus after both short- and medium-term implantation, indicating that relative to the other catheters studied, the Magic catheter is thrombogenic. However, the results observed in our swine model cannot be extrapolated directly into the human model, since coagulation may vary among species (23). The swine model was appropriate in that it allowed relative differences in catheter thrombogenicity to be assessed.

We included long-term implantation samples, since prolonged implantation of microcatheters may become useful in future endovascular therapies. The implanted Fastracker microcatheter caused no changes in the vessel wall, whereas the Transit microcatheter stimulated fibro-intimal hyperplasia that resulted in vessel occlusion. Unfortunately, the long-term implantation samples of the Magic and Tracker microcatheters embolized during implantation, so no useful data were available from these samples. It is possible that the changes induced in the carotid artery containing the Transit microcatheter resulted from irritation by the wire used as a stiffener within the implanted catheter. However, the Fastracker microcatheter sample contained a similar stiffener, and no hyperplasia was induced.

We included clean catheter samples in addition to implanted samples to control for potential changes induced by SEM fixation and processing procedures. Our results are useful in determining thrombogenicity of the catheters but do not necessarily reflect the appearance and morphology of native, unfixed catheters. For instance, it is possible that the pitted appearance of the Fastracker catheter resulted from the SEM preparation.

Our study had several limitations. Our results are qualitative rather than quantitative, as in many in vitro studies of thrombogenicity (14, 16). Our primary interest was in the visual appearance of thrombus formed on the catheter surfaces, so we applied SEM instead of more quantitative measures, such as radioactive fibrinogen binding assays (14, 16). Another limitation was that only a single sample of each catheter at each implantation time was harvested. This was done to minimize the number of animals required. Further, our focus was on thrombus adherent to the catheter surface rather than on end-organ thromboembolic phenomena. However, this practice is standard in studies assessing surface thrombogenicity. Last, we studied samples that had been retracted through other catheters rather than in situ, postmortem samples. Our methods allowed assessment of multiple catheters in a single animal. We minimized the effect of stripping thrombus during catheter withdrawal by using relatively large guiding catheters relative to the size of the catheter samples. The gross throm-
bus present on the Magic microcatheters suggests that our technique does not result in stripping of significant thrombus from the samples during retraction.

**Conclusions**

This study can serve as a paradigm for further in vivo hemocompatibility tests. We determined that some hydrophilic catheters were less thrombogenic than their nonhydrophilic counterparts. Polyvinylchloride was the most thrombogenic material among our samples. The degree of thrombogenicity depended to a greater degree on catheter material than on surface morphology. Medium-term implantation did not yield increasing thrombus formation compared with short-term implantation. Long-term implantation may be better tolerated with Fastracker rather than Transit microcatheters. The Fasguide guiding catheter was remarkably hypothrombogenic, even with prolonged implantation.

**Acknowledgments**

We acknowledge the assistance of Gina Wymer of Comparative Medicine and Bonnie Sheppard and Jan Redick from the Electron Microscopy, as well as secretarial assistance from Joyce Henderson.

**References**