Relative Contribution of Wall Shear Stress and Injury in Experimental Intimal Thickening at PTFE End-to-Side Arterial Anastomoses

Background: Intimal hyperplastic thickening (IHT) is a frequent cause of prosthetic bypass graft failure. Induction and progression of IHT is thought to involve a number of mechanisms related to variation in the flow field, injury and the prosthetic nature of the conduit. This study was designed to examine the relative contribution of wall shear stress and injury to the induction of IHT at defined regions of experimental end-to-side prosthetic anastomoses. Methods and Results: The distribution of IHT was determined at the distal end-to-side anastomosis of seven canine iliofemoral PTFE grafts after 12 weeks of implantation. An upscaled transparent model was constructed using the in vivo anatomic geometry, and wall shear stress was determined at 24 axial locations from laser Doppler anemometry measurements of the near wall velocity under conditions of pulsatile flow similar to that present in vivo. The distribution of IHT at the end-to-side PTFE graft was determined using computer assisted morphometry. IHT involving the native artery ranged from 0.0±0.1 mm to 0.05±0.03 mm. A greater amount of IHT was found on the graft hood (PTFE) and ranged from 0.09±0.06 to 0.24±0.06 mm. Nonlinear multivariable logistic analysis was used to model IHT as a function of the reciprocal of wall shear stress, distance from the suture line, and vascular conduit type (i.e. PTFE versus host artery). Vascular conduit type and distance from the suture line independently contributed to IHT. An inverse correlation between wall shear stress and IHT was found only for those regions located on the juxta-anastomotic PTFE graft. Conclusions: The data are consistent with a model of intimal thickening in which the intimal hyperplastic pannus migrating from the suture line was enhanced by reduced levels of wall shear stress at the PTFE graft/host artery interface. Such hemodynamic modulation of injury induced IHT was absent at the neighboring artery wall. [DOI: 10.1115/1.1428554]

Keywords: hemodynamics, anastomosis, intimal hyperplasia, wall shear stress, fluid dynamics, end-to-side vascular graft

Introduction

Progressive intimal hyperplastic thickening (IHT) remains a major cause of intermediate and long term failure of bypass grafts [1–5] and endovascular interventions [6–8]. Anastomotic IHT has been associated with hemodynamic factors [9], compliance mismatch between graft material and host vessel [10], biomaterials incompatibility [11], and mural injury [12]. However, quantitative relationships with any given factor have not been reported.

Previous studies have demonstrated wall shear stress plays a critical role in adaptive wall remodeling. Such adaptive responses tend to normalize wall shear stress to levels between 10 and 20 dynes/cm² [13–15]. A similar increase in intimal thickness along polytetrafluoroethylene (PTFE) grafts in response to reduced hemodynamic wall shear stress has also been observed [16]. However, the role of hemodynamic wall shear stress in modulating IHT in a relatively confined region such as the end-to-side anastomosis is yet unclear. The hemodynamic wall shear stress in this region is characterized by dramatic spatial variation of shear stress in both magnitude and direction.

A number of studies have suggested that wall shear stress or other hemodynamic forces may enhance the development of anastomotic IHT. Imparato [1] suggested that the locations of obstructive lesions in venous bypass grafts and atherosclerotic plaques in arteries may have a “common denominator of specific hemodynamic conditions.” Sottiurai et al. [17] reported that IHT in end-to-side PTFE iliofemoral grafts in dogs was located at the heel and toe of the graft and the floor of the host artery. Based on these observations and independent measurements of wall shear stress in an in vitro model of an end-to-side anastomosis, Ojha suggested that low wall shear stress [18] or high wall shear stress gradients [19] might be responsible for the localization of anastomotic IHT.

Numerical correlation between these in vivo and in vitro results could not be obtained because the in vivo data were only qualitative. Furthermore, standardization of the in vivo geometry is necessary to adequately compare the in vivo biological and the in vitro fluid dynamic data since geometric and flow variations strongly affect the hemodynamics environment [20]. Recently Keeyton et al. [21] have studied a model in which both IHT and wall shear stress were measured in vivo. They found a small but significant correlation between IHT and hemodynamic variables.

We have previously shown that regions of IHT in implanted canine iliofemoral PTFE and autologous vein grafts corresponded to locations of slow particle velocities in a scaled up in vitro model [22,23]. Increasing the flow rate over two-fold in experimental canine anastomoses by creation of a distal arterial-venous
fistula virtually eliminated anastomotic IHT at the suture line [23]. This is consistent with increased near-wall particle velocities in the in vitro flow model [24]. Furthermore, outflow limitation in a model of anastomotic intimal hyperplasia in a New Zealand White adult male rabbit enhanced progression of IHT to an occlusive lesion [25]. The findings of these studies suggest that anastomotic IHT is likely to occur in regions of low and oscillatory flow, but the qualitative nature of the in vitro data has not yet allowed quantitative comparisons of wall shear stress with IHT.

In order to establish the quantitative relationship between IHT at distal anastomoses and its hemodynamic environment, we conducted a carefully controlled study to measure IHT inside a canine model. Blood bypasses anastomosis by infusions simulating the same geometry. The correlation coefficients for this relationship were much lower than anticipated from previous qualitative observations. We propose that the difficulty in establishing such a relationship is caused by the interplay between multiple biological and mechanical factors (i.e., hemodynamics, surgical injury, and the presence of PTFE). In this paper, we present the results of our study and examine the statistical relationships between IHT, reciprocal of wall shear stress, distance from the suture line, and the nature of the vascular conduit (PTFE versus native artery wall). The comparison is performed by multi-regression with backward elimination [26].

Materials and Methods

1 Acute in Vivo Studies

Animal Model. Acute in vivo experiments were conducted to obtain the baseline blood flow rates and the graft geometry for the in vitro flow study. Adult male mongrel dogs (n = 4) weighing 20 to 25 Kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg), and maintained after endotracheal intubation with one percent to three percent halothane. The iliofemoral arterial segments were exposed retroperitoneally through inguinal incisions extending to the upper thigh. Femoral artery diameter was measured with calipers before manipulation. Iliofemoral bypasses were constructed using 6 mm thin-walled PTFE and mechanical factors

were in compliance with “Principles of Laboratory Animal Care” and “Guide for the Care and Use of Laboratory Animals” (NIH publication no. 80-23, revised 1985).

Hemodynamic Measurements. After the grafts were implanted for one hour, blood flow was measured in the common iliac artery proximal to the bypass graft and in the distal outflow segment (DOS) of the distal end-to-side anastomosis with transit time ultrasound flow probes (Transonics Inc., Ithaca, NY). Systemic blood pressure was monitored with an indwelling 21-gauge brachial arterial cannula connected to a Statham pressure transducer and a strip chart recorder (Gould Inc., Cleveland, Ohio). Preliminary studies using four dogs provided the necessary hemodynamic data for the in vitro experiments. Pulsatile blood flow rates were measured by electromagnetic flow meters (Carolina Medical Electronics) and stored on FM tape by a four channel Racal frequency modulated recorder and then analyzed on a Masscomp 5500 microcomputer (Concurrent, Westford, Mass.).

II Chronic Animal Studies. Chronic in vivo studies provided the quantitative IHT data. The chronic studies (n = 9) followed the same procedure as the acute studies. After the operation, all animals received 125 mg of aspirin every day to reduce platelet aggregation and promote graft patency. After 12 weeks, the animals were sacrificed with an intravenous overdose of pentobarbital, and the distal infrarenal aorta was cannulated. Of the nine PTFE grafts, seven were patent at the time of sacrifice (78 percent patency rate). The distal aorta, iliac arteries, bypass grafts, and distal anastomoses were fixed by pressure perfusion with three percent glutaraldehyde at 100 mm Hg. The distal anastomosis, including the graft hood, suture line, and proximal and distal outflow segments (POS and DOS) were harvested en bloc and cross sectioned at 200 micron intervals. Sections were embedded in paraffin, and stained with hematoxylin and eosin, and by the Gomori-trichrome-aldehyde fuchsin procedure for connective tissue differentiation. The resulting slides were examined for the presence of anastomotic IHT by light microscopy.

The histological slides were projected on a digitizing plate and IHT was quantitated after tracing the lumen and internal elastic lamina using computer assisted morphometric techniques every millimeter (i.e., every fifth cross-section). For the correlations, the in vitro locations were matched with in vivo locations separated by one sixth of the in vivo hood length for locations within the anastomosis. While variability in hood length was small, the in vivo locations were nondimensionalized by in vivo hood length to insure that all locations were compared to in vitro locations relative to both the toe and heel locations. Otherwise, positions in the POS of the in vivo model would potentially be matched with positions within the anastomosis in the in vitro model. The variability was due to varying amounts of shrinkage during fixation and differences in the hood length and artery diameter from graft to graft. The in vivo measurement positions ranged from 1.8 diameters proximal to the heel to two diameters distal of the toe. In
each histologic section, IHT was averaged circumferentially over ±30 degrees centered along the hood or floor as shown in Fig. 3. The mean and standard deviation IHT at each axial position was computed as the average value for the seven dogs. Positions without IHT were entered as zero in the averaging.

### III Model Flow Studies

#### Model Geometry.
A laser Doppler anemometer (TSI system, Lexel four watt Argon ion laser) was used to determine the velocity distribution inside an in vitro model of the anastomosis. The probe volume sample size was 0.5 mm in length by 0.05 mm waist diameter (manufacturer’s specifications). The model was constructed from a Sylgard elastomer (Dow Corning, Midland, MI) and scaled up nine times to increase the spatial resolution. Dynamic similarity between the original graft and the scaled-up model was ensured by maintaining physiologic Reynolds and Womersley numbers. The wall shear stress values were estimated from the near wall velocity measurements.

The in vitro model incorporated geometric parameters which were measured from a polysiloxane (3M company, St. Paul, MN) cast of an acutely harvested end-to-side anastomosis. These parameters included the graft to host artery lumen diameter ratio (1.6 to 1), the branching angle (5 degrees), the hood length to host artery diameter ratio (5 to 1, based on internal dimensions) and the shapes of seven cross-sections of the cast along the host artery axis (Fig. 4). The cast cross-sections were obtained from a high resolution computerized tomography scanner (GE 9800). The final model was symmetric about the bifurcation plane, had smooth contours at the junctions, and had a curved contour along the hood. Details of the model construction technique have been previously described by Loth et al. [27,28]. Axial wall shear stress was measured from 1.2 diameters distal to the toe to a position 6.0 diameters proximal to the toe at intervals of 0.8 diameters.

**Pulsatile in Vitro Flow System.** The model was mounted on a recirculating flow rig with flow entering the graft model via a straight plastic tube three meters in length and 5.08 cm in diameter allowing for fully developed pulsatile flow at the entrance. The fluid was a mixture of 42 percent water and 58 percent glycerin by weight in order to match the refractive index of the Sylgard model. This fluid has a refractive index of 1.41, a density of 1.16 g/ml and a kinematic viscosity of 9.046 centipoise as measured by a Wells-Brookfield cone and plate micro-viscometer at 26.5°C. The flow was driven by a centrifugal pump and modulated by a Target Rock control valve to generate the desired waveform (Fig. 5). The flow rate entering the graft segment and exiting via the proximal outflow segment were monitored by two Carolina Medical Electronics electromagnetic flow meters.

The in vitro flow waveform is representative of the femoral artery flow conditions measured during the acute canine experiments after graft stabilization. The mean, positive peak, and reverse peak Reynolds numbers were 222, 850, and 120, respectively, based on the total inflow rate and host artery diameter ($Re_p=4Q_{graft}/D_s^2 \mu$), where $D_s$ (host artery diameter) is 0.35 cm. In vivo values of dynamic viscosity, $\mu$, is 0.035 g/sec-cm, and the fluid density, $\rho$, is 1.05 g/ml. The frequency of the in vivo waveform was 1.5 Hz (90 BPM) yielding a Womersley number of 3.0 based on the host vessel diameter. The proximal to distal outflow division was set at 20:80.

**Wall Shear Stress Measurements.** Near wall velocity measurements were taken at 24 midplane locations along the graft inlet, hood, floor and inside the proximal and distal outflow segments (Fig. 4). Wall shear stress was obtained from the product of the instantaneous velocity gradient at the wall and the fluid coefficient of viscosity. The instantaneous velocity gradient at the wall was estimated from a linear regression of three velocity measurements near the wall. The velocity measurement nearest to the wall ranged from 0.5–2.2 percent of host artery diameter (0.16–0.70 mm) depending on the quality of the signal. The radial spacing for the other two velocity measurements was 0.8 percent of the host artery diameter (0.25 mm). The accuracy of this wall shear stress technique was determined for a straight tube and the mean values...
were estimated to be within ±10 percent of the theoretical mean value, while the peak values (both positive and negative) were estimated to be within ±20 percent [27,29]. Values of mean, maximum and minimum wall shear stress were determined. Also computed were the pulse shear index (PS) and oscillatory shear index (OSI) where the PS is defined as the maximum minus the minimum value of wall shear stress and the OSI is defined according to Ku et al. [30]. Wall shear stress gradient was not considered since good estimates of this parameter would require more finely spaced measurements.

IV Statistical Analysis. A multiple regression analysis was used to determine the importance of hemodynamics, surgical injury, and the presence of PTFE on the development of IHT. IHT measurements are expressed at each position as the mean value of the seven dogs with the corresponding standard deviation. The measurements are expressed at each position as the mean value of jury, and the presence of PTFE on the development of IHT. IHT spaced measurements. Since good estimates of this parameter would require more finely estimated to be within 20 percent [27,29]. Values of mean, maximum and minimum wall shear stress were determined. Also computed were the pulse shear index (PS) and oscillatory shear index (OSI) where the PS is defined as the maximum minus the minimum value of wall shear stress and the OSI is defined according to Ku et al. [30]. Wall shear stress gradient was not considered since good estimates of this parameter would require more finely spaced measurements.

IV Statistical Analysis. A multiple regression analysis was used to determine the importance of hemodynamics, surgical injury, and the presence of PTFE on the development of IHT. IHT measurements are expressed at each position as the mean value of the seven dogs with the corresponding standard deviation. The shortest distance along the curved surface of the anastomosis from the suture line along the sidewall of the host artery, but did not extend as far as the floor. IHT consisted of smooth muscle cells overlying the PTFE graft. There is no evidence of mural or luminal thrombosis. Floor IHT is represented in Fig. 6(a) consists of an intimal pan-

Results

I Chronic Animal Studies

In Vivo Measurements. Hemodynamic and dimensional variables for the chronic in vivo studies were comparable to the scaled values used in the in vitro study. These variables were measured and averaged over the seven anastomoses and are expressed as mean ± standard deviation. The mean blood flow rates in the graft and the distal outflow segment were 173±66 ml/min and 136±45 ml/min, respectively. This yielded a proximal-to-distal outflow ratio of 19:81. At the time of sacrifice, the mean diameter of the host artery was 3.19±0.35 mm based on the average of the POS and DOS diameters of each animal. Thus, the mean graft to host artery ratio was 1.7:1 based on internal dimensions (internal diameter of the PTFE graft was ~5.6 mm). The mean hood length of the grafts was 12.9±1.9 mm. This gave an average hood length of 4.0±0.6 host artery diameters. These measurements show the in vivo graft geometry to be 15–20 percent smaller than the in vitro model geometry after fixation. This difference is caused by shrinkage and is typically found when tissue is fixed with three percent glutaraldehyde [31]. The kinematic viscosity was assumed to be 0.035 cm²/sec. The mean Reynolds number was 262 based on the total graft inflow and the host artery diameter. This is 18 percent higher than that of the in vitro studies.

Fig. 6 Histomicrographs of graft hood and arterial floor IHT (×120 mag), cross-sections were stained using the Gomori-trichrome-aldehyde fuchsin procedure for connective tissue staining. Graft hood IHT (Fig. 6(a)) consists of an intimal pan-

Both graft hood and suture line IHT were present in all anasto-

Fig. 5 Flow waveform used for the in vitro velocity measure-
ments. The flow rate has been scaled to reflect the equivalent in vivo values. POS and DOS are the proximal and distal out-
flow segments, respectively.

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within a relatively abundant extracellular matrix. The graft hood and artery floor IHT were similar in structural composition (Figs. 6(a) and 6(b), respectively). There was no evidence of fresh or organized thrombi.

Quantitative Morphometry of IHT. The distribution of mean IHT at the different axial locations is shown graphically in Fig. 7. Quantitative morphometry demonstrated that spatially averaged IHT was substantial along the graft hood and the suture line at the toe and heel (~20.4 and ~25.2, respectively), but was absent along the floor of all of the digitized sections. IHT was present along the heel side of the POS but absent on the floor side. IHT involving the native artery ranged from 0.06 ± 0.03 mm to 0.09 ± 0.06 mm between the toe (position ~0.4) and position ~4.4. Significant IHT was also found on the graft-side of the heel ranging from 0.06 ± 0.04 to 0.17 ± 0.07 mm.

II Wall Shear Stress Measurements. Low hemodynamic wall shear stress was found on the hood of the anastomosis and near the flow stagnation region along the floor (Fig. 8). Along the hood, mean wall shear decreased to a minimum value of 1.2 dynes/cm² at a position two diameters proximal to the toe. On the floor, where flow divided into the proximal and distal directions, the measured minimum was located 2.8 diameters proximal to the toe and with magnitude 1.6 dynes/cm². At most positions, the wall shear stress was lower than the value typically cited for normal arteries (10–20 dynes/cm²) as a consequence of the relatively large graft diameter and the division of flow in the DOS and POS. Higher values of wall shear stress were located along the floor just proximal to the toe region and within the DOS. PS was significantly higher near the floor stagnation point (positions ~2.0, ~2.8, and ~3.6) than at the same axial positions along the hood (39 ± 0.5 versus 24 ± 0.3 respectively). However, values of the oscillatory shear index on the floor and hood were not significantly different (0.17 ± 0.02 versus 0.22 ± 0.02, p > 0.1 respectively).

Table 1 Linear regression analyses of various hemodynamic variables versus mean IHT at all locations and the different anastomotic regions

<table>
<thead>
<tr>
<th>Hemodynamic Variable</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean shear</td>
<td>0.31</td>
<td>0.143</td>
</tr>
<tr>
<td>Maximum shear</td>
<td>-0.30</td>
<td>0.157</td>
</tr>
<tr>
<td>Minimum shear</td>
<td>0.10</td>
<td>0.642</td>
</tr>
<tr>
<td>Reciprocal of mean shear</td>
<td>0.52</td>
<td>0.009</td>
</tr>
<tr>
<td>Reciprocal of maximum shear</td>
<td>0.43</td>
<td>0.350</td>
</tr>
<tr>
<td>Reciprocal of minimum shear</td>
<td>-0.15</td>
<td>0.470</td>
</tr>
<tr>
<td>Oscillatory shear index (OSI)</td>
<td>0.38</td>
<td>0.067</td>
</tr>
<tr>
<td>Pulse shear index (PSI)</td>
<td>-0.29</td>
<td>0.165</td>
</tr>
</tbody>
</table>

Fig. 7 Distribution of mean IHT at the different axial locations in the experimental end-to-side anastomosis. IHT is along the graft hood and heel is more prominent than other regions within the anastomosis. IHT was absent on the floor of the graft.

Fig. 8 Time-averaged wall shear stress for each axial measurement location at the midplane

Fig. 9 Linear regression of the reciprocal of mean wall shear (1/WSS) and mean IHT. Filled symbols are along the floor (native artery). Open symbols are along the hood (PTFE). The triangles are near the suture line. The diamond is the floor stagnation point. Locations other than the suture line and stagnation point are represented with boxes. While a correlation is seen between IHT and 1/WSS, the degree of correlation is reduced by the influence of material and injury. The IHT values along the native artery are generally lower than those along PTFE for a given level of shear stress. Also, IHT values near the suture line are higher than those away from the suture line for a given material and a given wall shear stress level.
III Quantitative Correlation Between Wall Shear Stress and Anastomotic IHT. Multiple correlations between wall shear stress and anastomotic IHT were examined to assess the role of wall shear stress at the various regions where IHT developed. All 24 anastomotic measurement positions were used to compute linear regressions between IHT and the hemodynamic parameters: mean shear, maximum shear, minimum shear, reciprocal of mean shear, reciprocal of maximum shear, reciprocal of minimum shear, OSI and PS (Table 1). The results revealed a significant correlation only for the reciprocal of mean shear ($r = 0.525$, $p < 0.01$, Fig. 9) and the reciprocal of maximum shear stress ($r = 0.42$, $p < 0.05$).

The nonlinear multivariable regression indicated significance for four variables, $1/d_{ij}$, ($p = 0.003$), $m/d_{ij}$, ($p = 0.004$), $m/\tau$ ($p = 3.8 \times 10^{-5}$), and $1/d_{ij}^2$, ($p = 0.006$). This indicates a model for IHT of the form: $IHT = 0.033/d_{ij} + 0.27(m/\tau) + 0.0092(m/d_{ij}) - 0.0019(1/d_{ij})^2 - 0.060$. Units for these variables are IHT (mm), $d_{ij}$ (cm), $\tau$ (dyne/cm²), and $m$ (non-dimensional). The measured IHT is plotted as a function of the predicted IHT from this model in Fig. 10. A linear regression analysis between predicted and measured IHT gives a good correlation coefficient ($r = 0.936$, $p = 1.9 \times 10^{-41}$).

Discussion

It is reasonable to suspect that hemodynamic stress plays a role in the development of intimal hyperplasia. Both animal and human studies have shown that arteries adjust their lumen diameter in response to long term changes in blood flow rate to maintain the mean wall shear stress between 10 to 20 dynes/cm² [13–15]. Atherosclerotic plaques have been shown to localize in low or oscillatory wall shear stress regions of the human carotid artery [30,32,33], the coronary arteries [34–40], and the abdominal aorta [41]. Shear stress has been shown to elicit specific matrix synthesis responses in smooth muscle cells and to inhibit smooth muscle cell proliferation [42,43]. Although these studies indicate that hemodynamics can play a role in adjustment of lumen caliber and in the pathogenesis of disease, they do not specifically address the type of vascular adaptation or growth found in bypass graft anastomoses. It is not known whether significant point to point variations in wall shear stress magnitude within a geometric configuration such as the vascular anastomosis could result in corresponding focal variations in nonatherosclerotic IHT. Furthermore, effects of other confounding variables may be so strong as to mask the effect of wall shear stress. Most investigations into the relationship between hemodynamics and local wall adaptation in end-to-side anastomosis models have not used quantitative intimal thickness data to correlate with wall shear stress [9,17–19]. The studies of Geary et al. [16] were quantitative, but they considered neointimal thickness in a relatively straight segment of PTFE, where spatial variations in hemodynamic wall shear stress are minimal compared to those within a distal end-to-side anastomosis.

The results reported herein are unique in that the in vivo canine model and in vitro flow model were developed concurrently. The in vivo model was standardized to maintain similar PTFE diameter and arteriotomy length in all of the animals. The in vitro flow model was designed to match the in vivo graft shape, dimensions, and flow conditions. This design allowed an objective point by point comparison of IHT in the in vivo model with hemodynamic wall shear stress in the in vitro model. The results demonstrate that a significant inverse correlation exists between wall shear stress and anastomotic IHT on the PTFE surface. The degree of correlation suggests that in the presence of PTFE, mean wall shear stress plays a role in the development of anastomotic IHT in addition to other factors, such as mechanical stresses and mural injury.

The data suggest that the intimal hyperplastic response to hemodynamic forces may differ in native arteries and prosthetic conduits. IHT in the native artery (filled symbols in Fig. 9) never exceeded 0.05 mm, whereas most measurements along the PTFE (open symbols in Fig. 9) were greater than this value. This may be related to phenotypic heterogeneity [44] in smooth muscle cells at these locations. The differential response of different smooth muscle phenotypes to specific levels of oscillatory wall shear deserves further investigation.

Curve fits with hemodynamic variables other than mean wall shear stress (maximum WSS, minimum WSS, OSI, PS, and the reciprocal of WSS maximum and minimum) produced smaller correlation coefficients and larger $p$-values. Thus, the relatively poor correlation with hemodynamics was not a result of selecting the wrong hemodynamic variable. Wall shear stress gradient was not examined in these correlations because only a rough estimate of the wall shear stress gradient can be obtained from measurements obtained in this study. A numerical study of this flow model, validated by the in vitro data, should provide sufficient shear stress gradient data to perform quantitative correlations.

There are several differences between the hemodynamics of the hood and the floor. The pulse shear was significantly higher along the floor than along the hood, but the oscillating shear index was not. Additionally, reversal of shear stress along the hood represents true flow separation, similar to that which occurs at the carotid artery bulb. In contrast, changes in direction of flow along the floor are caused by a division of flow between the proximal and distal outflow segments (stagnation flow region) and occur without separation.

Because the IHT was always contiguous with the suture line, and because there was a general decrease in IHT with $d_{ij}$, this study suggests that IHT is initiated along the suture line and migrates onto both artery and PTFE. It appears that this migration of IHT was not rapid enough to reach the floor within the three month period of this study (i.e. more rapid migration of IHT on the PTFE surface). An important question is whether a longer study would allow this migration to reach the floor and whether a stronger correlation with $1/\tau$ would then be found along the native artery.

The parameters in the final curve fit (Table 2) are notable. After elimination of terms that were poorly correlated, the only term remaining with mean wall shear stress was the cross-term with material ($m/\tau$). Since host artery is represented as $m = 0$, only shear stress in conjunction with PTFE produced a statistically significant correlation (i.e. no statistically significant correlation was...
produced with native artery IHT). The term \(1/d_{sl}\) is represented by both a linear and a nonlinear term. Material is represented only in combination with \(d_{sl}\) and \(\tau\), which suggests a strong coupling between material and the other two parameters. It must be recognized that the dependencies on \(\tau\) and on \(d_{sl}\) have singularities at \(\tau=0\) and at the suture line, respectively. The data used in the curve fit are sufficiently far away from these regions to avoid the singularities. For example, the dependence on \(d_{sl}\) peaks at about \(d_{sl}=0.09\) cm and the closest positions to the suture line are at \(d_{sl}=0.12\) cm. The model should not be extrapolated to values of \(d_{sl}\) or \(\tau\) smaller than those used in the curve fit.

Since IHT was small in all of the canines studied, there may be differences between the intimal thickening observed in the present study and that observed in human vascular anastomoses. Furthermore, the multivariable curve fit model is mathematical rather than physiological. Clearly a model must be developed in which the coefficients are directly related to physiological parameters such as rate of cellular migration, apoptosis and proliferation. However, the data presented here provide an initial basis for comparison with other experiments, and they could be used as an initial test data set for more physiological models.

With advances in computers, numerical simulations for each individual animal graft geometry and flow condition may be possible for future studies. This may be important since it is difficult to predict how small changes in geometry may impact the wall shear stress distribution in these complex three-dimensional geometries. Further, a single flow waveform and geometry may not have a wall shear stress distribution representative of each individual graft, which may impact the correlation results.

**Conclusion**

Quantitative and concurrent experiments have been carried out to determine the correlation between intimal hyperplastic thickening in vivo and the distribution of hemodynamic wall shear stress in vitro for a canine end-to-side anastomosis model. The spatial distribution of IHT and the correlation of mean wall shear stress were correlated \((r=0.525, p<0.01)\). This correlation was only present for positions located on the PTFE graft itself. The data indicate that IHT is most evident at the suture line and along the juxta anastamotic PTFE graft hood, in contrast to the native artery. The relationship between IHT development and hemodynamics is significantly affected by multiple biological and mechanical factors (i.e., hemodynamics, surgical injury, and the presence of PTFE). A mathematical model based on multivariable analysis can be used to describe this relationship.

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