CHAPTER 4

4 PARTICLE HEMODYNAMICS OF THE DISTAL END-TO-SIDE FEMORAL BYPASS: EFFECTS OF GRAFT CALIBER AND GRAFT-END CUT

4.1 Introduction

4.1.1 Peripheral Bypass Grafts and Success Rates

Atherosclerosis may significantly occlude the femoral and popliteal arteries, more distal arteries, e.g., tibial and peroneal, or a combination of these vessels (Fig. 4.1.1a). In such cases, vascular bypass grafting is often the favored surgical option to restore blood flow to the lower extremities. Peripheral bypass grafts typically originate at the femoral artery (Fig. 4.1.1b) with a proximal end-to-side anastomosis. In cases where the primary occlusive development resides in the lower femoral artery, the bypass typically terminates at the popliteal artery with an end-to-side distal anastomosis either above or below the knee, i.e., the femoropopliteal bypass (Fig. 4.1.1b). In cases where occlusive developments are more extensive, the distal bypass anastomosis may be positioned at the tibial or peroneal arteries, or at multiple sites, cf. Fig. 4.1.2, e.g., femorotibial bypass. The use of an end-to-side anastomotic configuration is generally preferred for peripheral bypass grafting as it provides blood flow to terminal branches both proximal and distal to the anastomosis (Fig. 4.1.3a).

Subsequent late-stage graft failures are predominately due to restenosis resulting from intimal hyperplasia and/or thrombosis at the distal anastomosis, i.e., distal anastomotic intimal hyperplasia (DAIH). Hyperplasia formation has been reported to localize along the anastomotic suture-line, particularly at the graft toe and heel, and along the arterial floor opposite the graft as illustrated in Fig. 4.1.3a (Sottiurai et al., 1983; Sottiurai, 1999; Keynton et al., 2001; Loth et al., 2002). A common bypass failure scenario consists of a moderately occluded graft-to-artery anastomosis. Thrombosis (platelet adhesion, cell aggregation, and coagulation) may then occur in the region of constricted flow, resulting in sudden vessel occlusion.

While the pathological mechanisms responsible for the development of DAIH have not been fully elucidated, certain hemodynamic parameters have been qualitatively linked to intimal thickening in arterial bypasses and other branching blood vessel configurations, both macroscopically and at the cellular level. These parameters include low mean and oscillatory wall shear stress, large spatial and temporal gradients in wall shear stress magnitude, and gradients in wall shear stress vector direction (Ojha et al., 1990; Keynton et al., 1991; Bassiouny et al., 1992; Sottiurai, 1999; Kleinstreuer et al., 2001). Other factors that have been implicated with DAIH formation include excessive intramural wall stress, graft-to-vessel compliance mismatch, blood particle stasis, and blood particle deposition (Kleinstreuer et al., 2001; Ku, 1997; Sottiurai, 1999).

To minimize DAIH occurrence, native saphenous vein is typically the conduit of choice for arterial bypass graft construction. Resulting long-term success (i.e., patency) rates have been reported as high as 80% at two years (Dalman and Taylor, 1993) and 49% at 4 years (Veith et al., 1986). However, the use of autologous saphenous vein is not an option in as many as 60% of patients requiring a lower-limb bypass (Pappas, 1999). In such cases, expanded polytetrafluoroethylene (ePTFE) conduits are typically implemented, which result in success rates similar to saphenous vein for applications where the distal anastomosis resides above the knee (Veith et al., 1986). For below-knee distal positioning, PTFE grafts typically perform poorly, with four-year patency rates of approximately 12%. To improve the success rates of below-knee applications, inter-positioned vein cuffs (Miller et al., 1984; cf. Fig. 4.1.3b), and vein patches (Taylor et al., 1992; cf. Fig. 4.1.3c) have been suggested and continue to show promise in clinical studies. For instance, Stonebridge et al. (1997) found a 52% success rate at 24 months for below-knee popliteal bypass grafts with inter-positioned vein cuffs.

4.1.2 Review of Distal Anastomotic Studies

Hemodynamic characteristics of distal graft-to-artery anastomoses have been widely studied with the femoral bypass configuration representing a primary test case. Flow conditions and geometric parameters can vary broadly among distal anastomoses. For

instance, parameters such as inlet waveform shape, outlet flow division, graft-to-artery diameter ratio, graft-surface shape and graft angle are generally not consistent among *in vivo* observations (Bertschinger et al., 2001). A variety of hemodynamic models have been constructed to characterize effects of these variations on flow structures generated within end-to-side distal anastomoses. A vast majority of recent studies with canines have focused on identifying areas of low and oscillating wall shear stress (WSS) and have proposed that these regions are the most susceptible to DAIH formation (Keynton et al., 2001; Li and Rittgers, 2001; Loth et al., 2002). Other hemodynamic parameters such as the wall shear stress gradient (WSSG) and particle residence-times have only been considered on a limited basis (Longest and Kleinstreuer, 2001). Selected *in vitro* and computational hemodynamic models are summarized below. Table 4.1 gives an indication of representative studies that have been conducted to evaluate the effects of various geometric and boundary conditions on the hemodynamics within the distal femoral anastomosis.

In Vitro and In Vivo Models

The effects of outlet flow division, Reynolds number, and inlet angle on anastomotic flow characteristics were visualized by Crawshaw et al. (1980). Using models of straight tubes connected at 15- and 45-degrees, flow disturbance was found to be minimal when the inlet angle was low and the proximal outflow segment was occluded. The flow visualization models of Ojha et al. (1990) and Keynton et al. (1991) indicated regions of low WSS at critical sites where DAIH is expected and characterized WSS for various graft angles and flow rates in smoothly connected tubes. Flow visualization experiments of Ojha et al. (1993) implicated large spatial and temporal gradients of wall shear stress as possible sources of DAIH on the artery floor. Hughes and How (1996) visualized flow patterns in cylindrical anastomosis models and characterized the effects of graft-angle and flow-division under steady and pulsatile conditions. The general consensus of these visualization models is that low graft angle, low retrograde flow (as with an occluded proximal outlet), and steady flow all reduce flow disturbances in end-to-side distal anastomoses.

Sottiurai et al. (1989) qualitatively characterized the location and biologic content of DAIH in distal canine PTFE iliofemoral grafts. As found in humans, DAIH was reported to localize in regions of the heel and toe of the graft and on the floor of the host artery; however, quantitative measurements and graft geometry details are not provided. Bassiouny et al. (1992) constructed canine model iliofemoral bypass grafts of saphenous vein and PTFE. Biologic content of DAIH and qualitative locations were considered after eight weeks. Transparent silicone cast models were also constructed for flow visualization experiments. Bassiouny et al. (1992) observed that suture-line intimal thickening was greater in PTFE anastomoses than in vein anastomoses while arterial floor IH was consistent among both groups. It was postulated that suture-line DAIH formation was due to surgical injury and compliance mismatch, while DAIH at other locations arose from hemodynamic mechanisms. Sottiurai (1999) suggests that compliance mismatch is not the cause of DAIH development, but it enhances the pathogenesis such that hemodynamic factors may still play a predominant role. Bassiouny et al. (1992) also visualized hemodynamic flow patterns in cast models and found a qualitative correlation between intimal thickening and sites of observed low-WSS as indicated by long particle residence times.

Using a cast model similar to the Bassiouny et al. (1992) canine distal anastomosis, White et al. (1993) employed neutrally buoyant particles to visualize flow features and characterize the effects of flow division, Reynolds number, and graft-hood length. They found that for their specific geometry, the flow tended to be skewed toward the graft hood, such that only a fraction of the anastomosis actually participated in flow delivery to the host vessel, regardless of hood-length. Via comparison with the studies of Sottiurai et al. (1989) and Bassiouny et al. (1992), White et al. (1993) suggested a relation between localized vascular intimal thickening and low shear stress regions characterized by long particle residence times. Loth et al. (1997) reported velocity and shear stress measurements in a similar *in vitro* model of the canine distal anastomosis with a graft-to-artery diameter ratio of 1.5:1. They showed that low graft angles and larger graft diameters reduce the magnitude of spatial WSSG contours on the floor of the graft. In a similar canine model, Keynton et al. (1999) measured near-wall velocities *in vivo* and concluded that graft size has a dramatic effect on wall shear stress magnitude.

As described in Section 3.6, several recent studies have implemented canine models to evaluate possible correlations between WSS-based hemodynamic parameters and sites of DAIH (Keynton et al., 2001; Li and Rittgers, 2001; Loth et al., 2002). For 30^o anastomotic configurations with no proximal outflow, Keynton et al. (2001) observed limited IH occurrence along the toe region while most significant DAIH occurred along the artery floor. Considering the toe and floor only, DAIH was found to weakly correlate with exponential functions of the inverse mean WSS ($r^2 = 0.23$) and the OSI ($r^2 = 0.36$). Interestingly, Keynton et al. (2001) observed that a vast majority of DAIH occurs in regions where the mean wall shear rate is below a critical value and that IH often remains absent over a significant range of wall shear rates. In comparison, for a low graft-angle (approximately 10^o) and a proximal-to-distal outlet flow division of 20:80, Loth et al. (2002) found DAIH to be *most significant along the graft hood and the suture-line at the toe and heel*, but was *absent along the arterial floor*. DAIH was found to strongly correlate with the inverse of the WSS along the hood; however, regions of equally low (or lower) WSS were observed at the floor (where no DAIH occurred) such that an overall relationship was relatively weak ($r^2 = 0.276$). Including factors such as distance from the suture-line and vascular conduit type resulted in a significantly stronger correlation (Loth et al., 2002); however, these variables do not necessarily indicate mechanisms responsible for DAIH at the cellular level.

Li and Rittgers (2001) evaluated the effect of proximal outflow on WSS, WSSG and OSI parameters under pulsatile flow in a canine anastomosis model. They found no significant difference in spatial WSSG along the artery floor and the graft hood for the outlet flow ratios of 0:100, 25:75, and 50:50. Considering that the site of greatest DAIH development has been observed to vary under different outflow conditions (Keynton et al., 2001; Loth et al., 2002), Li and Rittgers (2001) concluded that regions exposed to a combination of low WSS and high OSI may be the most prone to occlusive developments.

A number of studies have focused on visualizing vortical flow patterns in cuffed distal anastomoses. Qualitative angiograms and pathologic studies of Miller-cuffs have demonstrated that DAIH is redistributed away from critical areas such as the heel, toe, and arterial floor, and up to the cuff-to-graft interface, where a larger cross-sectional area is

available to accommodate occlusive developments (Tyrrell and Wolfe, 1997). To explain this phenomenon, da Silva et al. (1997) used illuminated neutrally buoyant particles to visualize anastomotic hemodynamics in Miller-style cuff geometries. They observed the formation of a vortex within the cuff area and speculated that this may increase wall shear stress thereby inhibiting DAIH development; however, values of WSS were not calculated. Noori et al. (1999) performed similar flow visualization experiments in cast replicas of conventional, Miller-cuff, Taylor- and Linton-patch designs. The latter two designs performed very similar to the conventional design with a vortex that decayed during diastole. The vortex within the Miller-cuff persisted for nearly the whole diastole, which Noori et al. (1999) interpreted as a beneficial continuous 'wash-out' of the cuff cavity.

Harris and How (1999) used neutrally buoyant particles to visualize anastomotic hemodynamics in models of direct end-to-side, vein cuffed, and preshaped PTFE junctions. They suggested that the presence of a large vortex formed in the vein cuff minimized regions of low wall shear stress and reduced the exposure of walls to activated platelets and mitogenic factors. Furthermore, Harris and How (1999) suggested that increased shear stress oscillation on the arterial floor (similar to the OSI) is protective for the case of the vein cuff design. Following the lead of Lei et al. (1996), Harris and How (1999) proposed a pre-shaped PTFE cuff to eliminate the need for vein collar construction. While the design objective of Lei et al. (1996, 1997) was to reduce 'disturbed flow patterns' in the junction region, the pre-shaped cuff design of Harris and How (1999) is intended to increase vortical flow and wall shear stress. Harris and How (1999) claim the pre-shaped cuff eliminates regions of low WSS; however, no quantitative details in support of this argument have been provided. The pre-shaped cuff of Harris and How (1999) is currently being marketed by IMPRA-Bard, Inc. under the trade name 'Distaflo'.

In a series of papers, Fisher et al. (2001a & b) have visualized vortical flow features in the pre-cuffed Distaflo^{TM} graft, verified that such features exist *in vivo*, and suggested 'optimal' Miller-cuff graft dimensions. Fisher et al. (2001a) observed a coherent vortex throughout the cardiac cycle within the Distaflo^{TM} graft, which is completely removed along with all particles at the onset of the next cycle. Fisher et al. (2001a) suggested that a widely varying stagnation point as observed in the Distaflo^{TM} graft is beneficial owing to the fact

that it minimized the localization of low WSS. Fisher et al. (2001b) visualized flow in Miller style cuffed geometry with either 50:50 or 75:25 distal-to-proximal outflow. From flow visualization snapshots, Fisher et al. (2001b) speculate that regions of low wall shear stress may be more common in lower and long cuffs (due to complex short lived vortices) and, therefore, suggest a high-cuff design.

Using representative models of distal femoropopliteal bypass grafts with and without vein-cuffs (Fig. 4.1.4), How et al. (2000) made pulsatile velocity measurements and calculated mean wall shear stress. These mid-plane symmetric models were characterized by a 12-degree angle of anastomosis, a 2:1 graft-to-artery ratio and two different outflow ratios, i.e., 50:50 and 75:25. How et al. (2000) identified an extended region of low WSS on the floor of the host artery in the uncuffed configuration and postulated that the absence of this region was responsible for the improved patency observed with the construction of a vein cuff in clinical applications. How et al. (2000) were unable to measure WSS distributions on the vein cuff surface. This study represents one of the only *in vitro* attempts to quantify wall shear stress within a cuffed style anastomosis.

Computational Studies

Steinman et al. (1993) numerically simulated 2-D pulsatile flow in a femoral anastomosis model geometry. Comparing their results to the qualitative data of Sottiurai et al. (1989), Steinman et al. (1993) suggested a correlation between locations of high temporal and spatial wall shear stress gradients with DAIH (based on propositions suggest by Morinaga et al. (1985)). Furthermore, Steinman et al. (1993) did not find a strong correlation between sites of low shear stress and DAIH development; hence, it was speculated that multiple hemodynamic parameters may be involved. Henry et al. (1996) showed DAIH corresponded to sites of low WSS, which were also sites of increased spatial WSSGs in some instances.

Fei et al. (1994) simulated the hemodynamic effects of modifying the graft angle and Reynolds number in tubular anastomotic geometries under steady flow conditions.

Compared with qualitative observations of DAIH, Fei et al. (1994) supported the low WSS hypothesis; however, no other hemodynamic parameters were considered.

Lei et al. (1996, 1997) and Kleinstreuer et al. (1996) used the finite volume method to evaluate the hemodynamics of a variety of distal end-to-side anastomoses and calculated different hemodynamic parameters including the WSS, WSSG, and OSI. Extrapolating from the results of Sottiurai et al. (1983, 1989), Lei et al. (1996, 1997) and Kleinstreuer et al. (1996) supported a direct correlation between the WSSG hemodynamic parameter and DAIH. Lei et al. (1996, 1997) showed that large anastomotic flow areas, small continuous changing bifurcation angles, and smooth junction wall curvatures reduce spatial WSSGs and should mitigate restenosis. Kleinstreuer et al. (1996) evaluated the effects of input waveform on hemodynamic parameters in the distal anastomosis.

Hofer et al. (1996) computationally analyzed wall mechanics and flow dynamics in compliant vascular distal end-to-side anastomoses in conjunction with an experimental study on DAIH in sheep. They stated that DAIH developed extensively at the suture-lines, moderately on the floor of the host artery, and continued downstream of the toe. Hofer et al. (1996) observed a qualitative correlation between DAIH and low wall shear stress in the region of the bed and proposed that intramural stress and strain were responsible for DAIH at the suture-line. Vessel wall compliance seemed to affect local hemodynamics only to a minor degree.

Ethier et al. (1998) computed WSS and WSSG hemodynamic parameters in an idealized end-to-side anastomosis under femoral, iliac and coronary input waveforms. They observed that temporal and spatial gradients of WSS on the host artery floor are much larger for the femoral waveform than for the coronary, even though mean WSS patterns were relatively similar.

Moore et al. (1999) addressed the use of simplified end-to-side computational models compared with more anatomically faithful replications. Beginning with a cast of a human femoral-popliteal bypass graft, certain features of the anastomosis were sequentially removed to produce a series of successively simplified models. *With respect to the hemodynamic parameters WSS and OSI, computational simulations showed that variations of the graft-to-artery diameter ratio induced the most significant change*. Local arterial caliber changes,

out-of-plane curvature, and small-scale surface topography were shown to have secondary effects on the WSS-field.

Recently, Sherwin et al. (2000) have specifically evaluated the effect of out-of-plane graft inlet curvature in a cylindrical model anastomosis under steady Newtonian flow conditions. It was found that severe out-of-plane curvature reduced the mean shear stress in the bed of the anastomosis by 10%. Kute and Vorp (2001) also analyzed steady Newtonian flow in an end-to-side geometry. They computed hemodynamic parameters such as WSS and WSSG to verify the qualitative *in vitro* result that proximal arterial flow increases aggravating hemodynamics in the junction area.

Lei et al. (2001) computed hemodynamic wall parameters under pulsatile flow in a realistic distal anastomosis similar to the canine ilio-femoral model employed by Loth et al. (1995, 1997). The primary focus of this study was to validate the numerical results with the experimental velocity and shear measurements made by Loth et al. (1997). Agreement was found to be sufficient. Although Loth et al. (1995) have quantified DAIH development in this geometry, Lei et al. (2001) contended that sufficient *in vivo* data is not currently available to establish a correlation between hemodynamic wall parameters and intimal thickening.

Leuprecht et al. (2002) investigated the influence of a vein cuff, material compliance, and flow division on hemodynamic behavior and the resulting intramural wall stresses. This study was conducted in conjunction with the *in vitro* work of Noori et al. (1999) and provides limited DAIH *in vivo* results for conventional and Miller-style grafts in sheep. As with Hoffer et al. (1996), the computational findings of Leuprecht et al. (2002) suggest that wall distensibility has a small influence on the flow field and the wall stress. The reported *in vivo* results indicate similar DAIH conditions in the artery of the conventional and Miller-style grafts. The higher failure rate of the conventional graft may then be attributed to conditions within the graft or along the suture-line. Leuprecht et al. (2002) found reduced intramural stress and lower DAIH occurrence along the suture-lines of the Miller cuff, which are also locations of reduced compliance mismatch compared to the conventional graft. However, Leuprecht et al. (2002) point out that a significant cause of the reported improvement in patency of the Miller-cuff may be due to the larger space, which better accommodates DAIH

development. In a related study, Perktold et al. (2002) reported WSS-fields for conventional, Taylor-patch, and Miller-cuff designs. Reduced oxygen flux to the wall was reported as a potential mechanism accelerating DAIH development, particularly in low WSS regions.

Cole et al. (2002) simulated hemodynamic characteristics of conventional and Taylor-patch graft designs. Due to the expanded anastomotic area, the Taylor geometry was found to mitigate fluid separation distal to the toe. Reduced WSS magnitudes and spatial variations were observed along the arterial floor. While the Taylor patch is associated with higher sustained patency rates in comparison to conventional designs (Taylor et al., 1992), reduced IH occurrence along the arterial floor is not observed in the *in vivo* results of Perktold et al. (2002).

4.1.3 Motivation for the Current Study

Research studies over three decades have established that hemodynamic and blood particle interactions with the vascular surface as well as surgical injury are inciting mechanisms capable of eliciting various cellular responses potentially resulting in DAIH. As reviewed above, qualitative comparisons with generalized regions of DAIH localization (Sottiurai et al., 1989) have implicated low and oscillatory shear (Bassiouny et al., 1992; Ojha et al., 1990; Keynton et al., 1991) as well as variations in mean WSS magnitude (Lei et al., 1996; Steinman et al., 1993) and direction (Kleinstreuer et al., 2001). Intimal hyperplasia along the suture-line is widely associated with surgical injury, suture technique, compliance mismatch, and intramural strain (Bassiouny et al., 1992; Leuprecht et al., 2002). As with atherosclerosis, long near-wall residence times and depositions of critical blood particles have also been associated with general qualitative sites of DAIH development (Bassiouny et al., 1992; Sottiurai et al., 1999; White et al., 1993). Recent studies in canine models have clearly reported specific sites DAIH as a function of anastomotic characteristics. For instance, Keynton et al. (2001) reported limited IH occurrence along the toe and most significant occurrence along the floor of a 30^o anastomosis with no proximal outflow. In comparison, Loth et al. (2002) reported most significant IH along the graft-hood and suture-line at the toe and heel with little to no occurrence along the arterial floor for a 10^o

anastomosis with 20% of the flow exiting proximally. In both studies, relatively weak but significant quantitative correlations were identified with the inverse of mean WSS and with the OSI. As reported in Section 3.6, computational results for geometries consistent with those of Keynton et al. (2001) and Loth et al. (2002) indicate weak and inconsistent relationships between the WSS-based hemodynamic parameters and system specific DAIH observations. However, WSSG and WSSAG parameters were consistently and significantly elevated along the suture-line providing a potential hemodynamic mechanism for continued IH occurrence at this location. Considering particle-wall interactions, the composite NWRT model for platelets, which includes biomechanical factors for both surface reactivity and platelet activation, was found to effectively capture significant regions of reported DAIH occurrence for different anastomotic configurations (cf. Section 3.6).

Primary geometric features influencing anastomotic hemodynamics include the graft-to-artery diameter ratio (Moore et al., 1999) and graft-hood shape (White et al., 1993). Such features are largely determined according to the graft caliber and initial graft-end cut selected by the vascular surgeon. Unfortunately, there is little clinical evidence identifying an appropriate graft-to-artery diameter ratio for distal end-to-side applications. Abbott et al. (1997) found that larger caliber grafts were typically associated with higher success rates (7 to 8 mm vs. 5 to 6 mm) for above-knee femoropopliteal bypass applications. However, the increased failure rate of below knee femoro-popliteal grafts (Stonebridge et al., 1997) is often speculated to be due, in-part, to hemodynamics induced by increased graft-to-artery ratios. An increased risk of technical error may as well account for the increased failure rate associated with below-knee applications (Stonebridge et al., 1997). Conversely, smaller grafts associated with lower diameter ratios, which may limit the occurrence of low-WSS, typically present an increased risk of early graft failure due to thrombosis (Binns et al., 1989).

Considering the problematic below-knee distal femoral anastomosis, clinical evidence indicates that inter-positioned vein cuffs (Miller et al., 1984; Stonebridge et al., 1997) and vein patches (Taylor et al., 1992) significantly extend graft function. Hemodynamic studies of these configurations have suggested that higher wall shear stresses, reduced compliance mismatch, and larger anastomotic areas which better accommodate DAIH development may account for the reported higher long-term success rates of the vein-supplemented designs

(Harris and How, 1999; How et al., 2000; Noori et al., 1999). Nevertheless, construction of a vein cuff or patch is an intensive procedure which increases the risk of surgical complications as well as technical errors. The recent availability of pre-cuffed or expanded grafts (Venaflo^{TM} and Distaflo^{TM}, Impra Bard; Tempe, AZ), as suggested by Harris and How (1999), Lei et al. (1996 & 1997) as well as Longest and Kleinstreuer (2000), has simplified the anastomotic procedure. However, it is questioned if the improved patency of these configurations is due to reduced IH occurrence, which may be unlikely in the lowered WSS environment of the expanded graft, or a result of increased anastomotic area. While vortical flow, as an example of a 'disturbed flow pattern', is generally associated with DAIH (Kleinstreuer et al., 2001; Liu, 1999), a number of researchers have speculated that *persistent* vortices engendered by vein and pre-cuffed designs may avoid critically low WSS-values resulting in reduced DAIH occurrence (Fisher et al., 2001a & b; Harris and How, 1999; Noori et al., 1999).

While expanded anastomotic configurations offer a promising alternative for below-the-knee applications, a number of issues remain unresolved for unexpanded designs. Clinically, traditional distal anastomoses are largely constructed according to the training or preference of the vascular surgeon. Depending on the graft diameter selected and the initial graft-end cut made by the surgeon, so-called 'conventional anastomoses' can vary significantly. In this study, the anastomotic configurations resulting from three common graft-end cut styles (straight, curved, and S-shaped) have been investigated including significant changes in the geometry of the recipient artery. Numerical simulations have been conducted in order to characterize the resulting differences in vascular hemodynamics in terms of velocity fields and selected particle trajectories. Assuming a comparable compliance among grafts, the potential for DAIH development will be evaluated based on hemodynamic wall parameters. Due to the qualitative correlations established in Sect. 3.6, particular emphasis will be placed on the NWRT model for platelet interactions with the vascular surface. Through a better understanding of the hemodynamics of various un-expanded vascular designs, it is expected that: (*i*) potential mechanisms responsible for the increased rate of failure of below-knee applications may be indicated, (*ii*) a preferred graft-end cut and resulting anastomotic configuration based on the hemodynamic parameters

considered may be established, and (*iii*) indications for anastomotic configurations that further reduce IH occurrence may be revealed.

4.2 Systems

Of interest are realistic femoropopliteal distal anastomoses with graft and arterial diameters representative of below-knee applications. Synthetic thin-walled PTFE grafts (Impra Bard, Tempe, AZ) of 8 and 6 mm were pressed flat and cut in three commonly implemented styles (straight 45^{o}, concave, and S-shaped; Fig. 4.2.1). The grafts were then sutured (by Dr. JP Archie, Jr.) in end-to-side fashion to 4 mm thin-walled PTFE grafts representing the recipient artery. The anastomoses were filled with RTV polyurethane rubber (Poly 74-30^{TM}; Polytek, Easton, PA) to a static pressure of 100 mmHg and cured. Internal cast of the grafts were excised and digitized via three-dimensional laser scanning (First Article Corp., New Hope, MN). Surface models were constructed to maintain key geometric features, such as graft and artery cross-sectional variations due to the construction of the anastomosis. Models constructed include two straight graft-end cuts of 8 and 6 mm grafts resulting in the common below-knee diameter ratios of 2:1 and 1.5:1 (referred to as Grafts 1 and 2; Fig. 4.2.2). Concave and S-shaped graft-end cuts were applied to 6 mm grafts resulting in Grafts 3 and 4 (Fig. 4.2.2). In all cases considered, the opening of the artery in the region of the anastomosis induces an elliptical arterial cross section and results in a raised vessel floor. This feature is more evident with the larger diameter ratio. The resulting artery configuration, which is due to the pressurized anastomosis, has also been faithfully reproduced. A gently curving inlet graft section, as observed *in vivo* (Bertschinger et al., 2001), was assumed and consistently reproduced for all models. The vessel walls were assumed to be rigid and symmetric about an axial centerline-plane, i.e., in-plane. Details regarding the construction of the computational mesh, numerical solutions, and convergence have been provided in Chapter 2.

A transient Type I input pulse, consistent with post-surgical observations of the femoral bypass (Okadome et al., 1991), has been implemented for all grafts (cf. Fig. 4.2.3). As described in Sect. 2.2.1, the input pulse selected is well within the range of typical mean

flow-rates for 8 and 6 mm femoral bypass grafts, and falls within peak velocity and Reynolds number guidelines for non-stenosed grafts (Nielsen et al., 1993; Papanicolaou et al., 1996). Consistent with Type I waveforms, only a small amount of net retrograde flow is observed, which occurs around t/T = 0. The resulting velocity profiles display a significant amount of retrograde flow in the near-wall region throughout diastole. With respect to anastomotic flow division, a distal-to-proximal outflow ratio of 80:20 has been assumed for all cases. This division ratio is considered to be appropriate for below knee applications where the anastomosis is often required to provide blood flow to both proximal and distal terminal branches.

4.3 Results

4.3.1 Anastomotic Hemodynamics

Mid-plane and cross-sectional contours of velocity magnitude as well as mid-plane velocity vectors for Grafts 1 through 4, during accelerating (t_1; Fig. 4.3.1) and decelerating (t_2; Fig. 4.3.2) flow, illustrate the complex vortical patterns inherent to distal anastomotic configurations. In order to characterize fluid motion in the displayed cross sections, secondary velocity vectors have been used to compute surface streamlines for two-dimensional (2-D) slices (Ethier et al., 2000; Tobak and Peake, 1982). Due to the 3-D nature of the underlying flow, conservation of mass is not satisfied between adjacent 2-D streamlines. Nevertheless, the 2-D traces provide an effective representation of the underlying secondary motion at an instant in time including axial vortices and regions of flow separation (Figs. 4.3.1 & 4.3.2).

Due to the curved graft-inlet configuration, Dean-type vortices arise upstream of the anastomosis. This vortical flow pattern can be explained by the interaction of inertial and viscous forces, as described by Berger et al. (1983). As the flow moves through the curved graft inlet, inertial and circumferential forces act to resist the imposed change in fluid direction, which moves the central core of highest velocity closer to the outer wall. The resulting partial impingement of the higher velocity flow on the outer wall induces a region

of elevated pressure. In the central core, where the axial velocities are highest, the inertial force dominates the pressure force resulting in an outward secondary motion of the fluid, i.e., circulation toward the outer wall of the bend. Near the graft surface, the pressure gradient dominates inducing circumferential motion of the fluid away from the outer wall of the bend. To characterize flow in curved tubes, the Dean number is often used, i.e.,

$$\kappa = \left(\frac{a}{R}\right)^{1/2} \frac{2aU}{\nu} \qquad (4.3.1)$$

where a represents the tube radius, R represents the radius of curvature of the bend, U is the mean velocity, and ν is the kinematic viscosity. As such, the Dean number represents the ratio of inertial and centrifugal forces to viscous forces. Considering that secondary flow is induced by centrifugal forces and their interaction with viscous forces, κ is a measure of the magnitude of secondary flow (Berger et al., 1983). For Grafts 1 and 2, assuming Newtonian viscosity, respective Dean numbers are $\kappa = 54$ and $\kappa = 46$. These nearly consistent values do not necessarily indicate the significantly skewed inlet profile observed with Graft 2, in comparison to Graft 1, during decelerating flow (Fig. 4.3.2). However, the larger diameter of Graft 1 reduces the luminal shear stress resulting in a 30% increase in viscosity due to non-Newtonian effects. The related increase in viscous momentum transport results in the more unified inlet velocity profiles of Graft 1, thereby reducing Dean-type vortices that enter the anastomosis. However, the effect of the adverse pressure gradient along the lower inlet-graft wall was magnified during decelerating flow inducing fluid recirculation within all grafts and contributing to significant secondary motion prior to the anastomotic junction (Fig. 4.3.2).

Due to the geometry of the anastomoses, flow is constricted just upstream of the suture-line. As the flow enters the artery, a sudden expansion occurs where an adverse pressure gradient results in separation across the junction and throughout the flow cycle. In the region of the toe, a significant separation 'bubble' extends downstream and is most pronounced during flow deceleration (Fig. 4.3.2). Viscous transport of axial momentum and an adverse pressure gradient near the arterial wall emanating from the reattachment point result in recirculation within the separation region. Furthermore, the separation region is characterized by low pressure such that a circumferential pressure gradient arises. The interaction of the downward inertia of the central fluid coupled with the existence of a

circumferential pressure gradient result in a set of mid-plane symmetric vortices, one of which is shown to rotate clockwise in Section B of Fig. 4.3.2b. The Dean-style vortices resulting from graft curvature are subsequently forced into the lower half of the arterial lumen, shown as the counter-clockwise vortex in Section B of Fig. 4.3.2b. For cases in which both pairs of vortices arise, such as with Grafts 2 and 3 during decelerating flow, a significant secondary mechanism exists that effectively transports centralized fluid elements toward the wall. Due to the elevated viscous and reduced inertial forces in Graft 1, formation of these counter-rotating vortices is delayed until approximately $t/T = 0.5$, and then only occurs for a brief period. Regarding Graft 4, the axial vortex induced by flow separation at the toe dominates the secondary motion such that the Dean-style vortex is not evident at Slice B during a majority of flow deceleration (Fig. 4.3.2d).

As with the recirculation region distal to the toe, a separation region forms at the heel and extends proximally. Low pressure within this separation bubble as well as axial flow reversal result in a single set of mid-plane symmetric vortices that are convected down the proximal section. The orientation of these vortices results in transport toward the lower arterial wall, i.e., the proximal arterial floor region. Proximal outflow also induces a surface of flow reversal emanating from the heel and extending to the arterial floor. The intersection of this surface with the vessel wall represents a curve of axial flow separation and, as such, is characterized by reduced axial shear stress and elevated pressure. The separation or stagnation point along the midplane is observed to move proximally during flow acceleration (t_1) and distally during flow deceleration (t_2).

Fluid expansion across the lateral suture-lines typically produces flow separation within the sinus region (Slice A of Figs. 4.3.1 and 4.3.2). As with any separation region, flow recirculation is dependent on two interacting mechanisms. One such force is viscosity driven lateral momentum transport which accelerates the upper layers of the separation region in the direction of main flow. In addition, the presence of a fluid reattachment point typically creates an adverse pressure gradient which drives the fluid near the wall counter to the bulk motion. The interaction of shear stress and an adverse pressure gradient results in fluid recirculation just below the suture-line in Graft 4 at t_1 (Fig. 4.3.1d Slice A). In contrast, Grafts 1 though 3 do not indicate recirculation within the sinus region at Slice A during flow

acceleration. This observation can be explained by consideration of the axial separation curve, and the associated elevated pressure, which is well proximal to Slice A during accelerating flow. Downstream of the separation curve, the raised arterial floor induces a negative pressure gradient in the vicinity of Slice A, such that the pressure at the floor is less than the pressure near the suture-line. Hence, both momentum flux and pressure gradient mechanisms direct secondary velocities toward the arterial floor, and flow recirculation does not occur. During flow deceleration, the axial separation curve moves beyond Slice A such that a region of relatively high pressure occurs along the arterial wall between the suture-line and the central floor location. As a result, the circumferential pressure gradient within Slice A reverses and fluid recirculation is evident just below the suture-line, particularly for Grafts 1 and 3 (cf. Figs. 4.3.2a & d). Apparently, axial motion of the separation curve along the arterial floor controls recirculation in the sinus region. Furthermore, these regions of significant fluid element stasis are eliminated at Slice A during flow acceleration in all configurations except for Graft 3.

Vortical flow features within the end-to-side anastomoses can also be characterized with selected particle trajectories (Fig. 4.3.3a-d). Monocytes entering Graft 1 at various times during the flow cycle indicate significant recirculation within the junction area, particularly in the region of the sinus (Fig. 4.3.3a). Some helical particle motion is observed in the proximal artery, whereas very little secondary transport is evident in the fast moving distal stream of Graft 1.

The more prominent Dean-style vortices in the inlet section of Graft 2 transport particles away from the outer wall centerline and toward the lateral graft and arterial sinus. However, particle recirculation in the sinus region is significantly reduced in comparison to Graft 1. Furthermore, particles in the distal and proximal arterial regions display a moderate helical pattern indicative of elevated secondary velocities.

The hood curvature of Graft 3, and the associated secondary motion, result in significant particle transport from the upper graft surface to the lateral suture-line and sinus regions. Significant particle recirculation is evident throughout most of the anastomotic area. As observed by White et al. (1993) for a similar configuration, significant skewing of the

flow toward the graft hood results in only a small fraction of the anastomosis being utilized for flow delivery.

Monocyte trajectories in Graft 4 highlight the significant axial vortices in the proximal and distal regions elicited by the abrupt anastomotic profile. Significant recirculation within the junction region as well as a highly focal separation area along the arterial floor are also evident.

4.3.2 WSS-Based Hemodynamic Parameters

For Graft 1, the mid-floor region, lateral sinus wall, and a significant potion of the inlet are characterized by low WSS and high OSI (Fig. 4.3.4). However, the anastomotic toe in the vicinity of the suture-line displays high WSS and low OSI. Changes in mean WSS magnitude and direction, as quantified by the WSSG and WSSAG, are most pronounced along the suture-line with elevated contours occurring at the toe and heel. Elevated contours of the WSSG and WSSAG also encompass the sinus region and extent to the arterial floor.

In comparison to Graft 1, the smaller diameter of Graft 2 significantly increases WSS and reduces OSI throughout the anastomotic inlet (Fig. 4.3.5). However, the increased separation region distal to the toe of Graft 2 results in coinciding regions of reduced WSS and elevated OSI. Owing to the small anastomotic area of Graft 2, WSS values are observed to change more rapidly over the surface, i.e., more compact contours lines. The resulting WSSG contours are moderately higher than observed with Graft 1. Similarly, time-averaged WSS vector directions vary more dramatically due to the smaller anastomotic area of Graft 2, resulting in an elevated occurrence of the WSSAG. As with Graft 1, WSSG and WSSAG contours for Graft 2 are most significant along the suture-line, particularly at the toe and heel.

Graft 3 exhibits low WSS and high OSI along the arterial floor, while the graft hood and toe regions are largely characterized by high WSS and low OSI (Fig. 4.3.6). WSSG contours are generally consistent in magnitude among the graft hood, sinus, and floor regions, with a maximum occurring at the toe in the vicinity of the suture-line. As illustrated by the WSSAG field, WSS-vectors change direction most severely along the suture-line.

A centralized axial separation region on the floor of Graft 4 as well as significant separation in the regions of the toe and heel result in corresponding low WSS and high OSI contours (Fig. 4.3.7). In contrast, the immediate toe region is characterized by high WSS and low OSI. The proximity of low and high WSS in the region of the toe results in significant WSSG contours, which extend across the suture-line region. Similarly, significantly elevated WSSAG contours are observed along the suture-line; however, maximum values occur at the graft heel.

4.3.3 NWRT-Based Models

Convergent profiles of the NWRT parameter, based on 400,000 platelet trajectories, indicate significant particle-wall interaction along the suture-line of Graft 1, particularly at the toe, as well as in the sinus and along the arterial floor (Fig. 4.3.8a). The composite NWRT model, which includes conditions for platelet activation and surface reactivity (cf. Sect. 3.3), emphasizes particle wall interactions throughout the anastomosis including the suture-line and sinus regions with critically elevated contours extend to the arterial floor (Fig. 4.3.8b). Consistent with the 4 mm artery and applied inlet conditions, a value of WSS_{mean} = 14 dyne/cm^2 was used to compute PSH and SR factors. Comparison to Graft 1 WSS values (Fig. 4.3.4) indicates that the elevated composite NWRT contours observed along the arterial floor are primarily due to the SR factor in the presence of significant particle-wall interactions. In contrast, elevated composite NWRT contours in the immediate high WSS region of the toe are due to the PSH factor, which increases significantly upstream for particles that travel near the outer graft surface.

The smaller inlet diameter and reduced sinus region of Graft 2 result in significantly elevated fluid and particle velocities such that NWRT occurrence is reduced throughout the junction, in comparison to Graft 1 (Fig. 4.3.8c). Significant regions of particle-wall interaction include the suture-line, particularly at the toe and heel, and the sinus region. Moderate particle interaction with the vascular surface is observed along the arterial floor, and, due to the counter-rotating Dean and anastomotic vortices, along the distal lateral wall. Including PSH and SR factors for Graft 2 diminishes NWRT-values in the sinus region and

magnifies values near the toe (Fig. 4.3.8d). In comparison to Graft 1, composite NWRT values along the arterial floor of Graft 2 are significantly lower due to reduced particle-wall interaction, as well as lower SR and PSH factors (Fig. 4.3.8d).

Due to secondary velocities instigated by the significantly curved hood of Graft 3, a large amount of platelet-wall interaction is observed in this region (Fig. 4.3.8e). Elevated NWRT contours are also evident along the suture-line at the toe and heel as well as in the enlarged arterial sinus. Interestingly, very little particle-wall interaction is observed along the arterial floor. Inclusion of PSH and SR factors magnifies NWRT contours along the graft hood and suture-line at the toe and heel (Fig. 4.3.8f). Due to a lack of particle-wall interaction, composite NWRT contours remain largely absent within the low shear stress environment of the arterial floor, which is consistent (cf. Section 3.6) with the *in vivo* DAIH observations of Loth et al. (2002).

Considering Graft 4, significant particle-wall interaction is observed throughout the inlet as well as in the sinus region and along the arterial floor (Fig. 4.3.8g). Inclusion of the PSH factor elevates composite NWRT contours near the anastomotic junction, whereas the SR factor mitigates NWRT values in the sinus and emphasizes a focal region on the arterial floor (Fig. 4.3.8h). In comparison to the other 1.5:1 diameter-ratio grafts, the S-shaped graft-cut appears to result in the highest NWRT values along the arterial floor. As with all other configurations, vortices instigated by the heel result in particle-wall interactions along the proximal floor region of the artery. Elevated axial velocities and higher shear stresses prevent similar NWRT occurrence along the distal arterial floor.

Monocyte trajectories have been implemented for the calculation of the appropriate NWRT model in Grafts 2 and 3. Significant regions of monocyte interaction with the vascular surface are similar to those observed with platelets. However, the WSS-limiter condition of the monocyte model (τ_{limit} = 14 dynes/cm^2) eliminates composite NWRT occurrence near and distal to the toe. While a significant correlation with atherosclerosis development has been established (cf. Chapter 3), it appears that the composite NWRT model for monocytes may not necessarily be appropriate to identifying regions of likely IH development throughout the distal anastomosis.

4.4 Discussion

The hemodynamic effects of graft-end cut and graft-to-artery diameter ratio have been assessed in four common un-expanded anastomotic configurations with respect to vortical flow patterns, WSS-based parameters, and critical blood particle interactions with the vascular surface. As described previously, a number of hemodynamic interactions with the vascular surface have been related to the formation of DAIH both at the macroscopic and cellular levels. However, of primary interest here are factors which most aggressively illicit a significant intimal hyperplasia response.

4.4.1 Criteria for Graft Evaluation

As described in Sect. 3.6, interactions of activated platelets with a reactive vascular surface were found to qualitatively correlate with system specific observations of DAIH in canine models. Sites of significant particle-wall interaction were quantified by the composite NWRT model, which included shear stress based factors for platelet activation as well as endothelial cell expression of thrombogenic and anti-thrombogenic compounds. Comparisons of other WSS-based hemodynamic parameters to system specific DAIH observations resulted in inconsistent correlations when considering multiple locations within a single anastomotic configuration. Moreover, it has been established that determining regions of low WSS alone is insufficient to predict localized sites of significant particle-wall interactions. Hence, the composite NWRT model for platelet-wall interactions will be most significantly weighted in assessing locations of most likely DAIH occurrence. Cellular level links between aggressive DAIH occurrence and platelet-wall interactions include activated platelet release of chemotactic and mitogenic growth factors such as platelet derived growth factor (PDGF) and vascular constrictive agents such as thromboxane A2 (TxA_2) (Liu, 1999). Permanent adhesion of platelets to the vascular surface may not be necessary for significant promotion of IT to occur (Savage et al., 1996). Alternatively, mural thrombi resulting from significant platelet adhesion and aggregation may evolve into active atherosclerotic plaque-like lesions (Leu et al., 1988; Sloop, 1999), particularly on synthetic surfaces (Sloope et al., 2002).

Despite relatively weak and inconsistent correlations between the inverse of mean WSS and DAIH over a broad range of WSS-values (cf. Sect. 3.6), significant evidence indicates that sufficiently low WSS, i.e., values below a critical threshold, strongly elicit IH occurrence. For instance, Keynton et al. (2001) observed that approximately 92% of IH in a canine anastomotic model occurred at or below a mean WSR equal to one-half that of the native artery. The biochemical mechanism responsible for this observation may reside in WSS-related endothelial expression of thrombogenic and anti-thrombogenic compounds as approximated in the composite NWRT model for platelets. For instance, a direct relationship has been identified between endothelial cell WSS exposure and the expression of anti-thrombogenic compounds such as PGI2, NO, and tissue factor pathway inhibitor (TFPI) (Grabowski et al., 1985; Harrison et al., 1996; Westmuckett et al., 2000; Grabowski et al., 2001). Alternative pathways by which WSS-values below a critical threshold elicit IH rely on endothelial response in the absence of particle-wall interactions. For example, endothelial secretion of platelet derived growth factor (PDGF), which is a potent stimulant of SMC migration and proliferation, has been associated with reduced shear stress in baboon prosthetic vascular grafts (Mondy et al., 1997). Endothelial cell production of other growth factors, such as endothelin, has been shown to increase at low and oscillatory shear in culture (Pearson, 1994; Sharefkin et al., 1991). Furthermore, endothelial expression of a smooth muscle cell *inhibitor*, nitric oxide (NO), has been shown to *decrease* in regions of low mean shear (Harrison et al., 1996). Hence, local WSS-values below one-half the native vessel mean (τ_{limit} = 7 dynes/cm^2 for the 4 mm femoral artery) will be considered indicative of potential intimal hyperplasia formation. Nevertheless, the comparison study conducted in Sect. 3.6 indicates that DAIH resulting from low WSS alone is secondary, whereas more aggressive formations may arise from significant platelet-wall interactions.

As with WSS, an endothelial shape and/or signaling response capable of producing IH formations has been related to the gradients of the time-averaged WSS magnitude and direction (Helmke and Davies, 2002; Kleinstreuer et al., 2001; Tardy et al., 1997; Vorp, 2002). Correlations were not identified between WSSG and WSSAG parameters and macroscopic observations of system specific sites of DAIH in Sect 3.6. However, it is proposed that signaling responses arising within focal regions of significantly elevated

WSSG and WSSAG values dominate the regulatory nature of the endothelium resulting in spatially corresponding aggressive IH formations. For example, significantly elevated WSSG and WSSAG values along the suture line of the anastomosis may be responsible for continued IH occurrence in this area beyond the reportedly short time required for healing of the surgical injury.

In summary, the hemodynamic factor expected to most aggressively elicit a localized hyperplasic response within the distal femoral anastomosis is assumed to be the composite NWRT model for platelets including surface reactivity and platelet activation conditions (cf. Sect. 3.3). As supported by a number of studies at the cellular level, endothelial response to regions of significantly low WSS will be considered a second pathway for DAIH development. Highly focal regions of significantly elevated WSSG and WSSAG values will be considered a third inciting mechanism for localized IH development. Factors such as compliance mismatch, intramural stress and strain, and surgical injury have not been assessed in this study.

4.4.2 Evaluation of Graft Performance

With respect to long-term graft performance, evaluation criteria include the expected degree of IH occurrence as well as the potential for graft survival (or patency[1]). Geometries that engender significant IH occurrence within certain non-critical locations may have an acceptable survival rate. However, the proliferative characteristics of IH occurrence make it likely that regions critical to flow delivery will eventually be affected. Alternatively, minor IH occurrence within a geometrically constricted region may result in mural thrombosis and ultimate graft failure. Hence, graft performance is to be evaluated in terms of the potential for IH development as well as the functional ability of the anastomosis to accommodate localized formations. Graft failures associated with technical error and/or thrombosis shortly after surgery have not been rigorously addressed in this study. Nevertheless, significant values of the NWRT parameter are indicative of platelet activation and adhesion, which comprise necessary steps in the formation of a mural thrombus.

[1] Here, as in the surgical literature, patency refers to graft survival as opposed to ‘openness’ of the lumen.

Of the configurations considered, Graft 2 illustrates significantly lower levels of composite NWRT occurrence (Fig. 4.3.8). While all configurations display significant potential for IH development in the constricted region of the suture-line, indications are most severe for Grafts 1 and 4. Furthermore, conditions appear likely for localized IH development along the arterial floor of Grafts 1 and 4, whereas composite NWRT contours are minimal at this location in Grafts 2 and 3. Comparison of Grafts 2 and 3 indicates significantly higher potential for IH occurrence within the latter configuration. However, sites of likely IH occurrence within Graft 3, based on composite NWRT values, appear to be localized in regions capable of accommodating such developments without significantly altering the function of the anastomosis. Significant IH occurrence with the sinus region of Graft 3 may reduce flow stasis resulting in a more unified arterial lumen. As observed with particle trajectories (Fig. 4.3.3a), only a small portion of the anastomotic area of Graft 3 participates in flow delivery. Non-constrictive IH developments along the graft hood will shift flow toward the center of the graft lumen where sufficient cross-sectional area in the region of the junction is available for continued graft functionality. In contrast, the potential for IH development in the heel region of Graft 3 appears stenotic in character, which may eventually occlude proximal outflow. While all configurations indicate potential IH development, particularly in the constricted region of the suture-line, it appears that minimum IH occurrence is expected for Graft 2 with respect to the composite NWRT model. Due to non-critical localization of IH, Graft 3 also appears to represent an equally viable option, particularly in cases where proximal outflow is non-essential.

Considering WSS-based hemodynamic parameters for Grafts 2 and 3, it appears that Graft 2 provides for elevated WSS values, particularly along the arterial floor (Figs. 4.3.5 and 4.3.6). However, as discussed in Sect. 3.6, IH did not occur along the arterial floor in a canine model similar to Graft 3 (Loth et al., 2002). While many other factors may be involved, this observation provides evidence that sufficient platelet-wall interactions may elicit an IH response more aggressively than endothelial signaling due to low and oscillatory shear. Considering focal regions of elevated WSSG and WSSAG values, it appears that the most significant contours occur along the suture-line of Graft 2, in comparison to Graft 3 (Figs. 4.3.5 and 4.3.6). However, as with all parameters considered, it is not known if the

elevated gradients observed are sufficient to upset the local endothelial maintained balance, thereby inducing a significant stimulus for IH occurrence.

Based on the factors considered in this study, it appears that IH development will be least severe for Graft 2. However, IH localization is expected to significantly occur along the constricted suture-line region, particularly at the toe and heel, threatening long-term survival of the Graft 2 configuration. In contrast, significant IH formation is expected at non-critical locations within Graft 3 with respect to distal flow. Proximal occlusion of the Graft 3 artery is indicated in the region of the heel. Hence, a decisively superior un-expanded configuration is not evident among the realistic anastomoses considered. Furthermore, it appears that 'conventional' end-to-side anastomotic features are generally conducive to IH formation via various hemodynamic pathways, regardless of the graft-end cut selected.

4.4.3 Comparisons to Other Studies

Factors such as compliance mismatch and the associated intramural stresses, as well as surgical injury have not been addressed in this study. It has been postulated that suture-line DAIH formation arises from surgical injury and compliance mismatch, while DAIH at other locations is the result of hemodynamic interactions (Bassiouny et al., 1992; Leuprecht et al., 2002). However, Sottiurai (1999) suggests that compliance mismatch is not the cause of DAIH development, but it enhances the pathogenesis, whereas hemodynamic factors provide the underling stimulus. For instance, graft and artery compliance may affect the anastomotic geometry and/or wall motion, particularly in the region of the suture-line. As evident in this study, geometric variations of the graft-to-artery junction area significantly influence particle-wall interactions, WSS-values and highly focal regions of WSSG and WSSAG occurrence. Hence, compliance mismatch provides a geometric potential for increased WSS-based hemodynamic parameter occurrence as well as altered particle-wall interactions. Furthermore, while some IH occurrence is expected due to surgical injury and subsequent healing, continued advancement of IH occurrence resulting in late-stage graft failure requires an ongoing stimulus. In this study, elevated WSS-based hemodynamic parameters as well as particle-wall interactions appear to provide a potential mechanism responsible for continued IH development in the suture-line region. In addition, other researchers have related intramural stress and strain to continued IH proliferation at the suture-line (Leuprecht et al., 2002; Liu, 1999; Perktold et al., 2002).

Comparisons of these results to clinical success rates of the femoropopliteal bypass are mixed. The increased failure rate of below-knee applications is speculated to arise from adverse hemodynamics induced by increased diameter ratios as well as an increased risk of technical error (Stonebridge et al., 1997). Results of this study indicate a significant increase in the potential for IH occurrence for Graft 1 (diameter ratio 2:1) in comparison to Graft 2 (diameter ratio 1.5:1), particularly in regions critical to graft-function. Slower velocities associated with the latter configuration result in lower values of WSS throughout the junction as well as increased values of the composite NWRT parameter. However, a consistent flow-rate waveform was assumed for both configurations, which may differ from *in vivo* conditions where larger proximal anastomoses are associated with higher values of flow

delivery. Furthermore, actual prediction of clinical anastomotic failure will require more refined models to approximate progressive IH and mural thrombus developments as well as simulations of the spatially evolving hemodynamic flow field.

Abbott et al. (1997) found that larger caliber grafts were typically associated with higher graft survival rates (7 to 8 mm vs. 5 to 6 mm) for above-knee femoropopliteal bypass applications. While the current study indicates an increased susceptibility to IH formation for the 8 mm configuration of Graft 1, results may not be comparable to the above-knee applications of Abbot et al. where diameter ratios are most likely less than 2:1. Moreover, while IH may occur more aggressively within Graft 1, the increased anastomotic area provided by the 8 mm graft may better accommodate formations resulting in the higher observed patency rates.

Sanders et al. (1980) studied the influence of graft caliber on patency in a canine anastomotic model and concluded that graft diameter should be approximately equal to or 2 mm greater than the recipient vessel. Considering that the likelihood of early graft thrombosis is reduced by larger diameters (Binns et al., 1989), the results of Sanders et al. indicate that the appropriate graft caliber for a 4 mm recipient artery is 6 mm, resulting in a 1.5:1 graft-to-artery ratio. In comparison to the current results, this observation corroborates the reduced risk of IH within Graft 2 in comparison to Graft 1.

4.4.4 Conclusions

In conclusion, graft caliber and initial graft-end cut selected for anastomotic construction were found to significantly alter hemodynamic characteristics including WSS fields and regions of significant particle-wall interactions. Considering a number of studies, including material of Sect. 3.6, most aggressive DAIH occurrence was expected in regions of significant platelet interaction with the vascular surface. The severity of particle-wall interactions was quantified by the NWRT parameter, including WSS-based surface reactivity and platelet activation factors. Regions of low WSS as well as regions of focally elevated variations in WSS magnitude and direction were also considered significant with respect to aggressive IH occurrence. Graft performance was assessed with respect to the potential for IH occurrence at locations critical to flow delivery. Of the configurations evaluated, straight and curved (concave-up) graft-end cuts with a graft-to-artery diameter ratio of 1.5:1 were found to significantly reduce the potential for critical IH development while maintaining a graft lumen sufficient to reduce the risk to early thrombotic occlusion. Nevertheless, the potential for significant IH occurrence via platelet and/or endothelial response pathways was evident in all conventional anastomoses considered, particularly along the critical suture-line region. Persistent indications for IH occurrence are in agreement with the observations of Sottiurai (1999) who suggests that the conventional distal anastomotic design is an “un-physiological structure” for which IH is inevitable. Nevertheless, surgical benefits of the end-to-side anastomosis, such as ease of construction and the ability to deliver proximal outflow, ensure its continued implementation until a better alternative is proven. Therefore, geometric modifications of the distal anastomosis in an effort to reduce hemodynamic wall parameter occurrence as well as to mitigate regions of significant particle-wall interaction is warranted. In addition to alterations of the junction region, the results of this study imply that upstream hemodynamics, such as inlet graft curvature, as well as arterial geometry resulting from the construction of the junction significantly influence the potential for IH and should be considered in anastomotic revisions. Ultimately, an anastomosis consistent with

other physiological vascular junctions yet capable of providing the surgical advantages of the end-to-side construct may be necessary in order to largely eliminate the clinical occurrence and related complications of DAIH.

Table 4.1: Representative Survey of Models that Evaluate the Effects of Geometric and Boundary Variables on the Hemodynamics of a Distal Bypass Configuration*

Parameter / Model	Outlet flow division	Graft angle	Graft-to-artery ratio	Reynolds number	Out-of-plane curvature	Inlet curvature (in-plane)	Anastomosis shape and length	Input waveform	Wall compliance and distensibility
In vitro and in vivo models	-Crawshaw et al. (1980) -White et al. (1993) -Hughes and How (1996) How et al. (2000) -Li & Rittgers (2001) Fisher et al. (2001b)	-Crawshaw et al. (1980) -Keynton et al. (1991) -Ojha et al. (1994) -Hughes and How (1996)	-Loth et al. (1997) -Keynton et al. (1999)	-Crawshaw et al. (1980) -Keynton et al. (1991) -White et al. (1993)		-Shu and Hwang (1991)	-White et al. (1993) -da Silva et al. (1997) -Noori et al. (1999) -Harris and How (1999) -Fisher et al. (2000a&b) -How et al. (2000)	-Ojha et al. (1990) -White et al. (1993) -Hughes and How (1996)	-LoGerfo et al. (1983) -Trubel et al. (1995) --Leuprecht et al. (2002)
Computational models	-Kute and Vorp (2001)	-Fei et al. (1994) -Lei et al. (1997)	-Lei et al. (1996, 1997) -Moore et al. (1999)	-Fei et al. (1994)	-Moore et al. (1999) -Sherwin et al. (2000)	-Moore et al. (1999) -Longest (1999)	-Lei et al. (1996 & 1997) -Moore et al. (1999) -Longest and Kleinstreuer (2000)	-Kleinstreuer et al. (1996) -Ethier et al. (1998) -Moore et al., (1999)	-Hoffer et al. (1996) -Perktold et al. (1998) -Leuprecht et al. (2002)

* Only a select number of models with direct implications to femoral bypass grafts have been included.