Late Positive Remodeling and Late Lumen Gain Contribute to Vascular Restoration by a Non-Drug Eluting Bioresorbable Scaffold: A Four-Year Intravascular Ultrasound Study in Normal Porcine Coronary Arteries

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Background—The interplay between mechanical dilatation, resorption, and arterial response following implantation of bioresorbable scaffolds is still poorly understood.

Methods and Results—Long-term geometric changes in porcine coronary arteries in relation to gradual degradation of bioresorbable scaffolds were assessed in comparison with bare metal stents (BMS). Intravascular ultrasound (IVUS)-derived lumen, outer stent/scaffold, and reference vessel areas were evaluated in 94 polymer scaffolds and 46 BMS at 5 days and 3, 6, 12, 18, 24, and 55 months, in addition to polymer scaffold radial crush strength and molecular weight (M_w) at 3, 6, and 12 months. BMS outer stent area and lumen area remained constant through 55 months (P<0.05, but within 1 standard deviation of 100%, and P=0.58, respectively), while significant increases were exhibited by polymer-scaffolded vessels with the maximum late lumen gain at 24 months, paralleled by the outer scaffold area increase, and then remaining at that increased level at 55 months (P<0.01). By 12 months polymer scaffolds experienced significant reductions in radial strength and M_w, while the animals underwent the largest weight gain. At 3 months and beyond, the patency ratio (lumen area/reference vessel area) of BMS remained constant (0.71 to 0.85, P=0.49). In contrast, that of polymer scaffolds increased and approached 1 (P=0.13).

Conclusions—Bioresorbable polymer scaffolds allow restoration of the treated segment’s ability to remodel outward to achieve level lumen transition between reference vessel and scaffold-treated regions, a process mediated by animal growth and scaffold degradation. This also introduces a challenge to standard analyses of IVUS outcomes relying on constant stent diameters over time. (Circ Cardiovasc Interv. 2012;5:00-00.)

Key Words: biodegradable polymer | coronary stent | IVUS | remodeling

The optimal outcome expected of an endovascular stent is to scaffold the vessel and prevent acute vessel closure and recoil, while containing the chronic constrictive remodeling and neoointimal hyperplasia that follow the arterial wall disruption occurring during angioplasty. A bioresorbable scaffold is differentiated from a metal stent by its ability to degrade over time within the arterial wall after this mission is completed. As a consequence, in contrast to a metal stent, a bioresorbable scaffold is expected to not only acutely dilate the obstruction and sustain the result, but also to allow active remodeling of the treated segment structurally and functionally over time. Specific compliance and vasoreactivity of the segment treated with bioresorbable scaffold are expected to be restored eventually to those resembling a native, unstented artery. For this reason, the cardiovascular use of bioresorbable scaffold has been termed “vascular restoration therapy.” However, specific mechanisms and temporal course of the complex interplay between mechanical dilatation, scaffold resorption, antiproliferative drug elution (when applicable), and corresponding changes in arterial anatomy and physiology are still understood poorly. Conceivably, these processes may vary between different scaffold designs and materials. In this study, we characterized by intravascular ultrasound (IVUS) the long-term arterial geometry changes that paralleled the gradual degradation of a novel bioresorbable (tyrosine-derived polycarbonate) scaffold implanted in normal porcine coronary arteries for up to 55 months (4.6 years), and compared with a bare metal stent.

Methods

Stents/Scaffolds

The polymer scaffolds evaluated in this study were bioresorbable slide-and-lock scaffolds made of a tyrosine-derived polycarbonate polymer: poly(86.75% iodinated desaminotyrosyl-tyrosine ethyl ester-co-10.0% iodinated desaminotyrsyl-tyrosine-co-3.25% polyethylene glycol 2000 carbonate) with a molecular weight of 270481±33181 Da (REVA Medical, Inc.; Figure 1). The 7F
compatible (0.072") polymer scaffolds (3.0×16 mm), mounted on rapid exchange percutaneous transluminal coronary angioplasty delivery catheters, were sterilized at 25 kGy with electron-beam irradiation (Sterigenics). The polymer scaffold treatment range was 2.9 to 3.4 mm. Scaffold areas (based on OD) were 43% scaffold free surface area and 57% arterial contact surface area. The overlap design of the sliding and locking parts allowed a single layer thickness of 102μ (0.004"), and a double overlap thickness of 204μ (0.008"). At nominal there was approximately 60% circumferential overlap and total of 43% longitudinal overlap. The bare metal stents (BMS) used as a comparative control were stainless steel Express Coronary Stents (3.0×16 mm; Boston Scientific Corp).

WHAT IS KNOWN

● The interplay between mechanical dilatation, resorption, and arterial response following implantation of bioresorbable scaffolds is still poorly understood.

● Clinical studies with polymeric bioresorbable vascular scaffolds have suggested that there is late lumen gain in the treated segments occurring years after implantation, but the mechanism(s) underlying this response are unknown.

WHAT THE STUDY ADDS

● Our study for the first time provides experimental evidence that without underlying atherosclerosis and an antiproliferative drug elution, the late lumen gain in the bioresorbable scaffold-treated arterial segments may be coupled with positive (outward) remodeling.

● The scaffold degradation permits restoration of the arterial segment’s plasticity and ability to remodel over time, a benefit unattainable with metallic stents.

● Standard efficacy measures that rely on a consistent stent diameter over time, such as late loss, may not be accurate for assessing restenosis and neointimal remodeling beyond the time point where bioresorbable scaffolds lose mechanical strength.

Radial Strength and Molecular Weight Analyses

The radial crush strength and weight average molecular weight (Mw) were obtained from scaffolds degraded in vitro, under static conditions, in saline at 37°C for 3, 6, and 12 months. The radial crush strength was measured in a hydrostatic pressure chamber, and the percent of original radial crush strength was determined from time zero samples.

Gel permeation chromatography (GPC) was used to determine Mw of in vitro samples and a subset of scaffolds excised from implanted vessels at 3, 6, and 12 months (ex vivo testing). Polymer scaffold (>6 mg) and polystyrene standards (approximately 100kDa narrowband and 200 to 300kDa broad band, Viscotek/Malvern) were prepared in 0.1% trifluoroacetic acid in dimethylformamide to a concentration of approximately 2 mg/mL. Samples were tested using 2 mixed-bed TSK-Gel columns in series (Mw range of approximately 10kDa to 1000kDa, Tosoh Biosciences) at a column temperature of 60°C and a flow rate of 0.7 mL/min. Mw was calculated using homopolymer model triple detection calibration versus the narrowband standard. GPC was performed using a Viscotek Model TDA302 with a GPCmax VE2001 pump/autosampler (Viscotek/Malvern), using low and right angle laser light scattering, refractive index, and viscosity detection. The Mw of nondegraded scaffolds (time zero) was measured and used to establish the baseline Mw and percent remaining for in vitro and in vivo scaffolds from each lot tested.

Animal Study Protocol

All procedures were approved by the test facility Institutional Animal Care and Use Committee and conducted in accordance with the guidelines of the United States Department of Agriculture Animal Welfare Act 9 CFR Parts 1 to 4 and the Guide for Care and Use of Laboratory Animals. Percutaneous femoral catheterization was performed according to standard procedures. Polymeric scaffolds and BMS were implanted in coronary arteries of Yucatan mini swine under IVUS guidance to achieve a 10% overstretch. Heparin (100–200 U/kg) was administered to achieve an activated clotting time of >250 seconds. Animals received 325 mg of aspirin, 75 mg of Plavix, and 180 mg Diltiazem daily for 3 days prior to device implantation, and were maintained on 81 mg of aspirin and 75 mg of Plavix daily. Plavix was discontinued in all animals after 24 months. Implanted arteries were re-examined by angiography and IVUS prior to termination. A total of 81 polymer scaffolds and 39 BMS were evaluated. Device distributions are listed in Table 1. Animals were terminated at 5−1 day, 3 and 6 months ±5 days, 12, 18, and 24 months ±7 days, and 55 months postimplant. For simplicity, variances in actual follow-up length have been omitted throughout this report. Two animals from the 18-month time point were reevaluated at the 24-month time point, and 1 of these animals was reevaluated again at the 55-month time point. The third animal from the 18-month time point also was reevaluated at the 55-month time point.

Table 1. Test Article Distributions Within Animals

<table>
<thead>
<tr>
<th>Time Point</th>
<th>No. of Animals</th>
<th>Implant Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 day</td>
<td>1</td>
<td>1 polymer</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 polymer, 1 metal</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2 polymer, 1 metal</td>
</tr>
<tr>
<td>3 month</td>
<td>1</td>
<td>1 polymer</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2 polymer</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 polymer, 1 metal</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 polymer, 1 metal</td>
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<tr>
<td>6 month</td>
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<td>1 polymer</td>
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<tr>
<td></td>
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<td></td>
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<tr>
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<td>2 polymer</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 polymer, 1 metal</td>
</tr>
<tr>
<td>18 month</td>
<td>3</td>
<td>1 polymer, 1 metal</td>
</tr>
<tr>
<td>24 month</td>
<td>1</td>
<td>2 polymer</td>
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<tr>
<td></td>
<td>4</td>
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<tr>
<td></td>
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<td>55 month</td>
<td>1</td>
<td>2 polymer</td>
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<tr>
<td></td>
<td>4</td>
<td>1 polymer, 1 metal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2 polymer, 1 metal</td>
</tr>
</tbody>
</table>

Figure 1. REVA Medical polymeric (tyrosine-derived polycarbonate) slide-and-lock bioresorbable scaffold.
IVUS Analysis
The ClearView IVUS Ultra imaging system (Boston Scientific) or the Galaxy 2 imaging system (Boston Scientific) were used to acquire IVUS images during procedures. Images were recorded on CDs or DVDs in a fashion preventing immediate distinction of the test articles from the control article (“blinded”). However, the appearance of the polymer test articles and metal control article in IVUS is slightly different, and thus complete blinding of IVUS analysis was not possible. Images were evaluated by an independent core laboratory (Methodist Hospital Research Institute, Houston, TX), with consistent verification by 1 of the coauthors (GLK). Still images of proximal and distal reference segments and proximal, mid-, and distal stent were frozen during playback, optimally at end diastole. Measurements of lumen and outer stent areas in early phases of the study were performed using planimetric software built into IVUS systems identical to those used to acquire images at the in life test facility, or later on the echoPlaque software package (INDEC Medical Systems).

Statistical Analysis
Statistical analysis was performed using R version 2.12.1 (The R Project for Statistical Computing). Linear mixed models were performed to assess statistical significance for polymer scaffolds and metal stents between time points by using the linear mixed effects model also was used to determine if there was any difference between in vivo and in vitro degradation rates. A probability value \( p \leq 0.05 \) was considered statistically significant.

Results
Changes in Radial Strength and Molecular Weight
After 3 months in vitro, the polymer scaffolds \((N=9)\) had retained \(84.6 \pm 8.8\%\) of their original radial strength. At 6 months the radial crush strength had decreased to \(53.3 \pm 10.8\%\) and further to \(18.8 \pm 5.5\%\) at 12 months, compared with that of time zero. Assessment of the radial crush strength of porcine vessels implanted with polymer scaffolds was not feasible.

There was no difference in in vitro and ex vivo \(M_W\) remaining at 3 months (in vitro \([N=9]\), \(46.0 \pm 9.3\%\); ex vivo \([N=6]\) \(45.1 \pm 8.8\%\)), at 6 months (in vitro \([N=9]\), \(35.7 \pm 8.4\%\); ex vivo \([N=7]\) \(27.72 \pm 4.3\%\)), or at 12 months (in vitro \([N=9]\), \(19.8 \pm 4.1\%\); ex vivo \([N=1]\) \(14.4\%\); \(p=0.31\)). The data showed that polymer scaffolds degrading in vitro under static conditions and those in vivo under hemodynamic conditions experienced the same rate of \(M_W\) loss. For biodegradable polymers, \(M_W\) reductions commonly are accompanied by a reduction in mechanical properties, as seen in Figure 2.

Trends in Lumen and Outer Stent/Scaffold Areas Over Time
Standard morphometric IVUS parameters (lumen area and outer stent area) in BMS demonstrated a typical pattern of behavior over consecutive time points ranging from 5 days to 55 months (Figure 3A). The initial lumen area loss at 3 months because of neointimal formation minimally was improved at later time points, whereas the outer stent area remained predictably unchanged over the study duration, as expected for a balloon-expandable bare metal stent.

In stark contrast, the same morphometric parameters characterizing the arterial segment implanted with bioresorbable scaffold revealed a uniquely different trend when compared over matching time points. After an expected decrease in lumen area resulting from neointimal development between scaffold implantation and an early time point of 3 months, a reverse trend became evident starting at 6 months (Figure 3B). Around 12 months, the average lumen area gradually returned toward the baseline value from before the scaffold placement. Lumen area continued to increase, reaching the maximum late lumen gain at 24 months in this study, and remaining stable afterward through 55 months. This late...
lumen gain pattern was paralleled by a very similar pattern of increase in the outer scaffold area, suggesting positive (outward) remodeling of the segment treated previously with a bioresorbable scaffold. Illustrative sequences of IVUS images are presented in Figure 4.

**Late Lumen Gain Versus Artery Growth**

Because the study used different animal cohorts to examine different time points, efforts were made to offset the impact of variable baseline artery size and vessel growth over time. To that end, additional indices were calculated from paired (baseline and follow-up) data in an attempt to normalize the changes in vessel and stent or scaffold morphometry over time. Lumen area change (%) was calculated as \((\text{follow-up lumen area}/\text{post-implant lumen area}) \times 100\%\). As such, the lumen area at immediately post implantation was defined as 100%, and the variation from 100% was scrutinized over time from implantation.

As shown in Figure 5A, there was no statistically significant lumen area change over time for BMS-implanted vessels \((P=0.58)\), indicating that the lumen area normalized to the postimplant value remained constant over time after initial loss at 3 months. For polymer scaffold treated vessel lumen areas, however, there was a statistically significant difference between time points \((P<0.01)\). Short-term (up to 3 months) arterial segments implanted with polymer scaffolds exhibited a decrease in the normalized lumen area to approximately 70% of postimplant level, also because of neointimal formation. By 6 and 12 months, the normalized lumen area increased. At 12 months the polymer scaffold treated vessels exhibited an additional increase in the stented vessel lumen area that was maintained to 55 months (Table 2 and Figure 5A). Angiography and IVUS imaging, as well as histological data (not presented in this manuscript) for these arterial segments ruled out the ectatic or aneurysmatic character of these late lumen dilatations at all time points.

**Outer Stent (Scaffold) Area**

Analogously to the lumen area, the outer stent (scaffold) area change (%) was calculated as \((\text{follow-up outer stent area}/\text{post-implant outer stent area}) \times 100\%\). As such, the outer stent area at immediately post implantation was defined as 100%, and the variation from 100% was scrutinized over time from implantation.
fold] area/post-implant outer stent [scaffold] area)×100%. As such, the outer stent (scaffold) area immediately post implantation was defined as 100%, and the variation from 100% was examined over time. Over time, the outer stent area of BMS stented arteries was slightly larger after 18 months and beyond, but remained within 1 standard deviation of 100% at all time points (P=0.05), as expected of a balloon-expandable metallic stent. Naturally, the variance from 100% between time points is attributable to the range of stent sizes deployed over a range of vessel sizes, not to actual geometric changes of single stents. In contrast, the normalized outer scaffold area of polymer scaffolds started increasing between 6 and 12 months, peaked at 24 months, and remained at that level at 55 months (P<0.01, Table 2 and Figure 5C). The 6 to 12 month duration corresponds to the time period where the largest amount of animal weight gain occurred. In contrast, the reference vessel area change in the BMS-treated arteries was not statistically significant (P=0.37), and remained constant over time. Relative changes of the reference vessel areas from the baseline also were calculated similarly to the lumen and outer stent area changes. However, these data were not considered reliable and thus not reported, as the reference segment spasm was observed in approximately 10% to 12% of the implants in this study and contributed to an artificially high ratio. The reference arterial segments of swine frequently undergo spasm proximal and distal to the freshly placed stent.8

Reference Vessel Lumen Area, Artery Growth, and Animal Growth

Any assessment of geometric changes in the arteries needs to account for changes inherent because of animal growth.8 To reduce the impact of animal growth on the results, the present study employed only mature Yucatan mini swine for all time points. Nonetheless, the animals experienced substantial growth over the course of the studies, with the largest amount of growth occurring prior to 12 months. The animals evaluated at 6 months postimplant and beyond were approximately 44 to 61 kg at implant. By 6 months postimplant, animals weighed 68 to 90 kg (27±6 kg gain); by 12 months the animals weighed 87 to 101 kg (40±5 kg gain). By 55 months the animals had grown to 104±36 kg, which was an additional 69±12 kg weight gain since implant. Animals from the 5-day and 3-month cohorts were larger at implant than other animals evaluated and therefore have been excluded from weight analysis.

Over the follow-up time, the reference vessel area of the arteries implanted with polymer scaffolds demonstrated a statistically significant increase (P=0.01; Table 2 and Figure 5C). The 6 to 12 month duration corresponds to the time period where the largest amount of animal weight gain occurred. In contrast, the reference vessel area change in the BMS-treated arteries was not statistically significant (P=0.37), and remained constant over time. Relative changes of the reference vessel areas from the baseline also were calculated similarly to the lumen and outer stent area changes. However, these data were not considered reliable and thus not reported, as the reference segment spasm was observed in approximately 10% to 12% of the implants in this study and contributed to an artificially high ratio. The reference arterial segments of swine frequently undergo spasm proximal and distal to the freshly placed stent.8

Patency Ratio

Consequently, to normalize the lumen changes to the variations in the reference vessel size, patency ratio was calculated as follow-up lumen area/follow-up reference vessel area, and its changes also evaluated at different time points. The patency ratio was calculated to determine the relationship between the caliber of the stent-treated (or scaffold-treated) vessel region versus the caliber of the reference vessel segments proximal and distal to the treated region. Excluding the 5-day time point, because little neointima had formed, from 3 months and beyond the patency ratio of BMS (from 0.71–0.85) remained constant (P=0.49; Table 2 and Figure 5D). However, a slight nonsignificant trend of a decrease was observed, possibly indicative of reference vessel growth without a corresponding growth in stented vessel lumen area. In contrast, the patency ratio of arterial segments implanted...

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Device (n)</th>
<th>Lumen Area Change</th>
<th>Outer Stent/Scaffold Area Change</th>
<th>Reference Vessel Area (cm²)</th>
<th>Patency Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 day</td>
<td>BMS (6)</td>
<td>93±21%</td>
<td>95±9%</td>
<td>8.53±1.98</td>
<td>0.92±0.17</td>
</tr>
<tr>
<td>5 day</td>
<td>Polymer (9)</td>
<td>86±23%</td>
<td>94±11%</td>
<td>9.33±1.96</td>
<td>0.85±0.18</td>
</tr>
<tr>
<td>3 month</td>
<td>BMS (7)</td>
<td>72±21%</td>
<td>93±6%</td>
<td>8.11±0.92</td>
<td>0.75±0.18</td>
</tr>
<tr>
<td>3 month</td>
<td>Polymer (24)</td>
<td>62±11%</td>
<td>99±15%</td>
<td>9.30±1.25</td>
<td>0.64±0.13</td>
</tr>
<tr>
<td>6 month</td>
<td>BMS (9)</td>
<td>77±9%</td>
<td>97±8%</td>
<td>8.16±1.66</td>
<td>0.76±0.17</td>
</tr>
<tr>
<td>6 month</td>
<td>Polymer (19)</td>
<td>85±21%</td>
<td>115±16%</td>
<td>9.10±1.70</td>
<td>0.79±0.15</td>
</tr>
<tr>
<td>12 month</td>
<td>BMS (4)</td>
<td>83±17%</td>
<td>97±9%</td>
<td>8.38±2.53</td>
<td>0.78±0.14</td>
</tr>
<tr>
<td>12 month</td>
<td>Polymer (10)</td>
<td>94±10%</td>
<td>126±13%</td>
<td>10.21±1.01</td>
<td>0.81±0.17</td>
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<tr>
<td>18 month</td>
<td>BMS (3)</td>
<td>99±18%</td>
<td>104±9%</td>
<td>8.50±1.55</td>
<td>0.85±0.19</td>
</tr>
<tr>
<td>18 month</td>
<td>Polymer (3)</td>
<td>97±33%</td>
<td>122±14</td>
<td>10.67±2.36</td>
<td>0.83±0.13</td>
</tr>
<tr>
<td>24 month</td>
<td>BMS (5)</td>
<td>99±23%</td>
<td>106±13%</td>
<td>10.87±2.28</td>
<td>0.73±0.12</td>
</tr>
<tr>
<td>24 month</td>
<td>Polymer (8)</td>
<td>105±23%</td>
<td>144±33%</td>
<td>11.99±2.86</td>
<td>0.92±0.19</td>
</tr>
<tr>
<td>55 month</td>
<td>BMS (5)</td>
<td>81±5%</td>
<td>106±10%</td>
<td>9.34±1.43</td>
<td>0.71±0.04</td>
</tr>
<tr>
<td>55 month</td>
<td>Polymer (8)</td>
<td>114±23%</td>
<td>140±22%</td>
<td>11.56±2.49</td>
<td>0.92±0.16</td>
</tr>
</tbody>
</table>

Data is presented as mean±standard deviation. For definition of patency ratio, see text.
with polymer scaffolds increased over time and approached 1; however, this increase still was not statistically significant (P=0.13; Table 2 and Figure 5D). An increase in the patency ratio to 1 indicates that the lumen of reference vessel regions and of polymer scaffold-treated regions were approaching uniformity of diameter.

**Discussion**

This study confirms that coronary arterial segments implanted with a polymer bioresorbable scaffold can experience lumen gain late (months to years) after implantation. It also demonstrates for the first time that this late lumen gain may be coupled with positive (outward) remodeling of the scaffold-treated segment. The device degradation over time permitted restoration of the arterial segment’s plasticity and ability to remodel. In this study of normal porcine arteries not altered by presence of atherosclerosis, it also allowed the arteries to grow similarly to arteries unconstrained by the presence of metallic stents. The net effect of this combined remodeling and growth was a restoration of the scaffold-treated lumen diameter to the normal reference diameter, despite regular and predictable development of neointimal growth and lumen loss early (up to 3 months) after scaffold placement. Of note, this outcome was observed without delivery of an antiproliferative drug off the scaffold surface.

Earlier clinical studies with polymeric bioresorbable coronary scaffolds have demonstrated the late lumen gain occurring late (years) after implantation. In the original Igaki-Tamai stent, minimal lumen diameter by angiography was observed to increase from 1.76 to 2.22 mm between 12 and 36 months, which was paralleled by a decrease of percent area stenosis from 38% to 25%. More recently, late lumen expansion was noted in the comprehensive endovascular imaging evaluation of the 2-year outcomes of the ABSORB trial with the Everolimus-eluting bioresorbable vascular scaffold.12 Our preclinical study employed a novel polymeric bioresorbable scaffold that differs in material (tyrosine-derived polycarbonate) and design (slide and lock)5 from previously characterized polylactic acid fenestrated mesh scaffolds.12 The results, obtained with this novel device in a controlled experimental setting of an animal study, without presence of atherosclerosis or antiproliferative drug elution, suggest that late lumen gain is an inherent outcome of bioresorbable scaffold treatment of a coronary segment, and may occur independent of the polymer material and design used.

The divergence between arterial lumen areas among the segments implanted with BMS and polymer scaffolds was evident as early as 1 year after implantation. The normalized lumen and outer stent areas for BMS-treated vessels remained relatively constant as the vessel is permanently constrained. Because of this, the patency ratio for BMS at 3 months and later remained relatively constant at between 0.71 and 0.85, and exhibited a slight nonstatistically significant trend of a decrease, indicative of reference vessel growth without a corresponding growth in stented vessel lumen area. In contrast, the lumen area and outer scaffold area for segments treated with polymer scaffolds increased over time and appeared to plateau when the lumen area approached the reference lumen area. This effect was most evident in the patency ratio, which approached 1 over time, indicating that the scaffold-treated region was able to outwardly remodel, align with the growth in the reference vessel segment, and eventually achieve a more level transition between the caliber of the reference vessel and that of the scaffold-treated regions (no step up or down). As substantial physical growth also occurred at this time, it is likely that arterial growth contributed to these changes in addition to outward remodeling.8,13 In the BMS the lumen remained permanently smaller than that of the reference segment, and the growth of the adjacent reference segment also was limited (Figure 6).

The idea of vascular restoration therapy by bioresorbable scaffold implies that the favorable geometric changes should be accompanied by return of arterial segment compliance and vasomotor function; this has been confirmed recently.2 Such return to structural and functional characteristics resembling those of an unstented artery is only possible because the polymer degrades and the scaffold loses its mechanical strength.14 This also was demonstrated in the present study. Using a standard hydrostatic pressure test chamber, polymer scaffolds in this study were shown to have maintained 85% of their original radial strength after 3 months in vitro degradation; by 6 months in vitro, the radial strength decreased to approximately 50%. This notable change at 6 months signifies when the polymer scaffold is no longer a substantial structural entity and has transitioned to a state that would allow late adaptive or expansive remodeling and subsequent luminal gain in vivo, which coincides with the continued lumen area growth observed beyond the healing period. In the naïve swine model, this permits the growth and remodeling of the adjacent nonstented reference vessels. This 6-month time point also coincides with when the polymer stent had lost 65% of its molecular weight. It is well established that decreases in molecular weight correspond to decreases in mechanical strength of a polymer device.15 It is not clear how the loss of mechanical strength in the scaffold and restored compliance of the treated segment translate into favorable geometric changes. However, previous research strongly suggests that transmural pressure and axial loading interactively regulate arterial remodeling.16 Also, in another study of small coronary arteries, constrictive remodeling was prevented by maintaining adequate flow.17

Overall, these biomechanical results directly relate to the restoration of vessel compliance, and while large amounts of vessel growth are not anticipated in the human clinical condition, the ability of a bioresorbable polymer scaffold to
remodel outward to align the caliber of the scaffold-treated segment with that of the adjacent reference vessel segments may provide unique clinical benefits not attainable with metal stents. Rigid metallic stents can change arterial geometry, causing longitudinal straightening and nonuniform shear stress.\textsuperscript{18,19} These alterations have been linked to the occurrence of adverse events and angiographic restenosis.\textsuperscript{18} Many studies have reported long-term endothelial dysfunction after coronary stenting. While abnormal endothelium-dependent vasomotion is present several months after coronary balloon angioplasty, endothelial dysfunction is more severe and prolonged in stented vessels in animal models,\textsuperscript{20} and through 6 to 9 months in humans.\textsuperscript{21} Most investigators have attributed this effect to the differences in injury levels and proliferative response between stenting and balloon angioplasty or to drug effect; however, the relationship to flow has not been made yet. Changes in flow patterns and decreases in the magnitude of blood flow both have been directly linked to increases in smooth muscle cell proliferation, delayed endothelialization, and endothelial cell dysfunction, as well as increased restenosis.\textsuperscript{22–24} It is possible that the changes in blood flow patterns due to stenting could be responsible for the endothelial dysfunction at 6 to 9 months and potentially beyond, as metal stents permanently alter the flow dynamics of stented vessels.

Thus, the restoration of vessel patency with a uniform lumen contour resembling a normal or near-normal (uninterven
d) artery may impact positively the blood flow pattern in the treated segment in comparison with metallic stent. This in turn may abbreviate the period of chronic endothelial dys
t function perpetuated by the intervention. Therein lies the possibility that restoring normal vessel function with the bioresorbable scaffold may provide unique physiological long-term clinical benefits to patients that are unachievable with any form of permanent metal stent.\textsuperscript{25}

Limitations of the Study

The present study had some limitations. First, different animal cohorts were examined at the time points reported, without the benefit of serial observations in the same animals. Further, at the longest time points (55 months), the visibility of the polymer features was less discernible by IVUS. In addition, IVUS measures were not performed before polymer stent placement, contributing to potential inaccuracies in poststent reference vessel measures due to spasm. Additionally, because the study was performed in healthy naïve animals without atherosomatous arteries, and because preclinical studies do not universally predict human clinical outcomes, the ability to generalize the hypothetical concepts put forward in this report remains to be seen in a human setting. Lastly, an assessment of vasomotion of the metal and polymer scaffold-treated vessels was outside the scope of this study; therefore, the impact of the reported geometric changes on physiological vascular tone remains undetermined.

Conclusion

These results demonstrate in the naïve swine model, without interference of atherosclerosis or antiproliferative drug elu-
tion, the ability of bioresorbable polymer scaffolds to restore the treated segment’s ability to remodel outward to achieve level transition between the caliber of the reference vessel and that of the scaffold-treated regions. As such, this change over time appears to be a phenomenon of vascular remodeling in response to the bioresorbable scaffold, which allows the treated segment and the adjacent proximal and distal host regions to establish a state of arterial homeostasis, a property that is augmented in the animal model where arterial growth does occur. A direct consequence of this property of bioresorbable scaffolds is that standard measures that rely on a consistent stent diameter over time, such as late loss, may not be accurate for assessing restenosis and neointimal remodeling beyond the time point where bioresorbable stents lose mechanical strength (in this case, 3 to 6 months).

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Disclosures

Dr. Strandberg and Ms. Zeltinger are employees, and Dr. Kaluza is a consultant of REVA Medical, Inc. REVA Medical Inc. sponsored the animal studies and the IVUS analyses that rendered the data for the present study. There were no other conflicts of interest.

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Late Positive Remodeling and Late Lumen Gain Contribute to Vascular Restoration by a Non-Drug Eluting Bioresorbable Scaffold: A Four-Year Intravascular Ultrasound Study in Normal Porcine Coronary Arteries

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