A View of Vascular Stents

Richard A. Schatz, MD

Despite innovative new techniques in percutaneous transluminal coronary angioplasty (PTCA) during the past 10 years, restenosis rates continue to occur at about 30% in subtotal lesions,1 about 50% in chronic total occlusions,2 and up to 80% in saphenous vein bypass grafts.3 Although mortality remains acceptably low, urgent bypass surgery after unsuccessful angioplasty continues to be necessary in up to 4% of patients with a significant morbidity.4

The purpose of this article is to evaluate vascular stents as a possible solution to abrupt closure and restenosis in humans. Early experimental work and clinical experience to date with various stents are considered, with particular focus on the stents developed by Dr. JC Palmaz and colleagues at the University of Texas Health Science Center, San Antonio, Texas.

Background

Dotter introduced the concept of stents when he published his landmark paper in 1964 on transluminal angioplasty. “Once a pathway has been created across the occluded segment, repeated dilatation or the temporary use of a Silastic endovascular (or, in some cases, paravascular) splint could maintain an adequate false lumen until natural processes of fibrosis and reimplantation have taken place. We believe reimplantation is as likely to occur on the walls of a lumen formed by the patient’s own tissues as on the fibers of a plastic prosthesis.”5 He later used stainless steel and then Nitinol coils in peripheral arteries of dogs with surprisingly good results.6,7 A number of stent designs by various investigators were developed thereafter, but each failed to maintain patency because of bulky and cumbersome profiles, unpredictable expansion, abrupt thrombosis, or gradual restenosis from intimal hyperplasia.8-12

Three stent designs are currently under investigation for use in coronary arteries. The first is a spring-like design that can be constrained to a small diameter and then can be expanded to a predetermined dimension when the constraint is removed13 (Figure 1A). Thermal memory stents are a second design. Such stents expand from small to large diameters by virtue of the peculiar properties of metal such as Nitinol, which changes shape upon heating.7,8 Originally pioneered by Palmaz et al,14-19 balloon expandable stents represent the third design, and these rely on plastic deformation of metal beyond its elastic limit (Figure 1B). Thus, once the metal is stretched beyond a certain limit, it cannot collapse.14-28

Gianturco later developed a stent with features of spring loading and balloon expandability (Figure 1C), which was reported by Roubin et al.29

The potential advantages of the Palmaz design over others were 1) ease of delivery, 2) an expansion ratio up to 6:1, 3) a streamlined profile (0.003 in.), 4) a minimal amount of metal comprising the surface area when expanded (10%), and 5) reliable expansion. Initial experimental and clinical success with this stent has been documented.14-28 In animal implants, biocompatibility has been shown with atherosclerotic rabbit aortas, surgically induced elastic lesions of canine and pig renal arteries, and normal canine coronary and pulmonary arteries.18,19,22,24 The cellular and histologic response to the stent in each model showed that as long as the outflow of the artery was maintained a sequence of mild thrombus formation, fibroblast proliferation, and growth of viable endothelium occurred. In diseased rabbit aortas, restenosis was not found at 6 months; instead, the stent became a scaffold on which a thin layer of nonobstructive fibromuscular tissue covered by endothelium grew.18 Schatz et al22 reported similar histologic findings in stented coronary arteries of normal dogs.

Because the amount of thrombus deposited initially may influence subsequent neointimal growth, an analysis of thrombogenicity merits discussion. Before investigation on humans, Palmaz et al28 tested the thrombogenicity of their design by treating 64 dogs who had undergone hind leg artery implants with various anticoagulation regimens. According to 111In-labeled platelet scans and gross inspection, stents in animals treated with aspirin, dipyridamole, heparin, and dextran showed consistently less thrombus than stents from controls and animals given various combinations of heparin, aspirin, and dipyridamole (Figure 2). The study

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FIGURE 1. Photograph of a spring-loaded stent (Medinvent) (Panel A). Reproduced with permission. Balloon expandable intravascular stent (Johnson and Johnson) (Panel B). This coronary stent prototype is 1.5 mm in diameter collapsed and 15 mm in length but can expand to 6 mm in diameter. Reproduced with permission. Variation of a balloon expandable stent (Cook) (Panel C). Reproduced with permission.
suggested that dextran contributes to reduced thrombogenicity and optimal neointimal growth by preventing uncontrolled platelet and thrombus deposition in stainless steel vascular stents. More important, the study shed light on the mechanisms of biocompatibility of these devices with regard to metal-blood interaction.

Need for Controlled Thrombosis

The success of a vascular stent should depend on minimal thrombosis and rapid endothelialization. After routine angioplasty, there is usually intimal or medial dissection or both and exposure of the subintimal space to the blood elements. This results in platelet deposition followed by thrombus formation, fibroblast proliferation, and intimal hyperplasia. Local disruption of laminar flow due to irregular intimal tears probably contributes to excessive platelet and fibrin deposition as well. Ultimately, with further thrombosis and intimal hyperplasia, restenosis occurs. The stent may represent a scaffold on which orderly thrombosis can occur without exposing large amounts of the subintimal space and without disruption of laminar flow. A recent study in human cadavers has suggested the ability of the expandable stent to tack up intimal debris and seal off the subintimal space (Figure 3).23

Because endothelium cannot grow on bare metal but can develop on a thin layer of fibrin and thrombus, thrombosis is essential for healing, but it must be controlled. Brisk antegrade flow appears to allow the dynamic process of fibrin deposition and lysis to occur in an orderly fashion, and ultimately, should allow endothelial cells to proliferate as rapidly as possible with the least amount of intimal hyperplasia. In our experience, intimal thickening plateaus by about 6 months and can be considered the footprint of biocompatibility. This thickening is not expected to exceed 50–100 μm for small stents in the coronary arteries; more extensive neointimal growth may be related to increased metal surface area, wire thickness, turbulence, or cyclical intimal trauma from constantly flexing spring-like devices.31 Stents with sliding metal filaments in constant contact may retard the development of an endothelial cover by preventing a uniform fibrin coating. Such

FIGURE 2. Photographs of stents harvested 3 hours after implantation that were randomized to no anticoagulation (Panel A), heparin, aspirin, and dipyridamole (Panel B), and heparin, aspirin, dipyridamole, and dextran (Panel C). There is striking absence of visible thrombus in Panel C.
FIGURE 3. Microphotograph of dilated but not stented human cadaver coronary artery with a typical intimal and medial dissection and lumen collapse (Panel A). Dilated and stented human cadaver coronary artery with a large intimal and medial tear “tacked up” by stent struts (Panel B) (arrow).
metal contact poses the additional problem of accelerated corrosion (fretting) as reported for other metal prostheses.\textsuperscript{32}

**Abrupt Closure and Restenosis**

Abrupt closure after failed PTC is usually the result of a combination of dissection, spasm, and thrombosis.\textsuperscript{33} With proper attention to stent design and anticoagulation, mechanical prostheses could prevent these problems.

The question of why a metal prosthesis should prevent late restenosis has not been fully answered, but analysis of data in animals and humans may provide some clues. In stented arterial segments, whether normal or diseased, analyzed microscopically by Palmaz and Schatz,\textsuperscript{19,22} a consistent histologic feature has been atrophy of the media during a 6-month period. This observation suggests that this muscular layer is no longer exposed to pulsatile stretch because wall stress is borne in part by the stent. Similar thinning of the media in heavily diseased coronary arteries of humans has been reported.\textsuperscript{34} In cholesterol-fed rabbits that received balloon expandable intravascular stents in diseased aortas that were observed for as long as 6 months, there was no restenosis in the stented section of the aorta, and optical analysis showed the plaque to be confined between the neointima and the atrophic media (Figures 4A and 4B).\textsuperscript{18}

In a recent study, Thubrikar and colleagues\textsuperscript{35} looked at a similar model in a different way. By first externally "casting" segments of rabbit aortas exposed to high wall stress (e.g., iliac bifurcations and renal artery ostia) and then by feeding the animals high cholesterol diets, they found relative absence of plaque in the casted compared with noncasted sections at autopsy. Thus, relief of wall stress externally by casting appeared to prevent or retard atherosclerosis development, whereas internal stenting appeared to confine the atheroma outside the stent yet inside the atrophic medial layer.

Other experimental and clinical observations tend to support these conclusions. The contribution of hypertension to abnormal wall stress and atherosclerosis is well documented.\textsuperscript{36} At necropsy, coronary arterial segments encased by a myocardial bridge have been noted to be free of atherosclerotic narrowing compared with segments of the same artery not encased by the bridge (Dr. Jeffrey Isner, personal communication). Arterial segments distal to high-grade vascular stenoses tend to show less atherosclerosis than do proximal segments.\textsuperscript{37} In each of these cases, arterial segments exposed to reduced wall stress seem less vulnerable to the atherosclerotic process. Nonflexing stents may create a localized region of reduced wall stress, thus inhibiting the cascade of events producing atherosclerosis. Perhaps, the media contribution to intimal hyperplasia and the atherosclerotic invasion of the subintimal space by smooth muscle cells are diminished in this model because of gradual atrophy. Thus, some theoretical support exists for the possible long-term reduction of restenosis based upon these observations.

**Desirable Stent Characteristics**

It is too early in the course of clinical trials to compare the various stents; even data from animal experiments are too sparse to warrant critical comparison. Nonetheless, certain design characteristics can be considered when evaluating results.

Table I summarizes the desirable characteristics of design for various vascular stents. A discussion of each characteristic follows.

**Flexibility**

There is no question that any stent design must incorporate flexibility as a principal feature for coronary artery implantation. Not only must the stent pass easily through the guiding catheter, it must pass through tortuous coronary arteries to arrive reliably at the target site. Roubin et al\textsuperscript{29} reported their experience with a flexible wire coil wrapped around a delivery balloon. Early results in 18 arteries of dogs was encouraging; in follow-up, however, intimal hyperplasia of 200–400 \( \mu \)m developed. Rousseau et al\textsuperscript{38} have reported similar intimal thicknesses at 6 months with a multifilamented self-expanding metal spring-like device. In both these flexible designs, two explanations for this degree of intimal thickening are possible. First, a relatively high concentration of metal may attract more thrombus early, thereby stimulating neointimal proliferation later. Second, in vitro studies have shown a specific collagen and medial cell turnover when vascular surfaces are exposed to multiple cycles of mechanical stress.\textsuperscript{31} Constantly flexing springs may result in cyclical intimal trauma and subsequent intimal hyperplasia.

Thus, flexibility, though an advantage, may come with the disadvantage of excessive intimal hyperplasia. A stent should be flexible enough to pass through narrow, tortuous passageways and yet, after expansion, still maintain a relatively stable, nonflexing, and nonshifting surface on which endothelial cells and neointima can grow most efficiently. One possible solution is shown in Figure 5. A modified Palmaz stent consisting of multiple short segments allows for "articulation" around bends of both guiding catheters and coronary arteries, but once expanded, it becomes a stable surface. It is, therefore, longitudinally flexible but radially noncompliant. Preliminary animal and human trials suggest that such a device can be used in curved segments of coronary arteries without complication.\textsuperscript{39}

**Biocompatibility**

Although flexibility is essential, equally important are biocompatibility and thromboresistance. The "Achilles heel" of stents in humans will surely be acute thrombosis. Therefore, a brief discussion
Figure 4. Microphotograph of cross section of an atherosclerotic rabbit aorta 1 week (Panel A) and 6 months (Panel B) after stenting. Note the thin layer of thrombus (T) covering the stent struts (*) and the thick media (M) at 1 week. By 6 months, thrombus is replaced with acellular ground substance and endothelium. A large plaque is evident (arrows) but does not encroach the lumen.
TABLE 1. Characteristics of the Ideal Stent

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<td>Flexibility</td>
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<td>Biocompatibility</td>
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<td>Thrombosis resistant</td>
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<td>Minimal neointimal growth</td>
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<td>Good visibility</td>
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<td>Reliable expandability</td>
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of metallurgic and rheologic principals is warranted as they relate to thrombosis.

Blood and metal compatibility has been studied previously. Briefly summarized, most metals are electropositive and, therefore, thrombogenic because blood elements are negatively charged. These metals are also relatively resistant to corrosion. Conversely, electronegatively charged metals are thromboresistant but highly susceptible to corrosion. The relative thrombogenicity of metals can be offset by various surface treatments to improve surface texture. Thus, certain positively charged metals, such as surgical stainless steel, are still considered desirable biomedical products.

In light of these facts, a metal stent should have 1) minimal surface area, 2) low surface potential, 3) minimal impurities, 4) a specularly smooth surface free of contaminants, 5) low profile, and 6) immunity to fatigue and corrosion despite millions of cycles of stress.

Visibility

A limitation of all stents in this analysis is lack of visibility under fluoroscopic guidance because of small mass. Although newer high-resolution imaging systems will increase visibility, most conventional systems may prove inadequate. This limitation may have serious consequences for placement of the stents. Not only may the “target” lesion be missed, but those instances may escape detection in which the stent “slips” from the delivery system during passage through the guiding catheter and, thus, fails to reach the target site.

At first glance, the solution to this problem of increasing the opacity of these devices appears simple. However, metals such as gold and platinum, which are more radiopaque, have other drawbacks (elastic modulus and expense) as vascular prostheses. Interestingly, tantalum has an ideal elastic modulus that makes it suitable for balloon expandability but not for spring loading (Figure 6). Biocompatibility testing of tantalum is not complete at this time; if, however, it proves to have characteristics similar to or better than stainless steel, it may become the metal of choice for balloon expandable vascular stents.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Photograph of articulated balloon expandable stent. Shorter segments in tandem can be delivered simultaneously. Spaces between segments allow for “articulation” around bends.
Reliable Expandability

Devices that cannot be accurately and reliably expanded to a precise and predetermined diameter (Nitinol, self-expanding springs) have an added risk of undersizing, resulting in stent migration and embolization or of oversizing, leading to progressive intimal or medial trauma. Incomplete release of springlike devices has also been reported. Nitinol stents may expand prematurely in the guiding catheter and inhibit deployment. Balloon expandable stents appear to have the advantage of precise expansion to the limits of the delivery balloon.

Expansion Ratio

The ideal stent should have a large expansion ratio as a measure of its versatility to allow for the smallest possible delivery catheter. In its collapsed state, a stent should be small enough in diameter to pass through narrow vascular passageways but, also, be able to expand to diameters many times its original size. Small expansion
ratios may require prohibitively large delivery systems, thus, offsetting any realistic clinical benefit. This becomes particularly relevant when the target artery may be as large as saphenous vein grafts or the pulmonary artery in children.24

**Human Trials**

The first human implants with vascular stents in the peripheral and coronary circulation were reported by Sigwart et al,13 who used a multifilamented self-expanding springlike peripheral device. Ten peripheral implants were done in six patients with peripheral vascular disease. A mean follow-up study after 6 months showed that all stents were patent with no reported complications.

In this same series, 24 coronary stents were also placed in 19 patients after 50,000–100,000 units intracoronary urokinase were administered. Patients were treated with aspirin and warfarin for 6 months. Two of the 19 implants developed thrombosis early, and one patient died from an acute infarction after undergoing an exercise stress test 2 days after stenting of the left anterior descending artery.13

Follow-up studies in this series and in additional patients (48 coronary implants) by Sigwart revealed three deaths, abrupt closure in five patients, restenosis in two, and an overall complication rate of 14%. In a preliminary study, other investigators using the same device in coronary arteries have reported acute thrombosis rates of 40%.44 This propensity for thrombosis in such a complex spring device with a high concentration of metal requires thrombolytic therapy during and full anticoagulation after implantation.

Sigwart later, in a preliminary study,45 described a higher complication rate in stents placed in the left coronary artery compared with the right, the incidence of which appeared to be inversely related to the length of the stent despite full anticoagulation. There were no significant complications in the patients who received stents in bypass grafts. The incidence of coronary spasm was diminished by pretreatment with intracoronary nifedipine. Long-term trials to assess restenosis with this device are underway in Europe.

A limited clinical trial on humans is now underway with the wire coil reported by Roubin et al used in the emergency setting of failed PTCA as a “bridge” to bypass surgery; the results of this study are still pending.

**Figure 7.** Prestent angiogram (Panel A). Arrow marks high grade restenosis of a human right common iliac artery. Inset, pressure gradient. Poststent angiogram (Panel B). Arrows mark stent. Inset, pressure gradient resolved.
After some 300 implants in the experimental laboratory and 3 years of successful follow-up in animals, the first human stent implants in the United States and Europe under an FDA-approved protocol were performed by Palmaz and colleagues in May 1987. Initially, 24 stents were placed successfully in the iliac arteries of 15 patients without thrombosis or abrupt closure (Figure 7). Follow-up procedures in this series now include over 98 stents in 64 patients. The longest follow-up is 15 months (range, 1-15 months; mean, 7 months), and all stents remain open with no evidence of restenosis by either angiography or noninvasive testing.

All patients have been treated with only aspirin and dipyridamole since discharge. Warfarin was used in only one patient after discharge. In this patient, a stent was placed incorrectly proximal to a high-grade lesion of the iliac artery. Although the lesion was dilated, a second stent was not available to be placed in the target lesion. The patient was discharged with a patent artery but developed abrupt thrombosis of the nonstented lesion 1 week later and subsequent thrombosis proximal to the stent. After lytic therapy, repeat dilatation of the lesion, and a short course of warfarin, stent and lesion remain patent at 9 months.

Complications in the series included distal thromboembolism in three patients with total iliac obstructions, perisheath thrombosis in two patients treated successfully with urokinase, and one patient with retroperitoneal bleeding from perforation of the external iliac by the delivery sheath without requiring transfusion.

Twenty-seven coronary stents (including eight of the articulated design) have been successfully placed electively in 17 patients with symptomatic coronary artery disease, 23 have been placed in the right coronary artery, and four have been placed in the left anterior descending artery. With clinical follow-up studies ranging from 1 to 8 months (mean, 2 months), all patients remain asymptomatic and have no evidence of ischemia as evidenced by exercise testing. Even when placed in fresh thrombus (Figure 8), all stents are patent. All patients were treated with heparin and dextran during the procedure, and only aspirin and dipyridamole were administered after discharge. There was no instance of abrupt closure, and no patient has required warfarin. Failure to deliver four additional nonarticulated stents...
occurred. One was incorrectly implanted proximal to a high-grade lesion of the right coronary artery that was suboptimally dilated. This patient developed asymptomatic restenosis of the nonstented lesion, which was documented by angiography, at 3 months. Two other stents were successfully withdrawn, and a third embolized inadvertently to the pelvis upon withdrawal with no adverse clinical consequences.

In this small initial group, there was no infarction, death, migration of the stent, or bleeding complications. One patient developed spasm of the right coronary artery in a gap inadvertently left between two stents placed in tandem; the spasm was treated successfully by implanting a third stent. A 6-month follow-up examination by angiography to assess restenosis in this group is pending.

These initial results suggest that this balloon expandable stent is relatively nonthrombogenic, which eliminates the need for both routine administration of lytic agents during the procedure and warfarin thereafter. Furthermore, inflexibility of the nonarticulated stent will limit its usefulness to relatively straight segments of coronary arteries. This delivery limitation seems resolved with the newer design.

The Future

With as many as 133,000 coronary angioplasty procedures performed in 1986, a solution to the dilemmas of abrupt closure and restenosis by stenting would represent an important contribution. The devices discussed here appear to be promising; however, there is no ideal stent. All have advantages and disadvantages, and none has been tested sufficiently in humans to claim success in achieving these desired goals. Despite extensive experience in the animal laboratory, extrapolation to humans is treacherous. The role of the stent in relation to other novel interventions such as laser angioplasty and atherectomy devices remains to be defined.

There is no substitute for clinical trials, and during the next several years, countless questions must be answered; thousands of patients must be studied prospectively, and data must be critically examined before the precise indications for stents are defined. Pending such trials, a healthy dose of skepticism is appropriate, despite encouraging initial results.

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