Implantation and Recovery of Temporary Metallic Stents in Canine Coronary Arteries

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Objectives. The purpose of this study was to test the feasibility of implanting and retrieving a heat-activated recoverable temporary stent and to determine its effect on the angiographic, gross and histologic appearance of a normal coronary artery wall.

Background. Permanent coronary stenting is associated with a significant incidence of thrombosis, bleeding and vascular complications. These may be avoided by temporarily stenting for a period of hours to several days.

Methods. Seventy-eight stents constructed from the shape-memory nickel-titanium alloy nitinol were deployed by balloon expansion in the coronary arteries of 28 dogs and left in place for up to 6 months. Thirty minutes to 1 week after implantation, 70 stents were recovered by flushing the coronary arteries with 3 to 5 mL of 75°C lactated Ringer solution, with collapse of the stent over a recovery catheter and subsequent withdrawal.

Results. All stents were successfully recovered and removed percutaneously. Mean vessel diameter after stenting was 12 ± 6% (p < 0.05) greater than baseline diameter. Mean vessel diameter after stent removal remained enlarged (6 ± 3%, p < 0.05). No angiographic or gross evidence of thrombosis, dissection, embolization, migration or spasm was associated with implantation or recovery. Microscopic examination revealed minor intimal injury in 40 segments (51%). Microscopic focal medial necrosis was associated with mural platelet-fibrin thrombus in 23 stented segments (29%) and media was interrupted in 7 (9%).

Conclusions. This study demonstrates the feasibility of a new method of temporary stenting that uses the thermoelastic properties of nitinol to permit reliable recovery of the stent in normal canine coronary arteries.

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creases the martensitic fraction of some variants as well as the axial flexibility of the device.

Austenitic phase transition occurs when the metal is heated above a specific temperature, which can be chosen according to the composition of the alloy. The transition temperature of the prototype stent was 55°C. On heating, the expanded stent undergoes a thermoelastic phase transition, resulting in collapse of the stent to its original unexpanded configuration (Fig. 1c). This phase change occurs at the speed of sound and with considerable force. The stent grips the recovery catheter tightly, providing a mechanism for recovery and removal of the deployed stent from the coronary arteries.

Animals. Animal experiments were performed according to the "Guide for the Care and Use of Laboratory Animals" (DHEW publication No. NIH-80-23), and the protocol was approved by the Institutional Animal Care and Use Committee of Cedars-Sinai Medical Center. Twenty-eight mongrel dogs weighing 25 to 30 kg were pretreated with aspirin (325 mg) and dipyridamole (75 mg) 1 day before the procedure. Anesthesia was induced with intravenous sodium thiopental (30 mg/kg body weight), and the trachea was intubated. The dogs were ventilated with 1 to 1.5 minimal alveolar concentration of isoflurane and oxygen. Procedures were performed with continuous electrocardiographic and blood pressure monitoring. An 8F side-arm introducer sheath was placed in the left carotid artery after surgical cutdown. Activated clotting time was measured, and 5,000 U of intravenous heparin was administered. Activated clotting time was maintained at >300 s until the stent was implanted. After stent implantation, the dogs received a daily dose of 10,000 U of subcutaneous heparin for up to 10 days. Low molecular weight dextran (Rheomacrodex, Pharmacia Inc.) was administered at a rate of 50 ml/h for the duration of the procedure.

An 8F percutaneous transluminal coronary angioplasty guiding catheter (Schneider) with a JR5 or hockey-stick curve was positioned selectively into the left coronary artery. Coronary arteriography was performed in the left lateral projection by hand injection of 4 to 5 ml of contrast medium (Angioview, Berlex Labs), and X-ray exposures were made with a Siemens (Erlangen) Gigantos cineangiography system using the 6-in. (15-cm) image intensifier. Images were recorded at a dose of 0.3 μGy/frame on 35-mm cine film at 30 frames/s and on U-matic 0.75-in. (1.9-cm) videotape.

Stent Implantation. The location and duration of stent deployment are summarized in Table 1. A custom-made 3.0- to 4.0-mm diameter over the wire balloon catheter (Advanced Coronary Technologies) 20% to 50% larger in diameter than the target vessel was chosen. The device was crimped over the collapsed balloon to comprise the stent delivery system. This was advanced into the selected coronary artery segment using standard angioplasty techniques and a 0.014-in. (0.036 cm) guide wire (Advanced Cardiovascular Systems, Inc.). Two dilations of 6 to 8 atm for 15 s were performed to expand the stent. Expanded balloon diameters of 3.0 or 3.5 mm were required for left anterior descending coronary artery implantation and 3.5 or 4.0 mm for left circumflex coronary artery implantation. The deflated balloon and guide wire were then removed, leaving the expanded stent embedded in the vessel wall (Fig. 2, A and B). Patency was confirmed by repeat angiography.

A total of 78 devices were placed in the mid to distal regions of the left circumflex, left anterior descending and diagonal branches of the left anterior descending coronary artery in 23 dogs.* A different segment of the same vessel

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<th>No. of Dogs</th>
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<td>LAD (n = 37)</td>
<td>LCx (n = 41)</td>
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LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery.

Table 1. Location and Duration of Stent Implantation

*One additional experiment was performed; however, the animal did not receive pretreatment with aspirin and dipyridamole. Because this was not according to protocol, the results are not included in the summarized data. One of the two stents implanted thrombosed after 30 min. Gross and microscopic inspection revealed a white, platelet-rich thrombus.
Figure 2. Left coronary arteriogram before and after stent delivery: A, Left coronary artery angiogram. B, Fluoroscopic appearance of delivered stent devices in the left anterior descending and left circumflex coronary arteries. C, Recovery catheter coaxially positioned through expanded stent in the left anterior descending coronary artery. D, Thermal collapse of stent on the recovery catheter. E, Left coronary artery arteriogram after recovery of both devices.
was chosen on 31 occasions to place a second stent after removal of the first (Table 1). There were 37 left anterior descending and 41 left circumflex coronary artery stent placements.

Stent recovery. Stent recovery was attempted 30 min to 6 weeks after deployment (Table 1). After angiographic confirmation of vessel patency, a J-tip 0.014-in. guide wire was placed through the stent and advanced into the distal segment of the artery. Multiple views were obtained, and particular attention was given to free mobility of the wire through the stent to ensure that the wire was coaxial within the stent. A recovery catheter (Advanced Coronary Technologies) was advanced coaxially through the implanted stent until two platinum markers that delineate a 20-mm stent recovery zone straddled the stent (Fig. 2C). To collapse the stent, 3 to 5 ml of lactated Ringer solution preheated to 75° to 80°C was hand injected as rapidly as possible into the proximal Y-adapter of the recovery catheter and exited through multiple side holes just proximal to the stent (Fig. 2D). In bench simulation this technique delivers a pulse of 60° to 65°C liquid at the distal delivery site.

The stent-catheter recovery system was then withdrawn from the coronary artery and either removed by exiting through the guide catheter or by pullback through the introducer sheath. Elapsed time from the guide catheter insertion to retrieval of the device did not exceed 5 min. Repeat angiography was performed, followed by euthanasia with intravenous potassium chloride while the animal was under general anesthesia. The coronary arteries were perfused in situ with formalin for 15 min. The heart was excised and fixed in formalin. Angiographic interpretation was by consensus of two observers (N.L.E. and M.J.K.). Relative vessel diameter was measured with handheld calipers.

Gross and microscopic examination. All recovered stents underwent gross inspection after removal for evidence of vascular tissue or thrombus under a dissecting microscope at ×25. The 16 stents implanted for >24 h were fixed in 2.5% glutaraldehyde, and scanning electron microscopy (Hitachi S405) of these stents was performed.

After fixation, all arterial segments were visually inspected for extravascular hemorrhage. Serial 2-mm segments of vessels were cut from the site of stent implantation and from areas distal and proximal to the stent. After routine processing, sections were cut and stained with hematoxylin-eosin for light microscopic evaluation by an experienced cardiac pathologist (M.C.F.). Pathologic findings were categorized according to the degree of vascular injury into three prospectively defined classes: class I, minimal intimal injury consisting of focal endothelial damage and disturbance of the internal elastic lamina in the stented segments; class II, intimal injury associated with platelet-fibrin thrombi and focal medial necrosis evident by absence of smooth muscle cell nuclei, and class III, medial disruption.

Analysis. Vessel diameter after implantation and recovery was compared with the diameter of adjacent unstented segments and shown as mean value ± SD. Statistical analysis was performed using the paired t test.

Results

Implantation of stents. The stents were easily visible under fluoroscopy. All stents were successfully delivered to the target vessels without embolization, migration, dissection, spasm or rupture recognizable on the postdelivery angiogram. All stented vessels remained patent without angiographic evidence of thrombus or side branch occlusion. The stented segments of the vessels were 12 ± 6% (p < 0.05) larger in diameter than the adjacent unstented segments (Fig. 3).

Recovery of stents. The transcatheter/sheath recovery procedure was successful in all 70 stents implanted up to 1 week. A single injection of 3 to 5 ml of heated lactated Ringer solution was successful in all cases in collapsing the stent. By fluoroscopy each stent was observed to collapse onto the recovery catheter between the angiographic markers without embolization. Stented arterial segments maintained a diameter equal to or greater than that of adjacent proximal segments after removal of the stent (Fig. 2C). The mean diameter of these segments was 6 ± 3% (p < 0.05) larger than that of the adjacent unstented segment by caliper measurements (Fig. 3). No arrhythmias or hemodynamic changes were associated with intracoronary injection of the thermal bolus. Segments measured after 6 weeks and 6 months of stent implantation had 22 ± 5% and 36 ± 8% diameter stenosis, respectively. The stents implanted for six weeks were not recoverable with a thermal bolus.
Figure 4. Histologic changes after stenting. a, Class I injury: stented segment of the left anterior descending coronary artery in Dog 12 after removal of the device, which had been implanted for 24 h. Mild intimal injury is present. Note fragmentation of internal elastic lamina (arrowheads). The media and adventitia are intact. b, Class II injury: section of a stented segment of the left circumflex coronary artery in Dog 13. The device was removed 24 h after implantation. A platelet-fibrin thrombus is seen attached to the vessel wall at a small branch site (asterisk). Nuclei are sparse in the media to right of the thrombus. c, Class III injury: section of a segment of the left anterior descending coronary artery in Dog 2, where perivascular hemorrhage was seen on gross inspection. The device was removed 30 min after implantation. Note site of medial disruption of the vessel wall (arrows) with hemorrhage into the adventitia adjacent to the rupture (r) site. Hematoxylin-eosin stains ×50 (a and b), ×25 (c).

Gross and microscopic histopathologic findings. No vascular tissue was noted on gross examination of the stents after removal. Under dissecting microscope the stents appeared to be free of thrombus or vascular tissue. A thin red layer was noted covering approximately 50% of the surface area of the stents.

Gross examination of the hearts revealed limited periadventitial hemorrhage at the site of stent deployment in 7 of 78 stented segments. This appeared as myocardial staining in the area immediately next to the arterial segment. In all such cases the ratio of expanded balloon size to vessel diameter exceeded 1:4:1.

Examples of the three injury classes are shown in Figure 4. There was evidence of class I injury in 40 (51%) stented segments. In addition, there were microscopic platelet fibrin thrombi in 23 (29%) stented segments representing class II injury. The seven (9%) arterial segments with gross periadventitial hemorrhage showed medial disruption on microscopic examination and thus were categorized as class III injury. The severity of injury did not correlate with the duration of implantation. In six cases of medial disruption, the stents were implanted for <5 h. Minimal endothelial injury was observed proximal to the site of the implantation. Vascular histologic findings were normal distal to the site of the implantation. There was no evidence of distal embolization on serial cuts through the myocardium. The stents that were left in place for 6 weeks and 6 months were overgrown with neointimal proliferation (Fig. 5, a and b). Scanning electron microscopy revealed a thin, amorphous layer covering the stents and occasional red blood cells. There were few platelets and fibrin strands (9).

Discussion

Deployment and recovery. This report is the first description of a heat-activated removable temporary stent. Seventy-eight stents were successfully deployed by balloon expansion. The stent had sufficient structural strength to maintain an arterial lumen diameter larger than baseline diameter for the duration of implantation. All 70 stents implanted for up to 1 week were successfully recovered on a coaxially placed catheter. Stents implanted for 6 weeks were not recoverable because of entrapment by neointimal proliferative tissue.

The ease of stent recovery was the most notable characteristic of the device. This was accomplished by briefly flushing the coronary artery with small quantities of crystalloid solution to achieve heating of the stent above its transition temperature of 55°C. The vessel and the device cool quickly to body temperature because coronary blood flow disperses the thermal bolus and results in collapse of the stent to its original dimensions. The dynamic recovery
process (stent collapse) was always well visualized by fluoroscopy. The recovery catheter, with the stent device firmly adherent to it, was successfully withdrawn through the guide catheter or the introducer sheath. There were no instances of device embolization during deployment or recovery. All vessels remained angiographically patent, without evidence of thrombosis or dissection.

**Histologic findings.** Placement and removal of the stent were associated with some evidence of vascular injury at the implantation site in all cases. This was generally limited to focal intimal or medial injury that was localized to the position of stent struts, with preserved intima in the intervening segments. With extreme dilation (≥1.4 to 1 normal diameter), there was disruption of the intima and media, with periadventitial hemorrhage. There was no relation between the extent of vascular injury and the duration of stent placement. Endothelial injury insufficient to cause sloughing proximal or distal to the stent or between regions of strut/vessel contact could have occurred that would not be appreciated on light microscopy. Pathologic findings of permanent stenting and of balloon angioplasty of normal arteries have been well defined (9). The present findings are consistent with a similar degree of vascular injury.

There was no angiographic or gross pathologic evidence of thrombus formation. Histologic study revealed microscopic mural thrombi in one third of the stented sites, and scanning electron microscopic examination of the recovered stents revealed occasional fibrin, red blood cells and platelets. The one experiment in which the dog did not receive aspirin and dipyridamole suggests the importance of antiplatelet therapy. Although the dog was sufficiently anticoagulated with heparin, a stent thrombosed shortly after implantation.

**Prospects for temporary stenting.** Removable metallic stents and permanent nitinol stents have been previously described. A mechanically activated relocatable stent was tested in the inferior vena cava of dogs, but this device is probably too large and too difficult to use in the coronary circulation (10). The very first permanent vascular stent, described by Dotter et al. (11), was made of nitinol (11). The present device differs significantly from the stent of Dotter et al. and its subsequent iterations, which use the thermoeelastic phase change of nitinol as a mechanism to deploy a permanent stent (12). To our knowledge, this report represents the first successful attempt to exploit the austenitic phase transition of nitinol to achieve stent collapse, thus creating a removable temporary coronary stent.

The clinical value of a removable stent has yet to be demonstrated. All metallic coronary stents are capable of restoring flow after acute intimal dissection or suboptimal balloon dilation. There is preliminary evidence that stents may lower the rate of restenosis when implanted in large, previously undilated coronary vessels or vein grafts (13). However, permanent stents are associated with a significantly increased incidence of subacute thrombosis (3% to 27%) that occurs from several days to 4 weeks after implantation (1.2). When stents are implanted as a bailout device after acute closure, the incidence of subacute thrombosis increases to between 16% and 27% (8). Consequently, extensive antiplatelet and anticoagulant therapy is required, which in turn necessitates an expensive, prolonged hospital stay. The antithrombotic measures are associated with a 7% to 10% incidence of major bleeding or vascular complications requiring transfusions or surgery, or both (1.14). A temporary stent may have a role in treatment of flow-compromising intimal dissection because prolonged balloon inflation for between 20 min and 15 h has been reported to stabilize lumen-compromising dissections (15-17). Potentially, intimal "tacking" for several hours to a few days could stabilize the dissection yet still allow the stent to be removed before the time of peak incidence of subacute thrombosis (days 4 to 10). Conceivably, anticoagulation would not be required after device removal, thereby potentially reducing hospital costs and complications related to prolonged anticoagulant therapy. Further study will be
needed to determine whether removing the stent days to hours after implantation confers any of these advantages.

A second application for stenting is to enlarge lumen diameter when balloon angioplasty results are suboptimal (4,8). It is possible that temporary stenting for hours to days could achieve a similar effect. Permanently implanted stents may reduce restenosis by eliminating elastic recoil; however, Schwartz et al. (18) have shown that such stents can also be a potent stimulus for smooth muscle cell proliferation and restenosis. It therefore appears that reduction in restenosis involves a trade-off between maximal lumen expansion and exaggerated intimal hyperplasia. It is conceivable that temporary stenting could inhibit elastic recoil, maintaining lumen expansion without inducing the degree of intimal proliferation associated with a permanent implant. As with the other hypothetic advantages of temporary stenting, these speculations will require extensive preclinical and clinical study.

Study limitations. Our study is preliminary and subject to several significant limitations. 1) The normal canine coronary artery is not necessarily comparable to the diseased human coronary artery. It may be more forgiving of mechanical intervention. Conversely, it is probably more prone to medial rupture under the study circumstances because the stents had to be expanded to a size greater than the vessel to ensure implantation in these normal vessels. 2) Our study did not examine the capability of this device to “tack” intimal dissections or to produce sustained vascular dilation after removal. On bench testing, the expanded device endures greater radial compressive force than is endured by currently available balloon-expandable stents. The device reported here is a handmade prototype that, when fully expanded, leaves substantial vascular surface unsupported. A refined version of the device is now being fabricated from nitinol tubing, which will have a transition temperature of 45° to 48°C and a geometric configuration similar to the slotted tube design of the Palmaz-Schatz stent. This new device may thus share many mechanical properties of the Palmaz-Schatz stent, with the added advantage of being removable. These issues will require careful evaluation in subsequent studies.

Summary. We have demonstrated the feasibility of a new method for temporary stenting of the coronary arteries that uses the special thermoelastic properties of nitinol to permit satisfactory deployment, balloon expansion and recovery of the device in normal canine coronary arteries. Extensive further research will be required to determine whether temporary stent placement has useful clinical applications.

References