Differential neointimal response to coronary artery injury in pigs and dogs. Implications for restenosis models.

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Differential Neointimal Response to Coronary Artery Injury in Pigs and Dogs
Implications for Restenosis Models


Abstract  Neointimal hyperplasia occurs in the coronary arteries after percutaneous revascularization procedures and is a reparative response that frequently causes recurrent stenosis. Prior animal studies have shown that neointimal tissue thickness is proportional to the depth of arterial injury. Because animal models are increasingly used to test therapeutic strategies against restenosis, the purpose of this study was to evaluate the degree of neointimal thickening formed in the coronary arteries of pigs compared with dogs in response to severe injury. Fourteen coronary arteries in six mongrel dogs and 18 coronary arteries in nine pigs underwent severe arterial injury using tantalum metal coils delivered on oversized angioplasty balloons. Animals were killed after 4 weeks, and all coronary arteries were pressure perfusion fixed. Mean histological injury scores and neointimal thicknesses for dogs were 1.9±0.3 and 0.30±0.11, respectively, compared with 2.1±0.7 and 0.71±0.36 for pigs. Thus, there was significantly less neointimal thickening in dogs compared with pigs (P<0.001) despite no differences in injury (P=NS). The neointimal thickening differences translated into significantly different percent area stenoses: 55±24% for pigs versus 27±13% for dogs (P<0.001). Linear regression modeled neointimal thickness versus injury assessed by an ordinal injury score proportional to the depth of injury for each species. This analysis confirmed the differences across multiple injury levels. The slope of the regression line for dogs was small, suggesting that no relation may exist between injury and neointimal thickness in this species. The pig may be a more appropriate model for the study of the genesis of stenosing neointima. If the lack of response in dogs could be better understood, insight into more effective restenosis therapies might be possible.

Coronary artery restenosis remains a major unsolved limitation for interventional cardiology.1,3 It results from arterial injury incurred during the revascularization of coronary atherosclerosis and is caused in large part by neointimal hyperplasia at the injury site.2,7 Little progress has been made against restenosis despite much investigative work in both patients and animal models. The relevance of animal models to restenosis in humans is unclear yet of paramount importance to clinical trials. Neointima develops in most animal models but to varying degrees and with variable histopathologic appearance. In the porcine coronary model, large amounts of neointima develop with histopathology identical to that in humans.10 The depth and extent of arterial injury appear to determine the thickness of neointimal response.11 In other models, less neointima may form in response to injury. If this suspicion is true, comparative study of animal models resulting in less neointima might be useful for understanding the mechanisms of neointimal growth and possibly for suggesting new therapeutic approaches to restenosis. Thus, the purpose of this study was to quantitatively compare the amount of neointima forming in the coronary arteries of dogs and pigs in response to severe injury.

Methods

Animals

Studies were performed with the approval of the Mayo Foundation Institutional Animal Care and Use Committee. Juvenile domestic crossbred pigs (weight, 25 to 35 kg) were used in this study. They were fed a normal laboratory diet and received no lipid or cholesterol supplementation. All pigs were premedicated with oral aspirin (650 mg) within 24 hours of coronary artery injury. General anesthesia was administered in the form of intramuscular ketamine (12 mg/kg) and xylazine (8 mg/kg).

Mongrel dogs were similarly fed a normal laboratory diet without lipid or cholesterol supplementation. All dogs were also premedicated with a single dose of oral aspirin (650 mg) within 24 hours of coronary artery injury. For general anesthesia the dogs were administered 4% thiamylal sodium (Biotal) and isoflurane for anesthetic maintenance.

Method of Coronary Artery Injury

Coronary injuries in dogs and pigs were performed by the same operators using identical techniques and equipment. The method of using severely oversized tantalum metallic coils to induce coronary artery injury has been described previously.10 Tantalum coil implant was performed in multiple coronary arteries of a single animal in both species.

Briefly, arterial access was obtained via either femoral or carotid artery cutdown. Standard angioplasty guide catheters were used to cannulate either the left main or right coronary artery ostium. Under fluoroscopic guidance, a commercial
coronary angioplasty balloon wrapped with a tantalum metallic wire coil was placed in the coronary artery such that balloon oversizing by a factor of 1.5 to 2.0 was obtained. Inflation of the balloon deployed the coil and severely injured the coronary artery. This coil injury method resulted in histopathologic injury by each coil wire segment. A spectrum of injury occurred in a spatially localized circumferential vessel wall region, yielding a neointimal response by the artery at each wire injury site. Fluoroscopy with contrast injection immediately after coil implant confirmed adequate coil expansion and vessel patency. The arterial sheath was removed and the skin wound closed with interrupted sutures. The animals were returned to their quarters.

**Histopathologic Tissue Processing and Measurement**

All animals were killed at 28±2 days after coronary artery injury using a commercial intravenous euthanasia solution (Sleepaway, Ft Dodge Laboratories). The hearts were removed immediately at death and the coronary arteries pressure perfusion fixed at 100 mm Hg for 24 hours with 10% neutral buffered formalin. After fixation, the coronary artery segments with metal coils were carefully dissected free. Sections were made at 2-mm intervals perpendicular to the vessel long axis. The residual metallic coil fragments were removed. Tissue from each arterial segment was embedded, cut, and stained with hematoxylin-eosin and elastic van Gieson's stains using standard methods. All histopathologic measurements

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**FIG 1.** Representative photomicrographs from stent-injured dog coronary artery (top) and stent-injured pig coronary artery (bottom). There are marked differences in neointimal thickening from comparable injury, with the dog showing substantially less neointimal thickening. L indicates lumen; M, media; N, neointima; and o, hole from coil wire (elastic van Gieson's stain, magnification x36 [top and bottom]).
and observations were made by an experienced cardiac pathologist (W.D. Edwards) using a calibrated microscope reticle. The pathologist was unaware of species when making measurements and thus was "blinded" to species.

For each artery, all 2-mm histological segments were examined to determine the section with the maximal luminal narrowing. This section was used for all measurements. The major and minor axes of both the original and stenotic (residual) vessel lumen were measured. The original vessel lumen was defined as the area enclosed by the internal elastic lamina in all measurements. Areas of the original and stenotic lumina were calculated assuming an elliptical cross section (area = π × major axis/2 × minor axis/2). Percent area stenosis for a section was calculated as

\[
\%	ext{ Stenosis} = 100 \times \frac{1}{\text{Stenotic Lumen Area/Original Lumen Area}}
\]

Vessel injury severity and neointimal response were measured as follows. Vessel injury at every wire site was assessed by two different methods. The first method used a prospectively determined ordinal injury score based on the anatomic structures penetrated by that coil wire. This score has been previously described and validated, with values of 0 (no arterial injury), 1 (internal elastic lamina lacerated), 2 (medial injury), and 3 (laceration of the external elastic lamina). The mean arterial injury score for a section was calculated as the mean injury caused by wires in that section:

\[
\text{Mean Injury Score} = \frac{\sum \text{Weights for Each Wire}}{\text{Number of Coil Wires Present}}
\]

Neointimal thickness at each wire site was measured. The mean neointimal thickness for all wire sites in the section was used as the index of injury response.

The second method of assessing arterial injury was by measuring the density of cell nuclei at arterial injury sites. This measurement was intended to assess cell death at the injury sites. Three separate measurements were made at the wire injury sites of all animals, and the mean was calculated. These measurements were made on hematoxylin-eosin-stained sections using digitized microscopic images evaluated with a calibrated area and software to count the cellular nuclei in a circumscribed (measured) area of interest. The value obtained was converted to cell density per square millimeter.

### Table 1. Dog Coronary Arteries: Diameter, Quantitated Injury, Mean Neointimal Thickness, and Percent Stenosis

<table>
<thead>
<tr>
<th>Vessel No.</th>
<th>Dog No.</th>
<th>Artery</th>
<th>Artery Diameter, mm</th>
<th>Mean Injury Score</th>
<th>Cell Density/(\text{mm}^2\times10^{-2})</th>
<th>Mean Neointimal Thickness, mm</th>
<th>Percent Area Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>LAD</td>
<td>2.29</td>
<td>1.8</td>
<td>28.5</td>
<td>0.28</td>
<td>15</td>
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<tr>
<td>2</td>
<td>2</td>
<td>LCX</td>
<td>1.38</td>
<td>2.0</td>
<td>30.1</td>
<td>0.29</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>LCX</td>
<td>1.80</td>
<td>1.6</td>
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<td>0.21</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>LAD</td>
<td>1.52</td>
<td>1.3</td>
<td>31.6</td>
<td>0.34</td>
<td>41</td>
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<tr>
<td>5</td>
<td>3</td>
<td>SEP</td>
<td>1.08</td>
<td>2.0</td>
<td>43.7</td>
<td>0.31</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>LAD</td>
<td>1.28</td>
<td>1.6</td>
<td>34.9</td>
<td>0.29</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>LCX</td>
<td>1.96</td>
<td>1.6</td>
<td>44.3</td>
<td>0.22</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
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<td>2.16</td>
<td>1.7</td>
<td>52.8</td>
<td>0.37</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>SEP</td>
<td>1.44</td>
<td>1.8</td>
<td>49.8</td>
<td>0.64</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>LAD</td>
<td>1.54</td>
<td>2.6</td>
<td>27.5</td>
<td>0.26</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>LAD</td>
<td>1.82</td>
<td>2.0</td>
<td>78.0</td>
<td>0.28</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>LCX</td>
<td>1.30</td>
<td>2.1</td>
<td>61.4</td>
<td>0.21</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>LAD</td>
<td>1.64</td>
<td>2.0</td>
<td>35.6</td>
<td>0.27</td>
<td>20</td>
</tr>
<tr>
<td>14</td>
<td>4</td>
<td>LCX</td>
<td>1.44</td>
<td>2.0</td>
<td>80.8</td>
<td>0.18</td>
<td>25</td>
</tr>
</tbody>
</table>

Mean±SD 1.61±0.34 1.9±0.3 45.1±17.6 0.30±0.11 27±13

LAD indicates left anterior descending; LCX, left circumflex, and SEP, septal.

Statistical Methods

Injury in this model is a strong covariate in the neointimal thickening; the neointimal thickness at an injury site is heavily dependent on the depth of injury. Linear regression modeling was used to measure and compare the neointimal responses of the species. The regression models were created for each set of data points (mean injury score versus mean neointimal thickness) in each species, a process that yielded a slope and y intercept for the relation.

The fundamental question was whether a difference existed between the regression relations for dogs and pigs. Differences between species might be manifested as (1) different slopes with similar intercepts, (2) different intercepts with similar slopes, or (3) both slopes and intercepts different. The analysis was accomplished as follows.

The dog and pig data were pooled into a single table of paired points (mean injury, mean neointimal thickness) in each species, a process that yielded a slope and y intercept for the relation. Between species might be manifested as (1) different slopes with similar intercepts, (2) different intercepts with similar slopes, or (3) both slopes and intercepts different. The analysis was accomplished as follows.

Three regression models tested for the differences of interest. The regression coefficients were denoted by μ, α, and β and were generated by the regression algorithm. Linear regression for mean injury versus mean neointimal thickness score was then performed on these data.

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The regression equation for the first model tested for differences of intercepts:

Neointimal Thickness = Constant + μ × Injury + α × DOG
The statistical significance of $\alpha$ (again, a coefficient generated by the regression algorithm) indicates the presence or absence of a difference in intercepts between dogs and pigs in this model.

In the second model, slopes were compared assuming arbitrary intercepts:

**Thicknessequal**

$\text{Constant} + \mu \times \text{Injury} + \alpha \times \text{DOG} + \beta \times \text{DOG} \times \text{Injury}$

The statistical significance of $\beta$ indicates a difference in regression slopes (dog versus pig) in this model.

The third model compared slopes assuming the same intercept. The regression equation for this model was

**Thicknessequal**

$\text{Constant} + \mu \times \text{Injury} + \beta \times \text{DOG} \times \text{Injury}$

In this model, the intercepts are "forced" to be the same; given this constraint, statistical significance of $\alpha$ would indicate that the forced equality of intercepts also forces the slope to differ. Statistical significance for the slopes and intercepts thus was established by evaluating the statistical significance of $\alpha$ and $\beta$ coefficients.

In all cases above, the respective $\mu$, $\alpha$, and $\beta$ were coefficients estimated by the multiple regression process. Statistical significance was established by evaluating the resulting $\alpha$ and $\beta$ coefficients. The $\alpha$ and $\beta$ in each regression model indicated the significance of the injury-neointimal response intercepts and slopes for each species.

**Results**

Eighteen injured arteries in nine pigs and 14 injured arteries in six dogs were studied. No animals experienced observable untoward clinical events after coronary arterial injury. All animals survived the expected 4 weeks.

**Histopathologic Examination**

Microscopic examination revealed neointimal thickening responses and luminal stenoses of varying magnitudes for both species. Dog arteries appeared grossly to have less neointima than pig arteries. The histopathologic features of this neointima have been described previously.\(^{10}\) The histopathologic examination of the neointima revealed it to be quite similar in both pigs and dogs. This consisted of a fibrocellular tissue with comparable size, shape, and density of cells.

Fig 1 shows representative low-power cross sections of dog and pig coronary arteries. Tables 1 and 2 show the mean artery diameters of uninjured vessel immediately distal to the coil, injury scores, cell density at injury sites, and the measured neointimal thickening for all arterial segments of both species. There was no statistical difference in the diameters (1.74±0.42 mm for pigs, 1.61±0.34 mm for dogs, $P=.36$) or amount of arterial injury between species (1.9±0.3 for dogs, 2.1±0.7 for pigs, $P=.35$). The neointimal thicknesses and percent area stenosis were significantly different for the species ($P<.001$).

Fig 2 graphically shows the raw measurement data and regression line plots for each species. The regression line of injury versus neointimal thickness in pigs is distinct from that of dogs. The relation in dogs shows a substantially lower slope. Thus for larger injuries, the
TABLE 3. Regression Coefficients for Dog Versus Pig: 
Neointimal Thickness Comparison, Model 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Standard Error</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-0.04</td>
<td>0.15</td>
<td>NS</td>
</tr>
<tr>
<td>μ</td>
<td>0.36</td>
<td>0.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>α</td>
<td>-0.34</td>
<td>0.07</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Regression parameters are for the equation Thickness = Constant + μ \times \text{Injury} + α \times \text{DOG}, where DOG is a binary variable (1 for dogs, 0 for pigs).

Table 4. Regression Coefficients for Dog Versus Pig: 
Neointimal Thickness Comparison, Model 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Standard Error</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-0.18</td>
<td>0.14</td>
<td>NS</td>
</tr>
<tr>
<td>μ</td>
<td>0.43</td>
<td>0.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>α</td>
<td>0.58</td>
<td>0.33</td>
<td>NS</td>
</tr>
<tr>
<td>β</td>
<td>-0.49</td>
<td>0.17</td>
<td>.009</td>
</tr>
</tbody>
</table>

Regression parameters are for the equation Thickness = Constant + μ \times \text{Injury} + α \times \text{DOG} + β \times \text{DOG} \times \text{Injury}, where DOG is a binary variable (1 for dogs, 0 for pigs).

FIG 2. Plot shows raw data and regression lines for pig and dog coronary artery injury. There is a proportionality between the neointimal thickness response to injury in pigs (P<.001) but not in dogs. PCT indicates percent stenosis; Inj, injury.

Group of pigs responded with more neointima. The regression equations for dog neointimal thickness and percent stenosis were:

\[
\text{Thickness}_{\text{DOG}} = -0.40 - 0.06 \times \text{Injury Score} \\
\%	ext{Stenosis}_{\text{DOG}} = 39.1 - 6.7 \times \text{Injury Score}
\]

The regression equations for pig neointimal thickness and percent stenosis as a function of injury score were:

\[
\text{Thickness}_{\text{PIG}} = -0.18 + 0.43 \times \text{Injury Score} \\
\%	ext{Stenosis}_{\text{PIG}} = 18.5 + 17.7 \times \text{Injury Score}
\]

Regression Models of Injury and Neointimal Thickness

The first comparative regression model tested for similarity of intercept between dogs and pigs, assuming constant slopes as described above. The regression parameters for this analysis (Table 3) demonstrate that the intercepts differed significantly for the two species. In the second model (Table 4), the slopes are significantly different for dogs and pigs, even if the intercepts are unconstrained. Results for the third regression model (Table 5) indicate that if the intercepts for dogs and pigs are constrained to be equal, the slopes are still significantly different. These results parallel those of the first model.

In summary, the statistical modeling results showed that both the intercepts and slopes of the regression lines for the two species differ significantly. Thus, the dogs developed significantly less neointima than pigs even after controlling for the injury covariate.

Cell Density Comparison

Results of the cell nuclear density measurements are shown in Tables 1 and 2. There was no difference in the mean cell density at injury sites for pigs was 43.7±10.0/(mm×10⁻²) and for dogs was 45.1±17.6/(mm×10⁻²). There was no statistical difference in arterial injury between dogs and pigs assessed by this cell density method using the unpaired t test (P=.78). These data are thus in agreement with the histological injury score method.

Discussion

The question of differences in neointimal formation across animal species has not been previously reported. This study compared the response of coronary arteries in two species commonly used for device testing in interventional cardiology. Linear regression modeling was used to control for the confounding variable of injury. This method has been used in prior pig studies to compare the efficacy of treatments on reducing the degree of neointimal thickening. In these prior studies, the intercept of the injury–neointimal thickness regression line was responsive to therapies, whereas the slope changed minimally. The differential arterial response to injury, measured by the slope of the injury–neointimal thickness regression line, appears relatively constant within the pig species. It is possible that each species may have a characteristic injury–neointimal thickness slope, determined by the linear regression methods of this study. If this hypothesis is true, identification of the species with a response most similar to the human response should be sought to better understand human neointimal formation.

Animal studies indicating efficacy of certain agents that failed in clinical trials may directly relate to the quantity of neointima. For example, neointima was markedly reduced in rat carotid arteries in a proportional context (roughly 80%) using the angiotensin-converting enzyme inhibitor cilazapril. However, the absolute inhibition was less than 0.06 mm, corresponding to a diameter change (twice the radius change) of approximately 0.12 mm. This represents a very small arterial injury measured by cell densities in the dogs compared with pigs. The mean cell density at injury sites for pigs was 43.7±10.0/(mm×10⁻²) and for dogs was 45.1±17.6/(mm×10⁻²). There was no statistical difference in arterial injury between dogs and pigs assessed by this cell density method using the unpaired t test (P=.78). These data are thus in agreement with the histological injury score method.

Table 4. Regression Coefficients for Dog Versus Pig: 
Neointimal Thickness Comparison, Model 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Standard Error</th>
<th>P</th>
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<tbody>
<tr>
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<td>NS</td>
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<tr>
<td>μ</td>
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<td>0.06</td>
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<tr>
<td>α</td>
<td>0.58</td>
<td>0.33</td>
<td>NS</td>
</tr>
<tr>
<td>β</td>
<td>-0.49</td>
<td>0.17</td>
<td>.009</td>
</tr>
</tbody>
</table>

Regression parameters are for the equation Thickness = Constant + μ \times \text{Injury} + α \times \text{DOG} + β \times \text{DOG} \times \text{Injury}, where DOG is a binary variable (1 for dogs, 0 for pigs).

Table 5. Regression Coefficients for Dog Versus Pig: 
Neointimal Thickness Comparison, Model 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Standard Error</th>
<th>P</th>
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<td>μ</td>
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<tr>
<td>α</td>
<td>-0.19</td>
<td>0.04</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Regression parameters are for the equation Thickness = Constant + μ \times \text{Injury} + α \times \text{DOG} \times \text{Injury}, where DOG is a binary variable (1 for dogs, 0 for pigs).
absolute change that would not have been observable if angiographic end points were used. Two subsequent clinical studies using angiographic end points indeed showed no effect of this drug on restenosis.13,14 The results of the present study comparing dogs with pigs would have shown a difference had angiographic end points been used, because the mean difference in thickness was 0.01 mm, a value that would correspond to a diameter difference of 0.82 mm. At higher levels of injury, the difference would be even greater because of the differential effect of greater neointima resulting from larger injuries.

This study addressed the question of species differences in coronary injury–neointimal thickness response. The principal finding is that there are substantial interspecies differences between pigs and dogs in neointimal thickness after coronary artery injury. This was true despite similar histopathologic appearance, artery size, degree of arterial injury, and drug regimens.

Results in dogs demonstrated that there was no statistically significant association between injury and neointimal thickening. This finding may imply that there is no association between injury and neointimal thickness in dogs. Alternatively, it might reflect that a positive relation does exist, but the slope of this relation is so small that it cannot be differentiated from zero. More data points would be necessary to strengthen the statistical power to answer this question.

The reasons for the observed species differences are uncertain. However, further study and elucidation of the reasons for these differences might yield insight into a solution to the restenosis problem. This overstretched wire injury model has been characterized in pigs and shows that thrombus plays an important role in determining neointimal thickening. The major determinants of neointimal volume remain unclear but may relate to thrombus deposition at the arterial injury site. Substantial differences in thrombolytic capacities of dogs and pigs have been described.15 The role of native thrombolysis in restenosis remains unclear but should be studied further based on our results. The dog is well known to be a difficult model to use in studies using prosthetic heart valves, because thrombosis results, followed by rapid lysis.16,17 The relation of the thrombotic response between these species and the genesis of neointima is unclear.

No animals were killed in this study early after injury. It appears that neointimal formation in pigs occurs closely related to the deposition of fibrin at the site of vascular injury. The neointimal formation in this study concentrated only on the thickness of mature tissue present at 28 days in both species. The cellular events of neointimal formation in dogs were not studied but clearly would be of interest for future studies.

Injury-response studies in other species may also be warranted to provide additional data on this hypothesis. It would be interesting also to know the comparative response of rats and rabbits, two other species commonly used for restenosis models.

The dog has been used extensively to evaluate various new technologies for coronary artery intervention.5-20 If the results of our current study confirmed elsewhere, the validity of the dog model for such studies might be questioned, especially if effects on neointimal thickening are a priority in device evaluations. The current study suggests that neointimal formation in patients may possibly be better modeled by the pig than the dog.

Acknowledgments

The authors are grateful for the support of the J. Holden DeHaan Foundation and Medtronic, Inc, which helped make this study possible.

References