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Temporary Arterial Stenting: Comparison to Permanent Stenting and Conventional Balloon Injury in a Rabbit Carotid Artery Model

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The objective was to assess the arterial wall response to temporary stenting with a removable nitinol stent in comparison with permanent stenting and balloon injury at 28 days in the rabbit carotid artery. Restenosis remains an important limiting factor after the implantation of permanent metallic stents and balloon angioplasty. We have developed a temporary nitinol stent that uses a bolus injection of warmed saline to collapse the stent for percutaneous removal. Vascular changes related to the thermal saline bolus injection required to remove a nitinol implanted stent were assessed in 12 rabbit carotid arteries at 7 and 28 days postinjection. Nitinol stents, inflated to 3.0 mm diameter, were implanted for 3 days (n = 6) and histology and quantitative histomorphometry examined at 28 days. Results were compared with permanently implanted stents (n = 5) and balloon injury (n = 9). Dual bolus injection of 10 ml at 70°C created an acute necrotizing injury and chronic neointimal proliferation, whereas injections of 5 ml at 63°C were minimally injurious. Temporary stenting resulted in the least neointimal proliferation measured by the intima to media ratio (0.22 ± 0.10 vs. 1.59 ± 0.31 for permanent stenting and; 0.49 ± 0.14 for balloon injury; $P < 0.001$). Temporary stenting maintained a significantly larger lumen than balloon (1.53 ± 0.72 mm^2 vs. 0.64 ± 0.14 mm^2; $P < 0.001$), which could not be explained by absolute changes in intimal cross sectional area (0.14 ± 0.07 mm^2 vs. 0.21 ± 0.06 mm^2 respectively; $P = 0.33$). Temporary stenting resulted in a relatively larger vessel area within the external elastic lamina than with balloon (2.28 ± 1.06 mm^2 vs. 1.30 ± 0.18 mm^2; $P = 0.007$). The thermal stent recovery process can create necrotizing vascular injury and neointimal proliferation at higher temperatures and injectate volumes. Stent removal after 3 days using 63°C saline bolus injection results in less neointimal proliferation than with permanent stents or balloon injury. In comparison to balloon injury, temporary stenting also may have a long-lasting beneficial effect on vessel recoil and remodeling, resulting in larger lumen size after stent removal. *Cathet. Cardiovasc. Diagn. 41:85–92, 1997.* © 1997 Wiley-Liss, Inc.

Key words: temporary stenting; carotid artery model; balloon injury

INTRODUCTION

Stenting of diseased coronary arteries and saphenous vein grafts with metallic permanent implants is safe, effective, and now a routine method of revascularization, which reduces angiographic and clinical restenosis [1–5]. Restenosis rates, however, remain a problem, especially in small vessels. Stents virtually eliminate restenosis due to elastic vessel recoil and remodeling, but late loss due to neointimal proliferation is actually greater after stenting compared with balloon angioplasty [4–7]. We have previously described temporary stenting with a prototype nitinol removable stent. This device uses a thermal bolus injection to collapse the stent to its predeployed diameter [8]. It was constructed of multiple segments of shape-memory, nickel-titanium alloy and stainless steel crimped together. This stent was constructed for testing basic concepts of removability and was not thought to be a clinical device. We have subsequently developed a slotted tubular stent design constructed from 100% nitinol as a single piece tubing that can be used clinically as a permanent or temporary device. The potential advantages

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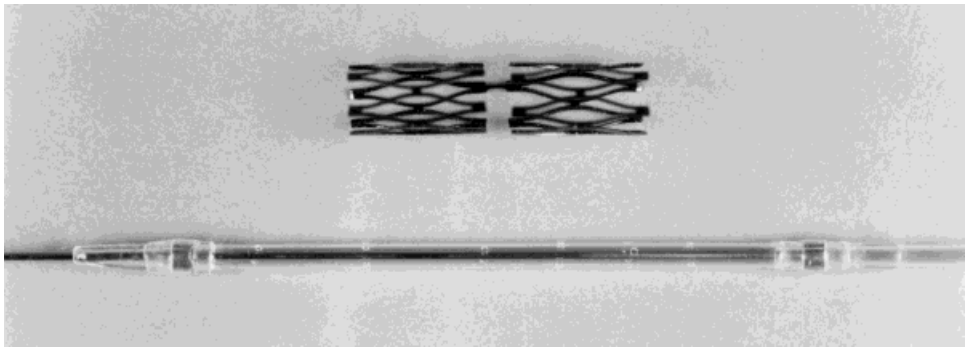

Fig. 1. Photograph of the heat-activated removable temporary stent (HARTS™) expanded to 3.0 mm. Below the stent is the distal section of the recovery catheter with a 0.014″ guidewire in place. Multiple sideholes for flushing the arterial lumen with warm saline are seen in the stent "landing zone" between the radiographic gold band markers.

over the previous device could include lower profile, greater stent flexibility, and possibly reduced thrombogenicity.

Our hypothesis is that temporary stenting may result in less neointimal proliferation than permanent stenting or conventional balloon injury. Using a rabbit carotid artery model, our specific goals were: (1) to determine if the thermal recovery process induces vascular injury with a subsequent healing response, and (2) to compare arterial injury and intimal thickening created by temporary stenting with permanent stenting and balloon injury.

MATERIALS AND METHODS

Stents

Heat Activated Removable Temporary Stents (HARTS™, Advance Coronary Technologies, Menlo Park, CA), made of the nickel-titanium alloy-nitinol, were used as either temporary or permanent implants. The stents have a slotted-tube design comprised of two 7 mm segments joined by a 1 mm articulated bridge (Fig. 1) and are balloon expandable up to 6.0 mm in diameter. Stents were mechanically crimped on 3.0 mm diameter, 20 mm long, balloon catheters (Progressive Angioplasty Systems, Menlo Park, CA). Transient heating of an expanded stent to 53°C induces crystalline phase transition with thermoelastic collapse of the device to its predeployment diameter. Stent removal is accomplished by placing a 3.5F multiple side-hole stent recovery catheter (Fig. 1) coaxially through the deployed stent and hand injection of 5 ml of saline heated to 63°C.

Animal Models

Animal experiments conformed to the guidelines of the American Physiological Society and were approved by Cedars-Sinai Medical Center Institutional Animal Care and Use Committee. Normolipemic adult male New-Zealand White rabbits (3.5–4 kg) were anesthetized by intravenous xylazine and ketamine. A 6F sheath was placed in the right femoral artery by cutdown, and heparin (500 units) was given. No antiplatelet agents or additional anticoagulants were administered. The site of arterial injury (thermal, balloon, or stent injury) was marked on the shaved rabbit neck with an indelible dye.

Thermal Injury Studies

Thermal loss through the recovery catheter was previously calibrated in rabbit carotid and pig coronary arteries ($n = 49$) using a thermocouple attached to its distal tip. Using hand-injections of 5 ml ranging from 63°C to 90°C, there was a strong linear correlation ($r = 0.96$) between catheter input temperature (T_{input}) and the peak vessel exit temperature (T_{output}), as estimated by the regression equation:

$$T_{output} = 0.75\ T_{input} + 8.5$$

The effects of the thermal recovery process in the absence of stent placement were studied in 12 rabbits. A recovery catheter was advanced over a 0.014 guidewire to the right carotid artery under fluoroscopic control. Ten ml plastic syringes filled with 0.9% saline were incubated for 15 min at specified temperatures (63°C, 65°C, 70°C) in a thermostatistically controlled syringe heater. In each rabbit, a syringe was quickly connected to the luer lock of the recovery catheter and a specified volume (5 or 10 ml) was rapidly injected. A similar thermal injection was repeated 1 min later. The animals were subsequently euthanized at 7 days or 28 days after thermal bolus injection.

Device Specific Studies

Three device injury models were studied: Group A ($n = 6$) consisted of temporary stents implanted for 3 days; Group B ($n = 5$) had permanently implanted stents;

and Group C (n = 9) had balloon dilatation to assess arterial wall response after balloon injury.

Stents were deployed by two consecutive balloon inflations of 30 sec at 6 atm. For stent recovery, a second anesthetic procedure was performed. A recovery catheter was placed across the deployed stent and a single 5 ml bolus of saline at 63°C collapsed the stent. The stent and the catheter were then withdrawn as a unit through the sheath. In group C, balloon injury was created with an identical 3.0 mm-diameter, 20 mm-length stent delivery system inflated at 6 atm pressure for 10 min.

Animals were euthanized at 28 days under general anesthesia. The carotid artery segments were removed en bloc and pressure fixed in 10% formalin. Arterial segments from groups A, C, and the thermal injury experiments were cut into 5-μm- thick cross sections at 3 mm intervals and stained with hematoxylin and eosin. Segments with permanent stents (Group B) required special processing to maintain the vascular architecture with metallic struts in situ [9]. Tissue blocks, cut with a diamond wafering blade, were embedded in methyl methacrylate. Sections were ground to a thickness of ~30 μ, optically polished and stained with toluidine blue (paragon stain). Sections were examined by an experienced cardiovascular pathologist (MCF).

Morphometric Analysis

Three to four sections from each vessel were analyzed with a computer-assisted morphometric program (Optimas, Bioscan). The mean cross-sectional areas of the lumen, intima, media, and vessel within the eternal elastic lamina were calculated for each artery. The area occupied by the stent struts was measured and subtracted to yield a net cross-sectional area. Intimal proliferation was also expressed relative to other measurements including the ratio of intima to media areas, and the residual lumen, calculated as the lumen area divided by the sum of the lumen and intima areas $\times$ 100.

Statistical Analysis

Multiple groups were by one-way analysis of variance (ANOVA). If significant differences were detected ($P < 0.05$), posthoc, pair-wise comparisons were performed by the adjusted t-test within ANOVA (Bonferoni test). Analysis of scattergram plots was performed using linear regression analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Thermal Bolus Experiments

Dual injections of 10 ml at a catheter input temperature of 70°C resulted in circumferential, transmural medial necrosis with acute inflammatory cell infiltration at one week. There was no vacuolization, carbonization, or basophilia. There was mild adventitial granulation and fibrous tissue proliferation. At 1 month, the histologic findings were prominent focal intimal proliferation in conjunction with underlying regeneration of medial smooth muscle cells (Fig. 2). Arteries injected with 2 boluses of 5 ml at 65°C showed no evidence of medial necrosis or inflammation at either time period. There was mild focal neointimal proliferation at 1 month. Arteries injected with two boluses of 5 ml at 63°C appeared normal at 1 week compared to noninjected contralateral controls. At 1 month, a single layer of hyperplastic endothelial cells covered the internal elastic lamina. There was no medial injury or inflammatory response. Two sections demonstrated small foci of neointimal proliferation (Fig. 2). There was no evidence of thrombi in any of the sections obtained at 1 week or 1 month postsaline injection.

Device Specific Injury Experiments

In the temporary stent group, radially distributed indentations, marking the sites of previous stent contact, were visible at 28 days. The internal elastic lamina remained intact in all sections taken from four stented arteries. There was occasional focal coagulative smooth muscle cell necrosis at the locations of previous stent strut contact. There was minimal neointimal growth, which tended to be localized over the foci of necrotic media (Fig. 3). There were no intraluminal or mural thrombi.

After permanent stenting, the struts were completely covered by neointima in all stented segments (Fig. 4a, b, c). The neointima was composed of morphologic smooth muscle cells and neovascularization was sometimes prominent around the struts. Occasional, microscopic organized mural thrombi were present and an organized intramural hematoma was noted in one section. Sections taken from two arteries showed focal medial necrosis with hemosiderin deposits and segmental breaks of the internal elastic lamina associated with the most deeply implanted struts. Intimal proliferation varied considerably between regions containing the struts and the intrastrut spaces with the latter showing relatively milder neointimal thickening. No foreign body reaction or inflammatory response surrounding the stent wires was seen.

At 1 month after balloon injury, there was mild to moderate neointimal proliferation overlying foci of necrotic media (Fig. 3). Deep medial injury was seen less commonly than after stent implantation. Sections taken from six arteries showed an intact internal elastic lamina.

Quantitative Morphometric Analysis

Table I summarizes the morphometric parameters at 28 days after device specific vascular injury. Permanent stents had the most intense neointimal proliferation. The

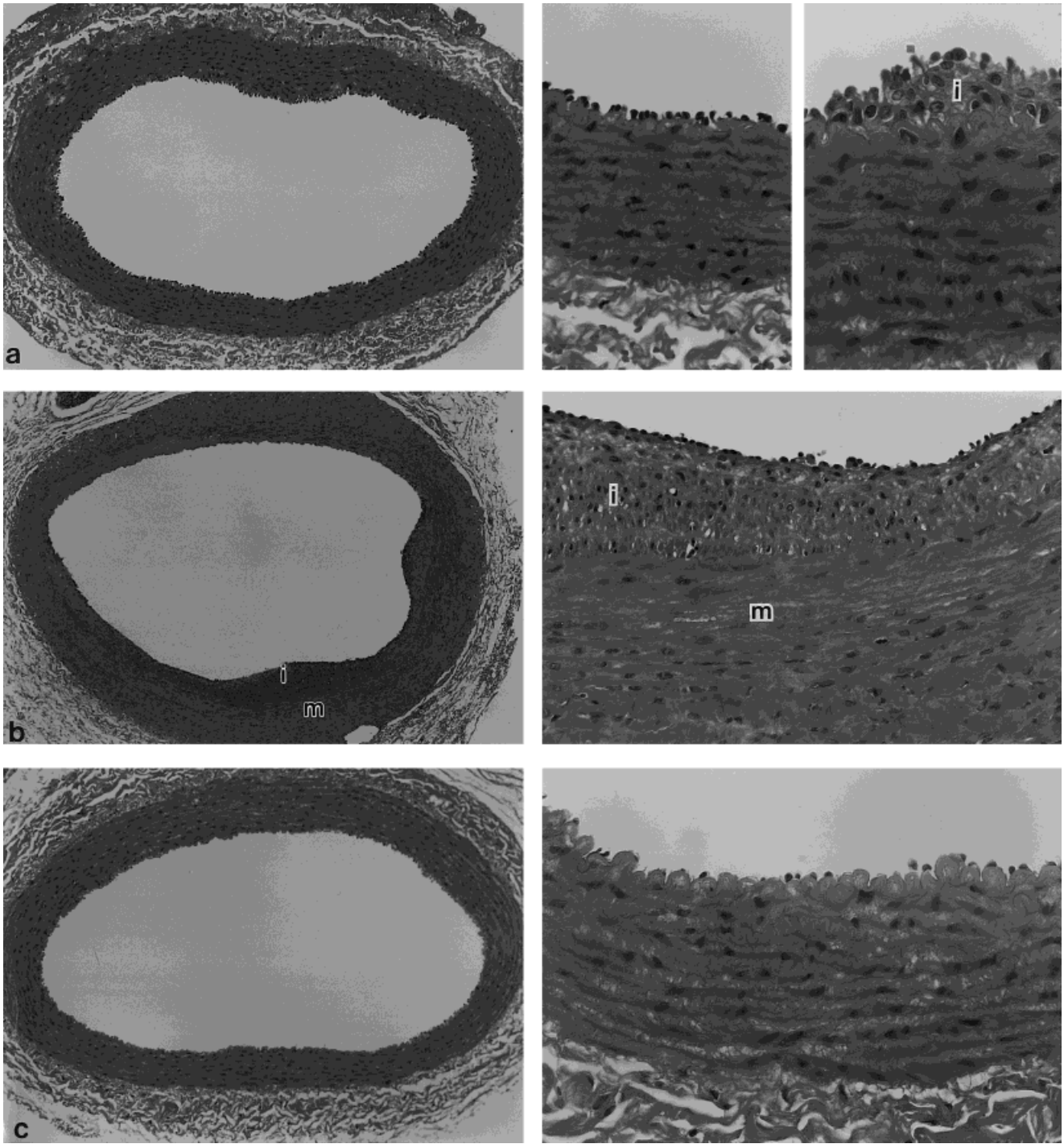

Fig. 2. Thermal injury histology. (a) Representative histopathology sections (hematoxylin-eosin stain 10×) of carotid artery at 4 weeks after injection of 5 ml saline heated to 63°C (left upper panel). Most of the intimal circumference was composed of hyperplastic endothelial cells (center upper panel ×50) with occassional small foci of intimal proliferation (*i*, right upper panel). (*b*) Representative low- (left 10×) and high-power (right 100×) sections of the right carotid artery 4 weeks after intraluminal injection of a 10 ml bolus of saline heated to 70°C. Medial necrosis (*m*) and a thick layer of neointimal proliferation (*i*) are visible. (*c*) Low- (10×) and high-power (100×) photomicrographs of the control left carotid artery at 4 weeks after injection of a 5 ml bolus of saline heated to 63°C into the right carotid artery. The artery shows normal histologic structure. Note the difference between the hyperplastic endothelium in (*a*) compared with the normal endothelial appearance in (*c*).

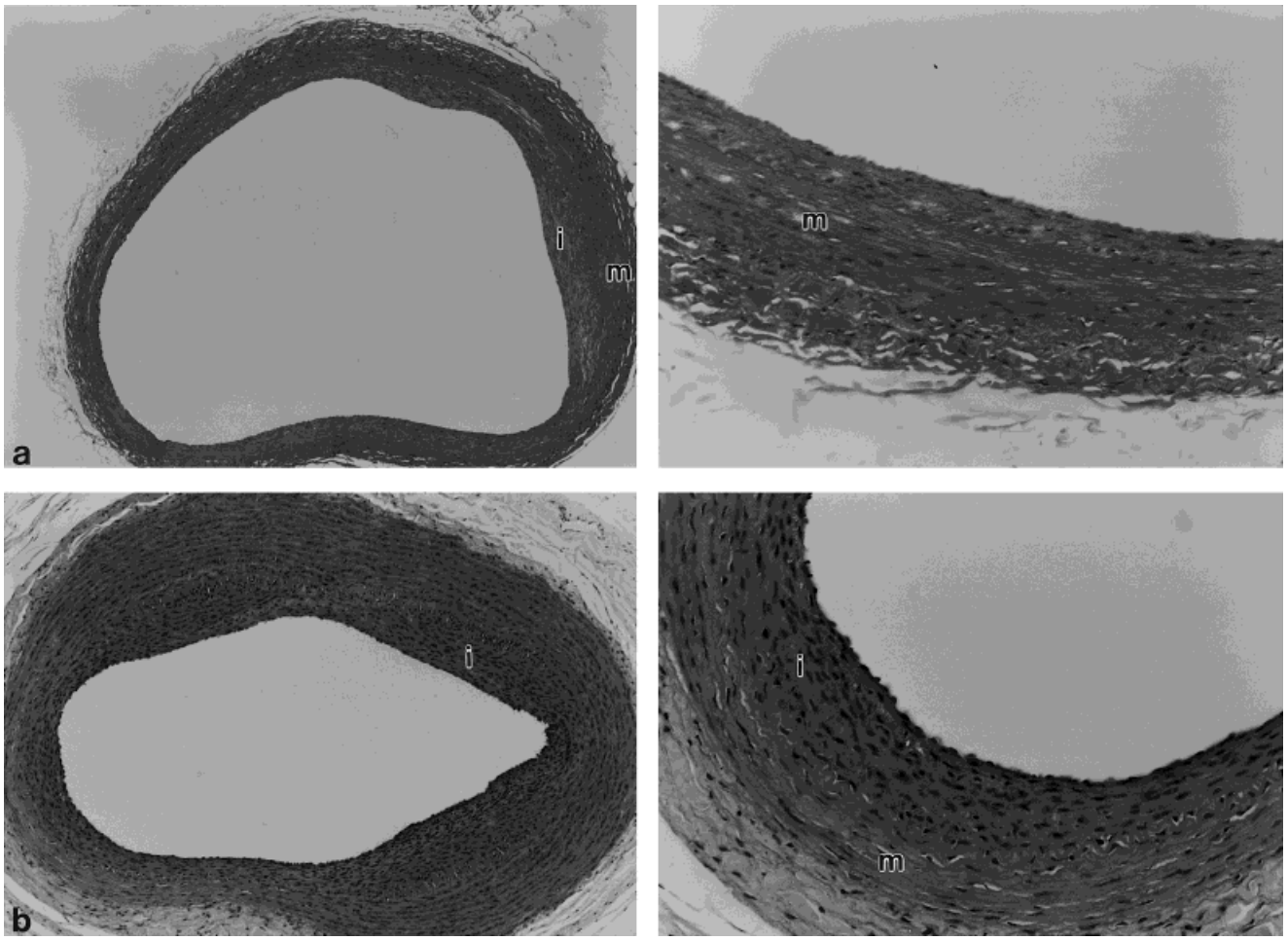

Fig. 3. Temporary stenting (*a*) and balloon injury (*b*). (a) Temporary stents (group A). Low- (10×) and high-power (100×) photomicrographs obtained at 4 weeks posttemporary stenting for 72 hr. Loss of smooth muscle cells can be detected in the medial layer (*m*) and the original structure of the media is disrupted. (b) Representative sections obtained at 4 weeks after balloon injury (Group C). Low- (10×) and high-power (100×) photomicrographs show concentric highly cellular neointimal proliferation (*i*) with foci of medial necrosis (*m*, right panel).

intimal layer covering the stent struts had on average thickness of 90 ± 5 μm. The intimal area after temporary stenting was significantly less than with permanent stents (5×) or balloon injury (1.5×). The medial area did not differ between temporary and permanently stented arteries and balloon-injured vessels. The ratio of intima to media showed a significant reduction with temporary stenting compared with permanent stents (7×) and balloon-injured vessels (2.2×). As expected, permanent stent sections that were not subject to fixation shrinkage had the largest lumen area and area within the external elastic lamina. Temporary stenting maintained a significantly larger lumen than balloon (1.53 ± 0.72 mm^2 vs. 0.64 ± 0.14 mm^2; $P < 0.001$), which could not be explained by changes in neointimal proliferation (0.14 ± 0.07 mm^2 vs. 0.21 ± 0.06 mm^2, respectively). The residual lumen, however, which relates lumen lost to neointimal proliferation, was best maintained in the temporary stent group, 92% compared with 75% in the two other groups. The area within the external elastic lamina was significantly greater (1.7×) with temporary stenting compared to balloon injured vessels (2.28 ± 1.06 mm^2 vs. 1.30 ± 0.18 mm^2; $P = 0.007$).

DISCUSSION

This study in the rabbit carotid artery model is one of several preclinical trials designed to evaluate the feasibility of temporary stenting with removable nitinol stent as an alternative to permanent stenting. The salient findings from these data are: (1) the thermal bolus recovery process must be controlled for injectate temperature and volume to avoid necrotizing vascular injury and subsequent neointimal proliferation, (2) rapid injection of 5 ml

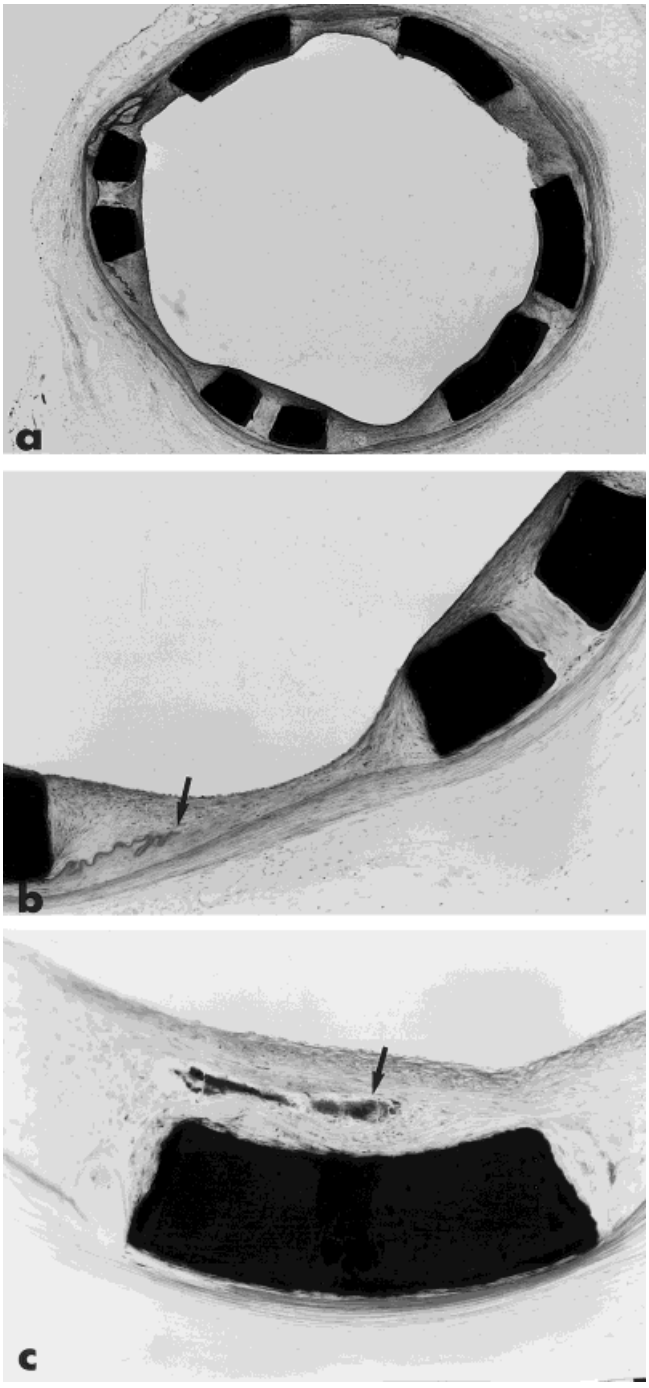

Fig. 4. Permanent stent sections. (a) (10×) shows mild intimal proliferation over the stent struts, and absence of inflammation; (b) (20×) shows a break in the internal elastic lamina; (c) (66×) deposition of hemosiderin pigment (all paragon stain).

of saline preheated to 63°C recovers the stent without additional thermal injury, (3) temporary stenting resulted in less late lumen loss due to neointimal proliferation than permanent stenting or conventional balloon angioplasty injury, and (4) the larger lumen seen after temporary stenting compared to balloon injury can in part be explained by less neointimal proliferation but may also be related to an effect on recoil or remodeling.

Neointimal Response to Intravascular Stenting

Previous animal model studies have shown that permanent stent implantation creates more severe arterial damage, which is associated with more abundant and prolonged neointimal smooth muscle cell proliferation than balloon injury [10–12]. We also documented increased vascular damage and neointima formation with permanent stenting relative to balloon injury despite using similar diameter and pressure balloon inflations. Although both stent groups would be expected to have similar extent of acute vascular injury, temporary stenting for 3 days was associated with a significant ($>5\times$) reduction in neointimal proliferation compared with permanent stents. This finding suggests that the chronicity of the injury or the maintenance of the foreign body response in the presence of the arterial injury plays an important role in modulation neointimal proliferation. Permanent stents may act as chronic stimulus for prolonged duration of proliferative response even when the stent surface is completely endothelialized [10,11,13]. Removing the stent within several days may facilitate vessel healing to progress more rapidly as with conventional balloon angioplasty. The most intriguing findings in this study, however, were in the comparison of temporary stenting to balloon injured vessels. The two types of injury were similar with respect to balloon diameter and inflation pressure but different in respect to duration (10 min for balloon vs. 3 days for the stent) and localization of the applied expansion force (more diffuse for balloon, more focal for stent). Temporary stenting was associated with significantly less intimal proliferation than balloon injury as measured by the intimal area, intima to media ratio, and residual lumen. The greater reduction of lumen area seen with balloon injury cannot be accounted for by intimal thickening. The reduced area within the external elastic lamina with balloon injury compared to temporary stenting suggests that the lumen loss may have been due to more recoil or remodeling.

Important unanswered questions remain about why temporary stenting would create less intimal proliferation or remodeling than balloon. We postulate that stent implantation produces focal, distributed medial injury with less stretch injury to the segments between struts. Stent removal allows repair of the media and internal elastic lamina such that intimal proliferation is also focal. This mode of injury may be more analogous to the cutting balloon device described by Barath et al. [14], which creates localized medial incisions and repair in the form of intimal proliferation at the incision site. Balloon angioplasty, however, causes a circumferential overstrech

TABLE I. Morphometric Parameters at 28 Days After Device-Specific Vascular Injury

	Group A temporary stent	Group B permanent stent	Group C balloon	ANOVA *P*-value	Posthoc t-test $P < 0.05$
No.	6	5	9		
Intimal area (mm^2)	0.14 ± 0.07	0.78 ± 0.29	0.21 ± 0.06	<0.001	A vs. B B vs. C
Medial area (mm^2)	0.62 ± 0.35	0.58 ± 0.27	0.44 ± 0.05	0.33	—
Intima/media ratio	0.22 ± 0.10	1.59 ± 0.31	0.49 ± 0.14	<0.001	all groups
Lumen area (mm^2)	1.53 ± 0.72	2.46 ± 0.20	0.64 ± 0.14	<0.001	all groups
Residual lumen (%)	92 ± 3	75 ± 8	75 ± 5	<0.001	A vs. B A vs. C
EEL[a] area (mm^2)	2.28 ± 1.06	3.83 ± 0.31	1.30 ± 0.18	<0.001	all groups

[a]External elastic lamina.

injury to most of the media resulting in a more diffuse healing response. The transient scaffolding effect of temporary stenting may act similar to prolonged balloon inflation, thus reducing vascular recoil. The current data is insufficient to separate immediate recoil from more chronic remodeling mechanisms.

Study Limitations

The present model illustrates potential mechanistic differences between devices. In the absence of performing similar studies in atherosclerotic coronary vessels, no extrapolation to human coronary artery disease is currently reasonable. Comparisons to the permanently stented group requires particular caution because of important methodological differences. Due to difficulty in sectioning arteries with stents in situ, tissue processing of permanently stented segments differed from temporary stents and ballooned vessels. In the latter two cases, there is expected to be shrinkage artifacts due to fixation and dehydration that can result in ~40% decrease in lumen area [15,16]. Such artifacts, however, would be expected to introduce bias in favor of smaller lumen dimensions with temporary stents and balloon-injured vessels. Shrinkage artifacts should have much less effect on relative parameters such as intima to media ratios or the residual lumen calculations, thus allowing us to make comparisons among the three groups. The same shrinkage artifact makes it impossible to compare remodeling parameters after temporary and permanent stenting. Finally, although there is are prior data that suggest inflation time alone is a factor related to degree of vessel injury, an exaggerated effect due to the 10-min duration of balloon inflation as compared with the two 30-sec inflation in the stented arteries cannot be excluded. These limitations not withstanding, the present data suggest that temporary stenting may result in less neointimal proliferation and remodeling than balloon injury. These findings now need to be reproduced in a coronary model with shorter, <24-hour duration implantation of the temporary stent, to simulate a more practical application. If subsequent studies confirm these preliminary results, a clinical trial of temporary stenting particularly in small vessels (<3.0 mm reference diameter) may be warranted.

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