In vivo model of intracranial stent implantation: a pilot study to examine the histological response of cerebral vessels after randomized implantation of heparin-coated and uncoated endoluminal stents in a blinded fashion

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Object. No animal model currently exists for the examination of time-dependent histological changes occurring in intracranial vessels after endoluminal stent placement. The authors’ goal was to develop a reproducible in vivo model of stent implantation in intracranial vessels in dogs that was capable of demonstrating stent-related vascular changes after the implantation of coated and uncoated devices.

Methods. The authors implanted heparin-coated or uncoated stents in the basilar arteries (BAs) of 11 mongrel dogs. In a 12th animal, one coated stent was implanted in the BA and a second uncoated one was implanted in the distal anterior spinal artery. All the devices were oversized to induce intimal injury. Surviving animals were observed for 12 weeks, after which they underwent repeated angiography before planned death and removal of the brain. Histological studies and computer-assisted morphometric analyses were conducted on stent-treated and untreated sections of the BAs to assess the percentage of stenosis, neointimal proliferation, vessel injury, and inflammation. Perforating vessels partially covered by stent struts (“jailing”) were studied for evidence of stenosis or occlusion. The pathologist, interventionists, histopathologist, histopathology technicians, and radiologist were blinded to the stent type.

Seven stents (three uncoated and four coated) were removed from the six animals that were observed during the follow-up period. The mean neointimal proliferation was 0.42 mm² in the group treated with uncoated stents and 0.18 mm² in the group treated with heparin-coated devices (p = 0.04). Neointimal thickness was significantly increased in the group with uncoated stents (p = 0.04). The mean percentage of occlusion was less (12%) in the group with heparin-coated stents, compared with 22% in the group with uncoated devices (p = 0.07). When comparing results between the heparin-coated and uncoated devices implanted in the five animals that received a single stent only, greater differences (indicating a benefit from heparin-coated stents) were observed in neointimal area (p = 0.009), neointima/media ratio (p = 0.001), neointimal thickness (p = 0.002), and percentage of occlusion (p = 0.009). All brainstem perforating vessels covered by stent struts remained patent.

Conclusions. This in vivo intracranial stent model was developed to assess proliferative and inflammatory responses to endoluminal stent implantation in the cerebrovasculature. The results indicate that a lower percentage of occlusion occurs 12 weeks after implantation of heparin-coated compared with uncoated stents.

Key Words • basilar artery • intracranial stent • dog

CLINICIANS are now using endoluminal stents with increasing frequency to treat medically refractory or severe symptomatic intracranial atherosclerotic disease. When left untreated after failed medical therapy, severe stenoses may lead to morbidity rates as high as 80%, with stroke rates as high as 10%. In one recent study, more than half of the patients with greater than 50% stenosis had recurrent symptoms, despite optimal antithrombotic and antiplatelet therapies.

Before endoluminal stent implantation procedures became available, surgeons treated high-grade intracranial stenoses that were refractory to medication with surgical bypass procedures, with relatively good success. Although excellent results were achieved with anterior circulation bypass procedures in a properly selected patient population, significant rates of morbidity (range 30–50%) were associated with posterior circulation bypass procedures. Some reports of endoluminal revascularization with stents have demonstrated similar rates of morbidity and mortality.

Stent placement for severe intracranial atherosclerotic
Canine basilar artery stent implantation model
disease has increased in popularity, yet no in vivo model has been
developed to examine the response of cerebral vessels
to the implantation of these devices. Although vascular re-
sponse to stent implantation in the coronary and peripheral
vasculature has been studied extensively in numerous in vi-
vo models, we cannot assume that a similar response ex-
ists in the arteries of the central nervous system. Intracranial
vessels differ substantially from peripheral and coronary
vessels in that they lack robust adventitia. These thin-
wall vessels are composed of a higher percentage of
smooth-muscle cells, which are believed to be responsible
for restenosis.4,9,10,35
The authors report the results of a study in which the pri-
mary objective was to develop an intracranial in vivo model
of stent implantation in dogs. To test the reproducibility and
reliability of this model, the authors conducted a pilot study
in which coated and uncoated stents were implanted in a
blinded, randomized fashion to ascertain whether potential
differences in cerebrovascular responses could be mea-
sured. To achieve this secondary objective, a limited num-
ber of stent implantations were performed using both hepa-
rin-coated and uncoated stents placed in the BAs of dogs.
These experiments were motivated by the hypothesis that
heparin-coated stents may impair platelet and thrombin-
mediated signaling of the cellular cascade responsible for
thrombosis and cell proliferation on the stent matrix.36,41 Al-
though heparin-coated devices have been shown to inhibit
acute and subacute stent-related thrombosis and to decrease
the incidence of restenosis in vivo in animal models of ex-
tracranial vessels,1,13,21,26,33 the effects of drug-coated stents
have not been studied in the intracranial circulation.47 An-
other secondary aim of this study was to examine the histo-
logical effects of flow alterations resulting from “jailing” of
brainstem perforating vessels after stent placement, which
has not been previously investigated in live animals. Stent
jailing is seen when the stent strut covers the ostium of a
branch artery and causes immediate obstruction of flow to
that vessel.

Materials and Methods
This study was approved by the University at Buffalo Animal
Care and Use Committee in accordance with guidelines established
by the Animal Welfare Act.35
Choice of Canine Model
For numerous reasons, dogs were chosen over pigs and other spe-
cifics for the animal model. Of greatest importance, canine vessels
behave more like human vessels than do those of pigs with respect to
vasospasm, recoil, neointimal proliferation, and thrombotic poten-
tial.18,34,48 Additionally, dogs are less susceptible to spontaneous
thrombosis of blood vessels than are other species because of a hy-
pervascular fibrinolytic system.27 This characteristic is especially im-
portant when endovascular devices are used to improve vessel paten-
cy. More importantly, the caliber and accessibility of canine vessels
permit the replication of conditions similar to those encountered dur-
ing intracranial stent implantation in humans. The diameter of the
BA in the canine model approximates that of distal intracranial ves-
sels in humans (~1.5–1.8 mm). The catheters and devices used in
humans can be used in dogs. The arteries are easily accessible and
can be easily removed and processed for histological analysis.49
Randomization Scheme
A predetermined order for the use of uncoated and heparin-coated
stents was devised before the first one was implanted. The lead inter-
ventionists (E.I.L., A.S.B., and R.A.H.) were blinded to this scheme
throughout the entire stent implantation procedure. The histopathol-
gist (F.O.T.), histopathology technicians, and radiologist (R.A.A.)
were also blinded to the stent properties. The devices used in this
study were 2.25 × 8-mm stainless steel, balloon-mounted heparin-
coated or uncoated BX Velocity stents (Cordis Corp., Miami Lakes,
FL). These two types of stents are identical in appearance (Fig. 1).

Endoluminal Stent Placement
Mongrel dogs, each weighing 15 to 25 kg, underwent diagnostic
cerebral angiography after the induction of general anesthesia with
1.5 to 2.5% isoflurane. Baseline measurements were obtained of the
BA lumen diameter along several points corresponding to the antici-
patated location of the stent. Dogs with arterial diameters measuring
less than 1.4 mm were excluded from the study and returned to the
housing facility; those with larger-diameter arteries underwent at-
temted stent placement. A No. 6 French guide catheter was inserted into the cervical VA
to the C-3 level by using standard cutdown access techniques. A mi-
croguidewire was then advanced through the guide catheter into the
distal BA by using conventional roadmapping techniques. The stent
was advanced over the wire, and, again using roadmapping tech-
niques, was positioned distal to the junction of the VAs within the
BA. In one animal, one stent was also placed in the distal ASA at the
level of the foramen magnum, just proximal to the VBJ. This animal
had a sufficiently large ASA that matched the size of the BA, en-
abling us to perform a dual stent placement, which allowed us to re-
duce the number of animals required for the study. Slow inflation
methods were used to expand the stent to the minimum implantation
diameter of approximately 1.9 mm (at 4–4.5 atm of pressure). After
angiographic confirmation of stent expansion and delivery, the bal-
loon-catheter system was withdrawn to a region proximal to the
stent. Nitroglycerine (20–50 mg) was administered through the bal-
loon catheter in the event of severe vasospasm (Fig. 2). Repeated
angiography was performed immediately after stent placement to de-
termine the presence of extravasated contrast material and vessel pa-
tency.
After successful implantation of the device, the animals were re-
covered and examined. In each case, the stent was intentionally over-
sized relative to the diameter of the arterial lumen to induce vessel
injury and activate the cytological cascade leading to the inflamma-
tion-mediated vascular healing response (as is seen after plaque for-
mation and rupture). This is not analogous to the clinical setting, in
which stents are precisely sized to the diameter of the parent vessel
and measured in nonstenotic segments.
Each animal received 2000 U heparin during the procedure and
was maintained on aspirin (81 mg daily, initiated 1 day before stent
implantation) throughout the 12-week follow-up period. Examina-
tions were conducted daily to assess the presence of any neurologi-
cal deficit.
and intimal smooth-muscle cell infiltration.

Objective lens for various histological changes, including inflammation.

Euthanasia. Formalin (500 ml of 10% concentration) was then perfused through the guide catheter that had been previously placed in the VA for angiographic studies. A craniectomy was performed, and the brain and brainstem were removed en bloc, maintaining the integrity of the vertebrobasilar vessels (Fig. 3). Microdissection techniques were used to remove the posterior cerebral vessels, which were then fixed in 10% formalin; the brain was placed in a separate container of 10% formalin.

Histological and Computer-Assisted Morphometric Analysis

The histopathologist and histology technicians were blinded to the type of stent (coated or uncoated). After en bloc removal of the brain and microdissection of the posterior circulation and circle of Willis, the specimens were then embedded in methyl methacrylate plastic (Sigma Chemical Co., St. Louis, MO) after dehydration in a graded series of ethanol. Using a Buehler Isomet saw (Buehler Ltd., Evanston, IL), serial sections of plastic-embedded specimens were obtained from the proximal to the distal end. All sections were polished and stained with metachromatic stain and inspected for perforating branches and technical suitability for measurement. Three to four cross-sections of stent-treated vessels sampled from along the length of the device, plus one from each of the adjacent untreated proximal and distal end segments, were measured and graded under a 4× objective lens for various histological changes, including inflammation and intimal smooth-muscle cell infiltration.

Sigmascan morphometric software (Jandel Scientific, San Rafael, CA) was used to calculate measurements (described later) of arteries inspected through a Nikon Labophot compound microscope integrated to the light-emitting diode–illuminated cursor of a standard digitizing pad through a drawing tube attachment. Three different areas were measured: 1) artery area, the area (in square millimeters) delimited by the junction of the adventitia and the tunica media (external elastic membrane); 2) stent area, the area within the stent; and 3) lumen area, the area within the inner surface of the intima. Neointimal thickness (in millimeters), percentage of occlusion, and neointima/media ratio were calculated from these area measurements. Neointimal area was calculated by subtracting the area of the lumen from that of the stent.

An inflammation score was assigned that was based on the presence of any significant inflammation surrounding the stent struts, as follows: 1) involvement of less than 25% of the artery; 2) involvement of 25% or more but less than 50% of the artery; and 3) involvement of 50% or more of the artery (Fig. 4). Intimal smooth-muscle cell content was scored according to the following scheme: 1) sparse density of smooth-muscle cells involving any portion of the artery or moderate infiltration less than the full thickness of the neointima involving less than 25% of the circumference of the artery; 2) moderate infiltration of less than the full thickness of the neointima involving 25% or more of the circumference of the artery; and 3) dense smooth-muscle cell content over the full thickness of the neointima involving less than 25% of the circumference of the artery. The percentage of occlusion was calculated according to the following formula: % occlusion = 1 – (lumen area/stent area) × 100.

Magnetic Resonance Imaging

For MR imaging of each formalin-fixed brain, T2-weighted (long repetition time–weighted) and gradient spin-echo imaging sequences were used to determine the presence or absence of infarction or hemorrhage. Imaging was directed to the brainstem, cerebellum, and posterior portions of the cortex, because each of these regions has a predominantly posterior circulation blood supply. All images were interpreted by a board-certified neuroradiologist (R.A.A.) who was blinded to the properties of the stent used in each specimen of the vasculature (Fig. 5).

Statistical Analysis

For each stent placement, various histological and morphological parameters were measured in triplicate, with one measurement taken at each of three stent-implanted regions. These measurements were
then averaged, as were similar reference measurements from two adjacent regions with stents. The mean values of these histological measurements were then calculated for both uncoated and heparin-coated stents. Group means were compared with the use of t-tests for the analysis of unpaired data, and two-tailed probability values were calculated. A probability value of 0.05 or less was considered statistically significant. Values are graphically expressed as the mean ± SEM. All statistics were calculated using the Instat statistical package (GraphPad Software, Inc., San Diego, CA).

Results

Stent Implantation Procedure

Stent placement in the BA was attempted in 12 mongrel dogs. Five animals suffered fatal vascular injuries as a result of either BA rupture or perforation of a branch vessel. Softer microguidewires (PVS; Precision Vascular Systems, West Valley City, UT, or Transcend EX; Boston Scientific, Natick, MA) were then used, and no further perforations occurred. Stent placement procedures were altered so that the devices were delivered over 3 to 5 minutes instead of within 1 minute, and no further BA ruptures occurred. Eight stents (three uncoated and five coated) were successfully placed intracranially in seven dogs (seven stents in the BA and one in the distal ASA adjacent to the foramen magnum, just proximal to the VBJ). The mean diameter of the BA lumen before stent implantation was 1.51 ± 0.08 mm (mean ± standard deviation, range 1.4–1.6 mm). Seven stents (in six animals) were removed at the end of the target follow-up period of 12 weeks, and one stent was removed 24 hours after implantation because of a brainstem perforating vessel injury resulting in lower-extremity paraparesis. This injury was caused by the inadvertent placement of the microguidewire in the perforating vessel and resulted in a small hole in the vessel, as evidenced by the presence of a transient extravascular blush of contrast material. The stent, vessels, and brain removed at 24 hours were prepared for histopathological and radiographic analyses. Histological analysis revealed the complete absence of endothelialization of the stent struts and intimal proliferation. The findings, however, were not included in any of the calculations comparing coated and uncoated devices, because the stent demonstrated no evidence of neointimal formation.

Follow-Up Angiography and MR Imaging

Follow-up angiography at 12 weeks demonstrated a normal angiographic lumen diameter through the treated portion and the immediately adjacent portion of the parent vessel in the six surviving animals (Fig. 6). All perforating vessels jailed by stents were patent on angiographic studies (Fig. 7). Despite angiographically confirmed filling of visible perforating vessels originating from the treated segment of the BA, stenosis was noted at the origin of the left AICA during follow-up angiography in two animals, one from the group treated with coated stents and the other from the group treated with uncoated devices (Table 1). These vessels filled normally, distal to their stenotic origins. In one of these dogs (Animal 2, uncoated stent group), pontine infarction was noted on MR imaging (Fig. 5). Despite these angiographic and MR imaging findings, no clinical sequelae were observed in any of the surviving animals.

Histopathological and Computer-Assisted Morphometric Analysis

The neointimal area (stent area — lumen area) was determined for the treated segments of the BA and the areas immediately adjacent to them in both the group receiving heparin-coated stents and that treated with uncoated stents (Table 2). The artery area delimited by the junction of the
adventitia and the tunica media (external elastic membrane) was similar in both groups. Nevertheless, the mean neointimal area was 0.18 mm² in the group treated with heparin-coated stents and 0.42 mm² in the group with uncoated devices. This reduction in neointimal proliferation was found to be statistically significant (p = 0.04). The neointima/media ratio was increased in the group treated with uncoated stents (p = 0.05), as was neointimal thickness (in millimeters, p = 0.04). The mean lumen area was similar in both groups, at 1.33 and 1.53 mm² in the dogs treated with coated and uncoated stents, respectively. The mean percentage of occlusion of the vessel lumen was 11.92% in the group treated with coated stents and 22.05% in the group with uncoated devices (p = 0.07). Segments of artery immediately adjacent to the stent demonstrated mean occlusion rates of 15.84 and 11.12% in the dogs treated with uncoated and coated stents, respectively. The mean intimal smooth-muscle cell proliferation score was 3 in the dogs that received uncoated stents and 1.6 in those with coated devices, indicating lower smooth-muscle cell density in the intima after implantation of a heparin-coated stent (Fig. 8). Significant inflammation (a score of 3) was seen within the neointima in only one dog (Animal 5) that received an uncoated stent.

As shown in Figs. 9 and 10, when comparing results between the group treated with heparin-coated stents and the one treated with uncoated devices in the five animals that had a single stent placed in the BA and that were observed for 12 weeks thereafter, greater differences (reflecting a benefit of heparin-coated stents) were demonstrated in the group receiving single stents (compared with dogs receiving either one or two stents), with respect to neointimal area (p = 0.009), neointimal area/media ratio (p = 0.001), neointimal thickness (p = 0.002), and percentage of occlusion (p = 0.009). For these specific parameters, the values in the animal that received both a coated stent (BA) and an uncoated one (ASA) fell between those for the uncoated stents and the coated ones in animals receiving one stent. From

Fig. 6. Follow-up angiogram obtained at 12 weeks posttreatment, demonstrating normal lumen diameter through the stent-implanted portion of the BA and the immediately adjacent portion of the parent vessel.

Fig. 7. Photomicrograph showing a stent strut covering the ostia of a perforating vessel (arrow). The vessel is patent, but a fibrin-platelet thrombus (arrowheads) is present in the lumen of the perforating vessel and surrounding the stent strut. Original magnification × 9.
Canine basilar artery stent implantation model

**TABLE 1**

*Neuroimaging assessment of heparin-coated and uncoated stents*

<table>
<thead>
<tr>
<th>Animal</th>
<th>Stent Type</th>
<th>MRI Findings</th>
<th>Angiogram Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X(p)</td>
<td>normal</td>
<td>no stenosis</td>
</tr>
<tr>
<td>2</td>
<td>X</td>
<td>lt pontine infarction</td>
<td>lt AICA origin stenosis</td>
</tr>
<tr>
<td>3</td>
<td>X</td>
<td>normal</td>
<td>lt AICA origin stenosis</td>
</tr>
<tr>
<td>4</td>
<td>X</td>
<td>normal</td>
<td>none; artery removed at 24 hrs</td>
</tr>
<tr>
<td>5</td>
<td>X</td>
<td>normal</td>
<td>no stenosis</td>
</tr>
<tr>
<td>6</td>
<td>X</td>
<td>normal</td>
<td>no stenosis</td>
</tr>
<tr>
<td>7</td>
<td>X</td>
<td>normal</td>
<td>no stenosis</td>
</tr>
</tbody>
</table>

* X = stent placed; X(d) = stent placed in the BA; X(p) = stent placed just proximal to the BA in the ASA.

**TABLE 2**

*Histopathological and morphometric analysis of heparin-coated and uncoated stents 12 weeks postimplantation*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Uncoated</th>
<th>Heparin-Coated</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of animals</td>
<td>3</td>
<td>4</td>
<td>0.13</td>
</tr>
<tr>
<td>artery area (mm²)</td>
<td>2.61</td>
<td>2.12</td>
<td>0.13</td>
</tr>
<tr>
<td>lumen area (mm²)</td>
<td>1.53</td>
<td>1.33</td>
<td>0.39</td>
</tr>
<tr>
<td>neointimal area (mm²)†</td>
<td>0.42</td>
<td>0.18</td>
<td>0.04‡</td>
</tr>
<tr>
<td>media area (mm²)</td>
<td>0.67</td>
<td>0.61</td>
<td>0.42</td>
</tr>
<tr>
<td>neointima/media ratio</td>
<td>0.66</td>
<td>0.29</td>
<td>0.05‡</td>
</tr>
<tr>
<td>neointimal thickness (mm)</td>
<td>0.09</td>
<td>0.04</td>
<td>0.04‡</td>
</tr>
<tr>
<td>occlusion (%)</td>
<td>22.05</td>
<td>11.92</td>
<td>0.07‡</td>
</tr>
<tr>
<td>smooth-muscle cell score</td>
<td>3</td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

* One of the six animals underwent a double stent placement, with an uncoated stent placed just proximal to the VBJ in its ASA, as well as a heparin-coated stent implanted in its BA. The five remaining animals each had a single stent placed in their BA, two uncoated stents and three heparin-coated ones.

† Neointimal area is calculated as stent area – lumen area. Although the measured stent area is not provided, it can be derived by subtracting the area of the media from that of the artery.

‡ Statistically significant.

this observation we infer that the interaction of the two stents created an environment in which the benefits of the heparin-coated stents were diminished by the uncoated ones.

**Discussion**

**Medical Impact**

Stroke is the third leading cause of death in the US, afflicting approximately 750,000 people annually. Severe intracranial stenosis is responsible for an unknown percentage of these strokes and, when left untreated, may result in morbidity rates ranging from 50 to 80%. Data from the Warfarin-Aspirin Symptomatic Intracranial Disease study demonstrate that patients with more than 50% stenosis are at a risk of stroke ranging from 6 to 11%, despite medical therapy. According to Thijs and Albers, approximately 50% of patients with severe intracranial stenosis who have neurological symptoms while receiving antithrombotic regimens will have another episode of ischemia. Endoluminal stent implantation for medically intractable or high-grade (> 70%) intracranial atherosclerotic lesions is becoming an increasingly popular intervention. Although morbidity rates following stent placement in the posterior intracranial circulation can be as high as those for surgical bypass procedures in the same region, little is known about the intracranial vascular response to endoluminal prosthetic devices (stents).

**Need For an In Vivo Intracranial Stent Model**

Coronary and peripheral vascular responses to endoluminal stents have been demonstrated in numerous studies. To our knowledge, however, no in vivo model has been developed to assess time-dependent changes in the histological microenvironment of stent-treated intracranial vessels. Neointimal proliferation, increased smooth-muscle cell density, and restenosis subsequent to stent-induced intimal injury have been demonstrated within 6 weeks of stent implantation in existing models. After angioplasty-related injury to the intima, a cascade of events involving the interaction of cytokines and growth factors produced by leukocytes, platelets, and damaged endothelial cells occurs in the arterial wall. This injury likely leads to cell-signaling pathways, resulting in the activation of smooth-muscle cells and their proliferation in the subintimal space. The proliferation of monocytes in the arterial wall, along with the proliferation of smooth-muscle cells, has been found to coincide with neointimal proliferation during the first 3 to 8 days after iatrogenic intimal injury related to angioplasty. In animal models of atherosclerosis, Geary, et al., observed that...
leukocytes invade the fractured plaque and intima within 48 hours and smooth-muscle cells within the 1st week. Smooth-muscle cells and the associated expressed proteoglycans are robust through Day 28 but their expression has subsided by Day 112. In another study this group has demonstrated that cell proliferation in the neointima approaches baseline levels by Day 28 after angioplasty, based on results of immunohistochemical studies performed after the administration of bromodeoxyuridine.

The proliferative cascade following iatrogenic intimal injury to the endothelium, and potentially to the deeper arterial wall structures, can be divided into three phases as follows: 1) an acute phase that leads to initiation of the cell-signaling pathways discussed earlier (24–72 hours); 2) an intermediate phase (1–4 weeks) during which the activated medial smooth-muscle cells replicate and migrate from the media to the subintimal layer; and 3) a chronic phase (4–12 weeks) characterized by the production of large amounts of extracellular matrix, which results in further remodeling of the neointima and vessel wall. Thus, we decided to retrieve the stent-implanted vessels at 12 weeks to ensure that the chronic phase of vascular remodeling was near completion. In one dog killed 6 months after implantation of an uncoated BX Velocity stent (this animal was not included in the analyses of the results of this pilot study — see Fig. 9, Bar graphs showing differentiation of cerebrovascular responses in which stent type (heparin-coated, three animals; uncoated, two animals; or both, one animal) and single (five animals) or double (one animal) stent placement are considered. Substantial differences were found in neointimal area, neointimal thickness, neointima/media ratio, and percentage of occlusion. Values for cerebrovascular responses in the animal that received a coated stent in one vessel and an uncoated device in another (mixed placement) fall between the values seen in dogs treated with coated and uncoated stents. Values are expressed as the means ± SEM.
Canine basilar artery stent implantation model for retinal artery occlusion.

Pathological findings in this case did not demonstrate per-artery correlated with ipsilateral stenosis of the AICA. Histo-

uncoated stents demonstrated ischemic injury to the left imaging in one dog (Animal 2) from the group treated with vessels remained patent (Fig. 7). As previously mentioned, MR imaging in such a way that the benefits of the heparin coating indicates that the coated and uncoated stents were interact-

ratio (p = 0.07), there was more neointimal proliferation in stent-implanted vessels in the group treated with uncoated devices (Fig. 10). These results are considered likely to be of statistical significance, given the small sample size (Table 2). With a larger study group, these results are likely to have reached statistical significance. Additionally, there was a greater “edge effect,” or stenosis of the parent ves-

jects or an understanding of potential consequences resulting from jailed perforating vessels.

Several in vitro models have demonstrated that jailed os-
tia of perforating vessels will remain patent if the stent struts do not entirely cover the vessel origin.31,32,49,50 Occlusion of brainstem perforating vessels resulting from an ostium jailed by a stent placed in the parent artery is potentially catastrophic. In addition to assessing the cerebrovascular response to stent-induced vascular injury, we attempted to position each BA stent over the labyrinthine and/or pos-
terior inferior cerebellar arteries to assess the clinical, his-
tological, and radiographic findings resulting from jailed brainstem perforating vessels. Although several sections of stent-treated arteries were obtained that demonstrated partial coverage of the brainstem perforating vessel ostia by stent struts, one section demonstrated a strut entirely covering the perforating vessel. In all cases, the perforating ves-
sels remained patent (Fig. 7). As previously mentioned, MR imaging in one dog (Animal 2) from the group treated with uncoated stents demonstrated ischemic injury to the left pons; however, the event was clinically silent. This im-

cerebral occlusion (p = 0.07), in-stent stenosis (percent-
age of occlusion) occur after treatment with heparin during the time of stent implantation. Mechanisms of heparin-in-
duced inhibition of restenosis include inhibition of nuclear transcription factors, modulation of growth factor activity or receptor binding, regulation of extracellular matrix produ-
don, inhibition of smooth-muscle cell proliferation, and restriction of inflammation.40,51 In human coronary vessels, heparin appeared to lower the rate of acute and subacute thrombosis; restenosis rates at 12 months appeared to be similar to those seen with uncoated stents.47 Although there have been mixed results with attempts to demonstrate the effectiveness of heparin in inhibiting restenosis, we believe that the cerebrovasculature might be responsive to the anti-

iproliferative mechanisms of heparin because 85% of the cellular composition of these vessels is smooth-muscle cells.26

In our study, no subacute or acute stent-related throm-

Table 2. With a larger study group, these results are likely to have reached statistical significance. Additionally, there was a greater “edge effect,” or stenosis of the parent vessel, immediately adjacent to the stent-implanted arteries in the group treated with uncoated devices (data not shown). Maximum smooth-muscle cell proliferation was seen in the group treated with uncoated stents; proliferation of these cells was more variable in the group treated with heparin-

coated stents. In all cases, the perforating vessels remained patent despite partial occlusion by stent struts.

When analyzing the data for animals treated with single stents only, greater differences were demonstrated in this group (compared with dogs receiving either one or two stents), reflecting a benefit of the heparin-coated stents with respect to neointimal area (p = 0.04), increased neointi-

media ratio (p = 0.05), and a greater percentage of occlusion (p = 0.07), there was more neointimal proliferation in stent-implanted vessels in the group treated with uncoated devices (Fig. 10). These results are considered likely to be of statistical significance, given the small sample size (Table 2). With a larger study group, these results are likely to have reached statistical significance. Additionally, there was a greater “edge effect,” or stenosis of the parent ves-

sults demonstrate significant stenosis of a brainstem perforating vessel (the left AICA in each case). One dog (Animal 3) had been treated with a coated device; the other (Animal 2) had received an uncoat-

Histopathological Differences in Vessels Treated With Heparin-Coated Stents

Using the canine BA stent model, we also attempted to ascertain whether a small number of animals could be used to examine vascular responses after endoluminal stent placement with heparin-coated and uncoated devices. The heparin-coated stent was chosen because this agent has been shown to prevent the development of subacute throm-

bosis. Additionally, in several animal studies it has been demonstrated that decreased neointimal proliferation, smooth-muscle cell proliferation, and restenosis (percent-
age of occlusion) occur after treatment with heparin during the time of stent implantation. Mechanisms of heparin-in-
duced inhibition of restenosis include inhibition of nuclear transcription factors, modulation of growth factor activity or receptor binding, regulation of extracellular matrix produ-
don, inhibition of smooth-muscle cell proliferation, and restriction of inflammation.40,51 In human coronary vessels, heparin appeared to lower the rate of acute and subacute thrombosis; restenosis rates at 12 months appeared to be similar to those seen with uncoated stents.47 Although there have been mixed results with attempts to demonstrate the effectiveness of heparin in inhibiting restenosis, we believe that the cerebrovasculature might be responsive to the anti-

iproliferative mechanisms of heparin because 85% of the cellular composition of these vessels is smooth-muscle cells.26

In our study, no subacute or acute stent-related throm-

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ed stent. The only infarct demonstrated on MR images in this study was the one in the left pontine region in Animal 2; no areas of hemorrhage were observed.

Future Applications

Newer, drug-coated stents dramatically reduced the rate of restenosis of stent-treated coronary vessels in recent clinical trials involving patients with coronary artery disease. Rapamycin-coated stents have demonstrated 0% restenosis at 6 and 12 months, compared with approximately 30% restenosis in uncoated controls. Taxol-coated stents have demonstrated similar results in the coronary vasculature, with 4% restenosis. Before such drug-coated stents can be used in the human cerebrovasculature, studies are required to measure possible absorption of the drugs into the CSF and subsequent neurotoxic effects. Future applications for the canine BA model include implantation of these newer drug-coated stents in a larger number of experimental animals and then assaying drug concentration in the CSF and monitoring canine behavior during the follow-up period. Additional studies with varying durations of endoluminal stent implantation may provide further insight into the time course of intracranial vessel restenosis.

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References

Canine basilar artery stent implantation model


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