Biaxial incremental homeostatic elastic moduli of coronary artery: two-layer model

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Lu, Xiao, Aditya Pandit, and Ghassan S. Kassab. Biaxial incremental homeostatic elastic moduli of coronary artery: two-layer model. Am J Physiol Heart Circ Physiol 287: H1663–H1669, 2004; 10.1152/ajpheart.00226.2004.—The detailed mechanical properties of various layers of the coronary artery are important for understanding the function of the vessel. The present article is focused on the determination of the incremental modulus in different layers and directions in the neighborhood of the in vivo state. The incremental modulus can be defined for any material subjected to a large deformation if small perturbations in strain lead to small perturbations of stresses in a linear fashion. This analysis was applied to the porcine coronary artery, which was treated as a two-layered structure consisting of an inner intima-media layer and an outer adventitia layer. We adopted a theory based on small-perturbation experiments at homeostatic conditions for determination of incremental moduli in circumferential, axial, and cross directions in the two layers. The experiments were based on inflation and axial stretch. We demonstrate that under homeostatic conditions the incremental moduli are layer- and direction dependent. The incremental modulus is highest in the circumferential direction. Furthermore, in the circumferential direction, the media is stiffer than the whole wall, which is stiffer than the adventitia. In the axial direction, the adventitia is stiffer than the intact wall, which is stiffer than the media. Hence, the coronary artery must be treated as a composite, nonisotropic body. The data acquire physiological relevance in relation to coronary artery health and disease.

stress; strain; media; adventitia; constitutive equation

There is mounting evidence that the vessel wall regulates its homeostatic level of stress and strain at in vivo physiological conditions (17). A perturbation of this state such as in hypertension or flow overload leads to growth and remodeling with increased predilection for atherosclerosis. Although deformation or strain can be measured, there is no instrument or method to measure stress. Stress must be calculated from the constitutive equation, i.e., the stress-strain relationship. In general, the stress-strain history relationships of arteries are highly nonlinear (7). A well-accepted approach to nonlinear elasticity uses the incremental formulation. A linearized relationship between the incremental stresses and strains is obtained by subjecting the vessel to a small perturbation about the in vivo condition. Using this approach, one can determine the relation between stress and strain within the physiological regime. In conjunction, measurement of strain under in vivo conditions would yield a value of stress. Hence, the present approach allows the elucidation of the full mechanical (stress, strain, and elastic modulus) status in the vicinity of the in vivo state. Furthermore, knowledge of the material modulus or stiffness is important because it represents an early risk factor for cardiovascular diseases (1, 14) and has been shown to be an independent risk factor for cardiovascular events such as primary coronary events, stroke, and mortality (4, 19).

Before the 1980s, the vessel wall was modeled as a homogeneous material and the no-load state was considered as the zero-stress state. In the 1980s, the vessel wall was largely considered as homogeneous, but the state of zero-stress resultant and zero-stress moments was measured and found to be quite different from the no-load state (7). The present view, since the 1990s, is that the vessel wall is made of several layers each of which has its own elasticity constants and its own state of zero-stress resultant and zero-stress moments. The present study was devoted to the determination of the biaxial incremental elastic moduli in the layers of the coronary artery under homeostatic conditions. The theory is adopted from a recent paper on the mechanical properties of pulmonary vessels treated as a homogeneous layer (15). We wanted to extend the analysis to a two-layer composite model of the coronary artery.

The major goal was to clarify the mechanical properties of the coronary vessel wall, not as a homogenized whole but as a two-layered structure: one layer of endothelial cells and vascular smooth muscles, including elastin and some collagen, and another layer of collagen, fibroblasts, and elastin. These are the intima-media and adventitia layers, respectively. The vessel wall was initially mechanically tested as a whole and subsequently as the intima-media or adventitial layer. Two experiments were done for each layer that included inflation and axial stretching. The incremental elastic moduli in the individual layers under in vivo (homeostatic) conditions can be computed from the stress-strain relation and zero-stress state of the whole tube and the individual layers with the method of analysis presented here. A simple biomechanical model is proposed to compute the incremental modulus of adventitia from that of the intact vessel and media or that of the media from the intact vessel and adventitia. The material properties and physiological implications are discussed.

METHODS

Experimental Measurements

Biaxial test: intact vessel. The triaxial (inflation, extension, and torsion) testing of coronary arteries was recently described by our group (21). Although that experimental protocol included torsion, we limited the present analysis to inflation and longitudinal extension at zero torsion. Briefly, 10 porcine hearts, weighing 316 ± 56 g, were obtained from a local abattoir. The right coronary artery (RCA) and left anterior descending coronary artery (LAD) were dissected and tested biaxially. The arterial specimen was mounted on the cannula and treated biaxially. The arterial specimen was mounted on the cannula and treated biaxially.
horizontally on both ends in an organ bath. The organ bath chamber was designed to maintain the specimen immersed in a physiological solution. The cannulas were made to pass through the holes on the sidewalls of the chamber, and then a circulatory pump was used to maintain the volume of the solution in the chamber. One side of the cannula was connected with a pressure transducer (Summit Disposable Pressure Transducer, Baxter Healthcare; error of ±2% at full scale) through a Y tube. A pressure regulator was used to control the luminal pressure in the arterial specimen. The cannula was mounted on a linear stage (Daedal Positioning Table, type 402006 LNMS D L2 C2 M1, Parker Hannifin) where the motor for linear motion (type SDL 603, Parker Hannifin) drove the stage and recorded the axial force by a load cell (Senotec model; Senotec error at 0.15–0.25% at full scale). The load cell was calibrated with a series of weights, and a linear relation (correlation coefficient of 1.000) in the range of 0–2.45 N was confirmed. The longitudinal stretch ratio ($\lambda_c$) was varied from 1.3 to 1.5 in increments of 0.05. The transmural pressure ($P$) was varied from 110 to 163 cmH$_2$O in increments of 13.3 cmH$_2$O at every $\lambda_c$ with the use of a Ca$^{2+}$-free Krebs solution to prevent vessel tone.

*Biaxial test: dissected vessel.* The segment was removed from the biaxial machine and then transferred to a dish in cold Krebs solution. Two rings were cut from the two ends of the segment for the measurements of no-load and zero-stress state of the intact vessel as described in *No-load and zero-stress state*. In five hearts, the adventitia of the arterial segments was carefully dissected away from the media at the external elastic laminae with the aid of a stereomicroscope. The intima-media layer of the arterial segments remained intact and was then tested in the biaxial machine according to the same protocol as the intact LAD. In an additional five hearts, the vessel was inverted inside out and the media was dissected away, leaving the adventitia intact. The adventitia was then reinverted and tested in the biaxial machine according to the protocol as described above. The same procedure was repeated for the intact RCA and its medial layer in the same hearts used for the LAD. The adventitial layer was only tested for the LAD.

*No-load and zero-stress state.* After the mechanical tests, the coronary segment was placed into a Ca$^{2+}$-free Krebs solution (composition in mM: 117.9 NaCl, 4.7 KCl, 1.2 MgCl$_2$, 25 NaHCO$_3$, 1.2 NaH$_2$PO$_4$, 0.0027 EDTA, and 11 glucose). Each ring of the intact and dissected coronary artery was transferred to a Ca$^{2+}$-free Krebs solution, aerated with 95% O$_2$-5% CO$_2$, and photographed in the no-load state. The ring opened into a sector and gradually approached a constant mean curvature. Each ring was then cut radially by a scissor at the anterior interface of the media and adventitia and the average of inner and outer radius. The inner radius ($r_i$) and outer radius ($r_o$) at the loaded state and wall area in the no-load state, respectively. The total wall thickness ($h$) was computed as $h = r_o - r_i$. Because all the quantities on the right-hand side of Eq. 2 are measured, the loaded inner radius can be computed.

The mean Kirchhoff stresses in the circumferential ($S_0$) and longitudinal ($S_z$) directions are given by:

$$S_0 = \frac{P r_i}{h \lambda_0}$$

and

$$S_z = \frac{F}{\lambda_o^2} \left[ \frac{1}{\pi (r_o - r_i)} + \frac{P r_i^2}{h (r_o + r_i)} \right]$$

where $F$ and $h$ are the longitudinal force and wall thickness, respectively.

*Equations 1–4* were also applied individually to each separate layer. If the radii of the interface of the media and adventitia and the outer boundary of the adventitia are denoted by $r_0$ and $r_a$, respectively, the two components of the mean stresses were computed according to Eqs. 3 and 4 with the respective radii and wall thicknesses. Similarly, the strain was computed with the respective circumferential and longitudinal strain as given by Eq. 1. Finally, the wall thickness of each individual layer was similarly determined by Eq. 2 with the appropriate radius and wall area.

*Incremental moduli.* The foregoing analysis is based on several assumptions. We consider the material of each layer of the vessel wall to be homogeneous, incompressible, and orthotropic and to obey linear elasticity law with distinct moduli. The classic theory of thin-walled elastic shells is applicable to each cylindrical layer. The major simplification is to ignore the radial stress, and radial shear, so that each layer is treated as a two-dimensional shell.

The subsequent formulation is consistent with Fung and Liu’s (9) analysis. Briefly, it is well known that a constitutive stress-strain relationship for an artery can be reduced from a strain energy function, $\rho_o W$, which represents stored deformation energy per unit volume of arterial wall; $\rho_o$ denotes the density of the material in the unstressed state, and $W$ is the strain energy per unit mass. Under the assumptions that the arterial wall is homogeneous and pseudoelastic, the strain-strain relationship can be expressed as follows:

$$S_{ij} = \frac{\partial (\rho_o W)}{\partial E_{ij}}$$

where $S_{ij}$ and $E_{ij}$ are components of Kirchhoff stress and Green strain, respectively.
The incremental theory is developed under the assumption of linear elasticity. If we consider a small perturbation of stress and strain from a homeostatic in vivo state, defined by stress \( S_0 \) and strains \( E_0 \), then the perturbations may be written as:

\[
S_y = S_0^y + \delta S_y, \quad E_y = E_0^y + \delta E_y \tag{6}
\]

in which \( \delta S_y \) and \( \delta E_y \) are infinitesimal and quantities with a superscript \( \delta \) are homeostatic values. Substituting Eq. 6 into Eq. 5, we have, on omitting higher-order terms, the following result:

\[
\delta S_y = \frac{\partial^3 \rho_0 W}{\partial E_y^i \partial E_y^j} \delta E_\im \delta E_\ad = C_{ijkm} \delta E_\im \delta E_\ad \tag{7}
\]

\( C_{ijkm} \) are the values of the second partial derivatives of \( \rho_0 W \) evaluated at the homeostatic state. The summation convention is used such that a repetition of an index in a single term means a summation over the range of the index, 1 and 2 (circularferential and longitudinal directions, respectively). If \( E_j^y \) are uniform at the homeostatic state, then \( C_{ijkm} \) are constants in each layer. Equation 7 is a linear incremental stress-strain relationship. We can write the result in the following form to introduce the definition of the incremental elastic moduli:

\[
\delta S_{11} = Y_{11} \delta E_{11} + Y_{22} \delta E_{22}, \quad \delta S_{22} = Y_{11} \delta E_{11} + Y_{22} \delta E_{22}, \quad \delta S_{12} = 2G\delta E_{12} \tag{8}
\]

\( Y_{11} \) and \( Y_{22} \) are the classic incremental Young’s modulus in the circumferential and longitudinal directions, respectively, and \( G \) is the incremental shear modulus; \( Y_{11} \) and \( Y_{22} \) have no equivalents in classic mechanics and have been denoted as cross-modulus by Fung and Liu (9). The existence of the strain energy function requires that \( Y_{11} = Y_{22} \). These equations are Hookean but not isotropic. When Eqs. 5–8 are applied to the intima-media and adventitial layer of the blood vessel, every symbol should have a superscript im and ad, respectively.

**Least-squares method for determination of elastic moduli.** Because the loading does not involve shear, we need to determine three elastic moduli, i.e., \( Y_{11}, Y_{12}, \) and \( Y_{22} \). The method for computation of elastic moduli is clearly outlined by Huang et al. (15) and will not be reproduced here. Briefly, a least-squares method is used to minimize the error between the theoretical stresses given by Eq. 8 and the experimental measurements. The result is a 3 × 3 matrix whose solution is the 3 × 1 matrix of elastic moduli:

\[
\begin{bmatrix}
A_{11} & 0 & A_{12} \\
0 & A_{22} & A_{21} \\
A_{12} & A_{21} & A_{11} + A_{22}
\end{bmatrix}
\begin{bmatrix}
Y_{11} \\
Y_{22} \\
Y_{12}
\end{bmatrix}
= \begin{bmatrix}
B_{11} \\
B_{22} \\
B_{12}
\end{bmatrix}
\tag{9}
\]

in which

\[
B_{11} = \sum n \Delta S_{11} \Delta E_{11}^n, \quad A_{11} = \sum n \Delta E_{11}^n \Delta E_{11}^n, \\
B_{12} = \sum n \Delta S_{22} \Delta E_{11} + \sum n \Delta S_{11} \Delta E_{22}, \quad A_{12} = A_{21} = \sum n \Delta E_{11} \Delta E_{22}, \\
B_{22} = \sum n \Delta S_{22} \Delta S_{22}, \quad A_{22} = \sum n \Delta E_{22} \Delta E_{22}
\]

where

\[
\Delta S_{11} = S_{11}^0 - S_{11}, \quad \Delta S_{22} = S_{22}^0 - S_{22}, \quad \Delta E_{11}^a = E_{11}^a - E_{11}^0, \\
\Delta E_{22}^a = E_{22}^a - E_{22}^0, \quad n = 0, 1, 2, \ldots
\]

Obviously, the in vivo state is denoted by \( n = 0 \) and consequently \( \Delta S_{11}^0 = \Delta S_{22}^0 = \Delta E_{11}^0 = \Delta E_{22}^0 = 0 \). We dropped the symbol \( \delta \) for convenience, but it should be recalled that the quantities of stress and strain are all defined in the incremental sense (Eq. 8). The constants \( A \) and \( B \) are determined from the \( n \) experiments, and the matrix is solved for the three elastic moduli.

**Linear composite model.** Because the artery cannot be separated into two layers without damage to one of the layers, it is useful to have a model in which the incremental modulus of one of the layers can be computed from the moduli of the other layer and the intact vessel. To develop a simple model, we consider two springs in parallel representing the two layers as shown in Fig. 1. The total tension (T) is equal to the sum of the tensions in each layer for the circumferential and longitudinal directions, i.e.,

\[
T_{11} = T_{11}^\im + T_{11}^\ad \tag{10a}
\]

and

\[
T_{22} = T_{22}^\im + T_{22}^\ad \tag{10b}
\]

For an incremental analysis, we assume a linear stress-strain relation as given by Eq. 8. If we further assume that the cross-modulus is significantly smaller than the circumferential and longitudinal moduli, then Eq. 8 is reduced to:

\[
S_{11} = \frac{T_{11}}{h} = Y_{11} E_{11} \tag{11a}
\]

and

\[
S_{22} = \frac{T_{22}}{h} = Y_{22} E_{22} \tag{11b}
\]

Equations 11a and 11b can be substituted into Equations 10a and 10b for each of the layers to yield:

\[
Y_{11} h E_{11} = Y_{11}^\im h m E_{11}^\im + Y_{11}^\ad h m E_{11}^\ad \tag{12a}
\]

and

\[
Y_{22} h E_{22} = Y_{22}^\im h m E_{22}^\im + Y_{22}^\ad h m E_{22}^\ad \tag{12b}
\]

Because the deformation or strain, \( E \), is the same for each of the layers in the parallel model, i.e., \( E = E^\im = E^\ad \), we obtain:

\[
Y_{11} = \left( \frac{h^\im}{h} \right) Y_{11}^\im + \left( \frac{h^\ad}{h} \right) Y_{11}^\ad \tag{13a}
\]

and

\[
Y_{22} = \left( \frac{h^\im}{h} \right) Y_{22}^\im + \left( \frac{h^\ad}{h} \right) Y_{22}^\ad \tag{13b}
\]

Hence, the composite modulus can be obtained from the moduli of the two individual layers and their respective wall thicknesses. Equations 13a and 13b correspond to the circumferential and longitudinal directions, respectively. The incremental moduli were considered at the same level of stress in the neighborhood of in vivo loading conditions.

**Statistical analysis.** Values are means ± SD. A linear least-squares regression was used to curve fit the data. Student’s \( t \)-test was also used.
The opening angles for the intact RCA and LAD were 140 ± 30.3° and 134 ± 35.5°, respectively. When the adventitia was dissected away, additional compressive residual strain was relieved and the opening angle of the adventitia for RCA increased to 210 ± 38.6° and 198 ± 36.5°, respectively. When the media were dissected away, additional tensile residual strain was relieved as reflected by the decrease of opening angle of the adventitia for RCA and LAD to 98.1 ± 36.5° and 108 ± 35.8°, respectively. The differences between the opening angles for the intact segments and the individual layers were statistically significant.

The data on the circumferential incremental moduli for the intact LAD and media and adventitial layers are summarized in Table 1 for each individual animal. In five animals the intact LAD and its media were measured while the adventitia was calculated from Eq. 13 at a mean stress level of 45–48 kPa. In five additional animals the intact vessel and adventitia layers of the LAD were directly measured while the media were similarly computed. In order of increasing moduli, we found that media > intact vessel > adventitia, as seen in Table 1. Furthermore, the computed value of adventitia in the first group of animals was not statistically different from the measured adventitia in the second group of animals (Table 1). Similarly, there was no statistically significant difference between the computed and measured media. Table 2 shows equivalent data for the axial direction in the same vessels. In the axial direction, we found the moduli to increase in the order of adventitia > intact vessel > media. Furthermore, the vessel is nonlinearly stiffer in that the circumferential and axial material properties are different. The intact vessel is stiffer in the circumferential direction (P < 0.02), the media are also stiffer in the circumferential direction (P < 0.005), and the adventitia is stiffer in the longitudinal direction (although not statistically significant; P = 0.075) at the in vivo loading (45–48 kPa). The differences in the calculated and measured values of longitudinal incremental moduli were also not statistically significant (P = 0.21). Hence, the linear model provides a reasonable approximation for prediction of incremental moduli.

The conclusions are similar to those of the LAD in relation to the relative stiffness of the two layers and the intact vessel. Furthermore, there were no statistically significant differences between the RCA and the LAD for the intact vessel (P > 0.1), media (P > 0.09), and adventitia (P > 0.3). It should be noted that the comparison of the LAD and the RCA was made at different homeostatic ranges of stress (LAD: 44–48 kPa; RCA: 36–38 kPa) for the same distension pressure and longi-
The mean area in the no-load state was 2.82 ± 0.12 mm², which was also not significantly different (P = 0.096).

The incremental moduli of blood vessels have been studied for over 50 years (2) both for laws of elasticity (10, 20, 22) and laws of viscoelasticity (11, 22). The development of experimental and theoretical bilayer models of arteries has been pursued only in the past two decades (3, 5, 24–26).

Despite extensive studies, the incremental moduli of the individual layers of coronary artery are unknown. This study extends a previously developed theory for determination of the incremental elastic moduli for a homogenous model in the vicinity of the in vivo state to a two-layer model.

The coronary arterial wall is a composite of intima, media, and adventitia. Because the intima consists of endothelial cells and basal lamina that are fairly soft, the intima can be combined with the media to make up a two-layer model consisting of intima-media and adventitia. On the basis of the analysis we find that the intima-media layer and the adventitia layer have different elastic moduli and different residual strains in the circumferential direction. Furthermore, the incremental moduli under homeostatic conditions are higher in the circumferential than in the longitudinal direction. Hence, the coronary arterial wall must be considered as a composite, anisotropic structure.

**Mechanical Implications of Model**

It is generally accepted that the media bears the majority of tension under in vivo conditions while the adventitia serves to protect the vessel from overstretch. This paradigm applies to the circumferential direction with no equivalence for the longitudinal direction. The present model can be used to predict the distribution of tension on each layer in the two respective directions under in vivo loading. Using the data on the moduli in the circumferential and longitudinal directions as summarized in Tables 1 and 2 and the data on the wall thicknesses of the individual layers in Table 7 along with Eqs. 10 and 11 will yield the desired results. Under in vivo loading, we found that the media and adventitia bear 62 ± 13% and 38 ± 13% of the circumferential tension, respectively. Under the same loading, the media and adventitia layers carry 24 ± 15% and 76 ± 15% of the longitudinal tension, respectively. These results validate the notion that the majority of circumferential tension lies in the media under homeostatic conditions and predicts that the converse is true for the longitudinal direction. Under increased...
loading, such as in hypertension or angioplasty, the moduli in the adventitia increase significantly and the burden of tension bearing shifts to the adventitia.

Although the circumferential incremental elastic modulus is well documented in the literature, we want to call attention to the axial incremental modulus. It is apparent that the magnitude of the axial modulus is quite significant, particularly for the adventitia, which bears the majority of the tension in the axial direction. The physiological implications of the axial properties of blood vessels are becoming apparent. Han et al. (13) recently studied the effect of axial stretch on vascular cell function and remodeling of blood vessel wall in an ex vivo system. They found that axial stretch promotes cell proliferation while maintaining arterial function.

**Experimental and Theoretical Limitations of Model**

The dissection of a vessel wall into separate layers invites injury. Future studies are needed to elicit the material properties without dissection to verify the present model. In the present study, we were careful to preserve one layer while dissecting away the other layer. A cleavage plane exists at the external elastic laminae where the dissection of the two layers is possible without significant damage to one of the layers (21). We previously showed that there is no significant evidence of tearing or damage to the media as determined from histology (21). Furthermore, the difference in the thickness of the media measured from the intact wall and that of the media where the adventitia was dissected was not statistically significant (21). Incidentally, we dissect the vessel at the same plane where coronary artery dissection occurs clinically in patients, which is well known as the nemesis of an invasive cardiologist (16).

The major underlying assumption for the linear composite model shown in Fig. 1 and expressed by Eq. 13 is that the cross-modulus is small compared with the circumferential and longitudinal moduli. An inspection of the data for the LAD (Tables 1, 2, and 5) shows that the approximation is reasonable. For example, the circumferential modulus is three times larger than the cross-modulus whereas the longitudinal modulus is twice as large as the cross-modulus for the intact wall. For the media, the circumferential modulus is five times larger than the cross-modulus, whereas the longitudinal modulus and cross-modulus are comparable. For the adventitia, the circumferential modulus, and cross-modulus are comparable whereas the longitudinal modulus is twice as large as the cross-modulus. Overall, the assumption that cross-modulus is generally smaller than the moduli in the principal directions is supported by the data.

It should be noted that the present model is purely elastic and does not consider the features of viscoelasticity (creep, relaxation, and hysteresis). A future model would have to consider the stress-strain-history relation. Although the present model is elastic, the experimental protocol may include both elastic and viscoelastic properties. The vessel is initially stretched axially at a given stretch ratio, followed by inflation to a given pressure followed by continuous twist; the twist is then repeated for a different pressure and so on. The entire protocol is then repeated for a different axial stretch. Hence, there may be relaxation of axial stress as well as circumferential creep. This protocol is necessitated by the need to photograph various deformation states. Future implementation of ultrasonic crystals for continuous measurements of dimensions during loading will allow us to test the vessel continuously and hence primarily extract the elastic response.

Finally, the incremental moduli are meaningful only if the initial state from which the perturbations are applied is known, because these moduli are strongly dependent on the initial state of stress. Usually the incremental law is derived for the homeostatic or in vivo state. Experimental data in the literature on the incremental modulus often lack such information. Additionally, it should be noted that the incremental modulus is not equivalent to the slope of the stress-strain curve or tangent modulus. The incremental moduli must be determined by incremental experiments (7). Finally, the simplicity offered by the linearization has led to some abuse, as when Hooke’s law of an isotropic elastic body is used in each incremental step.

**Significance of Study**

Data on the mechanical properties in various layers are important for understanding of physiology and pathophysiology of the blood vessel wall. For example, in problems like arterial pulse-wave propagation, in which the stresses and strain perturbations are small, the use of the incremental law of elasticity and viscoelasticity simplifies the problem significantly. Furthermore, such moduli data allow the characterization of the stress and strain field in the vicinity of baroreceptors (12) and vasa vasorum (18) under in vivo loading conditions. We previously showed (21) that the shear modulus is different in the two layers. To add to this, we now find that circumferential and axial moduli are also different, which is equally important for determining the local stress and strain properties at the receptor or vasa vasorum sites. Furthermore, information on the various layers is essential to the understanding of various diseases (e.g., hypertension, flow overload, diabetes, etc.) that may remodel the tissue geometry and biomechanical properties of the two layers differentially. Finally, the outcome of coronary artery bypass surgery depends on matching the geometry and mechanical properties of the graft. The present study provides the needed data to devise a procedure that may be designed to prestress the different layers of tissue to prevent restenosis.

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