Changing Paradigms in the Management of Peripheral Vascular Disease: The Need for Integration of Knowledge, Imaging, and Therapeutics

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Clinical Problem

Peripheral arterial occlusive disease (PAD) due to atherosclerosis of the lower extremities affects 3–7% of the population and up to one in five patients over 75 years of age. It is associated with decreased measures of quality of life [1–3] and is an underrecognized marker for multisystem atherosclerotic vascular disease. The risk of disease increases two- to threefold for every 10-year increase in age after the age of 40 years [4–6], with males developing claudication about twice as commonly as females. Mortality in patients with PAD is up to four times that of the nonPAD age-adjusted population [7]. Most (55%) die from heart disease, 10% from a stroke, and 10% from abdominal vascular pathology [8–12]. Less than 20% of PAD sufferers will die from a nonvascular cause. PAD is easily measured by the ratio of the systolic blood pressure in the upper arm and the systolic blood pressure at the ankle – the ankle brachial Index (ABI). The normal ratio is 1.0. The strength of association is so strong that even an asymptomatic patient with a slightly reduced ABI of 0.9 has a twofold relative risk of a coronary event [13]. Anatomic distribution of PAD is important. Patients with PAD can have disease in the aortic, iliac, femoral, and tibial vessels of the lower extremity. Patients with isolated aorto-iliac vessel disease tend to be younger and have a lower likelihood of pre-existing coronary heart disease. Those with femoral vessel disease, tibial vessel disease, or disease in all three vessels tend to have the lowest ABI and the highest likelihood of coronary heart disease [7, 14–19]. There is at present no current national US database on vascular interventions to allow realtime analysis of the trends in therapy and outcomes.

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Anatomy

The superficial femoral and tibial arteries are muscular arteries. The superficial femoral artery is unique in that it is the longest artery in the body, and courses through the thigh in the muscular adductor canal, exiting at a fixed point. The tibials course through muscular skeletal compartments and are end arteries to the foot. The geometry and the elasticity of the SFA and tibials are significantly influenced by its proximity to musculature and its continuous mobility. They are further influenced by their location between two joints. Thus, they undergo additional mechanical forces not seen in other arteries. Both have unique elastic wall recoil properties that affect their conformability and resilience [20–22]. The flow in the SFA and tibial arteries also differs from that in many vessels that are treated with angioplasty, as they have high resistance characteristics and disturbed flow [23–25]. Nonlaminar flow results in increased predisposition to the development of atherosclerosis and intimal hyperplasia [26, 27]. One can model the wall and movement of the SFA, but little data has been published in this field. The ability to model such conditions would allow preoperative planning and intervention.

Pathophysiology and Classification of Disease

While atherosclerosis is a systemic disease affecting all arteries within the human body, the lower extremity arteries, because of their anatomy and physiology, are very susceptible to the development of atherosclerosis, and can demonstrate all aspects of atherosclerotic plaque development. Atherosclerosis may be considered as a space-occupying lesion within the arterial lumen that has significant influence on the structure of the vessel wall and is a dynamic biological structure undergoing inflammation, expansion, contraction, and remodeling, depending on both local and systemic conditions [28, 29]. Various types of lesions have been described in the fatty streak (Types I, II and III lesions), fibrofatty lesion (Types III, IV and Va,), and the fibrous plaque (Types Vb, Vc and VI) [28, 29]. The SFA and tibial vessels demonstrate all these lesions, but by the time the lesion is symptomatic (i.e., manifested by claudication), the fibrous plaque or advanced complicated lesion predominates, commonly with associated in situ thrombosis or occlusion [30]. The dynamic nature of the plaques has increased the interest in medical therapies to induce stabilization and/or regression in plaque morphology. Plaque growth, whether slow or abrupt, is usually associated with surface erosion, internal hemorrhage, luminal thrombosis, a combination of these processes, or gradual vessel occlusion [28, 29]. The most hazardous component of the atherosclerotic lesion is the plaque margin, where the fibrous cap of the lesion is thinned and eroded by macrophages and the metalloproteinases they secrete [31]. Sudden deaths from myocardial infarcts or acutely ischemic limbs are due to these ruptures or fissures in the margins of the fibrous cap [32]. Numerous clinico-pathologic investigations have demonstrated that surface weakness is the most common feature of

an unstable plaque [28, 29, 33]. Microscopically, the observed sites of injury span a broad morphologic range from minimal surface erosions to lacerations that extend deep within the plaque. The result of these injuries is exposure of the luminal blood to a thrombogenic surface, thereby setting the stage for acute thrombosis. Plaque rupture can also lead to hemorrhage within the atheroma [34]. Although the region of hemorrhage consists primarily of red blood cells, the surfaces along the ruptured tract are often lined by aggregates of platelets. Plaque hemorrhage can also develop by an entirely different mechanism. Within the core of a soft atheroma, primary disruption of capillary channels derived from the vasa vasorum may occur and lead to rapid plaque enlargement. Small hemorrhages are frequently observed in nonruptured plaques [34]. Mechanical stress points for eccentric lesions have been identified at the junction of the plaque with the more normal appearing arterial wall and at the center of the plaque [32–34]. In addition to the atherosclerotic lesion characterizations, there is an anatomical classification of disease based on angiography or alternative imaging modalities (duplex ultrasound, computed tomography angiography (CTA) or magnetic resonance angiography (MRA)). The TransAtlantic interSocietal Commission (TASC) has stratified femoropopliteal disease into four categories, A, B, C and D [35, 36]. These categories are used as an aid to guide intervention and for clinical reporting purposes. Integration of a bioinformatics approach to the analysis of plaque characteristics and the biomechanics of the SFA has not been achieved.

Pathology of Angioplasty and Stenting

Angioplasty is a controlled injury to the vessel wall. In the immediate aftermath of angioplasty, programmed cell death or apoptosis can be identified at 1–2 h and appears to disappear by 4 h [37]. No apoptosis can be identified in the wall after injury at 3 days, but by day 7, 50% of the cells again show signs of apoptosis and by day 14, the number of apoptotic cells is again markedly decreased. Smooth muscle cell proliferation within the media, which is normally less than 1%, increases to over 20% within 48 h after angioplasty [38–40]. The fraction of cells proliferating reaches a maximum between 3 and 7 days and occurs as a synchronous wave of entry into the S phase of the medial smooth muscle [41, 42]. Four weeks after injury, the medial proliferative response returns to baseline levels. Intracoronary radiation after angioplasty inhibits this first wave of cell proliferation and prevents adventitial proliferation [43]. By day 8 after the injury, smooth muscle cells are observed on the luminal side of the internal elastic lamina and appear to have migrated to the luminal surface through fenestrations in the internal elastic lamina. The number of smooth muscle cells in the intima increases to a maximum at 2 weeks after injury and about 30% of medial smooth muscle cells may migrate from the media to the intima. This migration of cells requires the proteolytic degradation of the cage of matrix surrounding each cell and the synthesis of new matrix molecules. Smooth muscle cell migration is unaffected by irradiation and anti-mitotic drugs

[44–47]. Once within the intima, approximately 50% of the smooth muscle cells proliferate (a second phase of mitosis). In the intima, a second phase of cellular proliferation is first noted at day 7 and reaches a maximum at 14 days before returning to baseline by 28 days [42]. However, it may continue for up to 12 weeks in those areas where re-endothelialization takes longer to complete. This second phase of smooth muscle cell replication in the intima appears to be mediated by autocrine and paracrine factors and remains poorly understood. It also appears that the thickness of the intimal hyperplasia peaks within 1 month and its rapid development is due to both cellular elements and the production of proteoglycans. Associated with the changes in the intima and media, there are substantial changes in the adventitia, as evidenced by an increased cell proliferation and growth factor synthesis in the adventitia relative to the media after angioplasty. In the adventitia, there is a marked infiltration of cells termed as "myofibroblasts" by day 2, which by day 14 can represent up to 50% of cells within the intima [48, 49]. The presence of myofibroblasts is common in wound healing and leads to contraction of the wound. A similar phenomenon may occur in the healing vessel. Injured vessels may undergo chronic elastic recoil or negative remodeling, which results in loss of luminal dimensions without a further increase in neointimal area. The degree of intimal hyperplasia that develops in a vessel is dependent on the length and depth of the injury [50]. The length of the injury influences the duration of the re-endothelialization process. Re-endothelialization occurs from the margins of the denuded area and possibly from the endothelial cells of the vasa vasorum. The longer there is an incomplete endothelial cell covering, the greater time the smooth muscle cells are without the modulating influence of the endothelial cells, and the longer the replication phases of the smooth muscle cells will be [39, 51]. After deep vessel wall injury, luminal narrowing may be less dependent on intimal hyperplasia formation and more dependent on vessel wall remodeling [52]. Medial damage is accompanied by a massive adventitial cell proliferation [53], which in time provides cells capable of contraction and negative remodeling. If angioplasty fails to achieve adequate luminal increase, causes vessel dissection or results in abrupt occlusion, intravascular stents are placed. At present, there is no systems biology approach to angioplasty, complications of angioplasty, and intravascular stenting (vide infra).

Intravascular Stents

The biology of in-stent restenosis is different than that seen after balloon angioplasty [54]. A stent is generally used if the result of balloon angioplasty is technically unsatisfactory or if there is arterial occlusion, immediate elastic recoil, flow-limiting dissection or restenosis. The response of a vessel to a stent is dependent on the stent design, length, composition, delivery system, and deployment technique [55]. In-stent restenosis is classified on the basis of length of restenosis in relation to stented length. Four categories of in-stent restenosis have been defined (1) focal ($\leq$10 mm length), (2) diffuse (>10 mm length), (3) proliferative (>10 mm length

and extending outside the stent), and (4) occlusion [56]. After balloon angioplasty, there is thrombus formation, intimal hyperplasia development, elastic recoil, and negative remodeling. In contrast, after stent placement, elastic recoil, and negative remodeling are eliminated [57] and thrombus formation followed by intimal hyperplasia development are the main contributors to in-stent restenosis [58, 59]. Stent placement in a vessel results in both a generalized injury to the length of the vessel exposed as well as the more focal injuries at the areas of stent placement. Intravascular ultrasound has demonstrated that stents do not always completely oppose the vessel wall along its entire length, thus resulting in uneven injury along its length [57]. After stent placement, the surface of the metal implanted into the vessel is covered within 5 s by a strongly adherent monolayer of protein. After 1 min, the surface is covered by fine layers of proteins, predominantly fibrinogen [60]. The holes between the stent wires are filled with thrombus and the adherence of platelets and leukocytes is enhanced by disturbance of the electrostatic equilibrium [61, 62]. The basic mechanisms of smooth muscle cell proliferation and migration after stent placement are the same as those after balloon injury [63]. The intimal hyperplasic process in a stent is more prolonged and robust than in a balloon injured artery and is proportional to the depth of injury the recipient vessel sustains [64] and the inflammatory response induced [65]. It can often be much more significant at the ends than in the body of the stent. In addition, the adventitial response is prolonged, with adventitial giant cell body formation being noted. Stents prevent chronic elastic recoil and cause progressive atrophy of the media [66]. The presence of a stent changes the dynamics of the vessel wall both at the site of implantation and distally by changing the flexibility of the entire vessel. The stresses on the stent have led to fractures of the stent and these fractures are increased by increased patient mobility. A combination of systems biology and CAD may allow a better definition of the causes and possible remedies for these stent related problems.

Diagnostic Imaging

Imaging of the arterial system can be achieved through the use of Duplex ultrasound (Doppler and B-mode ultrasound combined), computed tomography arteriography, magnetic resonance angiography and conventional arteriography with the use of intravascular ultrasound modalities. Duplex allows real-time imaging, integrating blood flow, and two-dimensional imaging and can quantify flow, degrees of obstruction, and plaque characteristics. When duplex ultrasound (DUS)-derived gray-scale median (GSM) is used to interrogate the distal portion of an occluded native femoral-popliteal arterial segment, it can predict the success of lumen re-entry for subintimal angioplasty. When the GSM was less than 25, the absolute reduction in plaque thickness on day 1 post-percutaneous transluminal angioplasty (PTA) was 3.3 ± 1.8 mm, in contrast to 1.8 ± 1.6 mm when GSM was more than 25 ($P < 0.03$) [67]. The restenosis rate (peak systolic velocity ratio (PSVR) more than 2) was 41% at 6 months and remained unchanged at 1 year. When the GSM was less than 25, restenosis occurred in 11% of lesions, in comparison with 78% when the GSM was

more than 25 ($P < 0.001$). Failure to recannulize occurred in 90% of 19 cases with GSM > 35, in 71% of 24 cases with GSM > 20, and in 50% of 34 cases with GSM > 25. Plaque echogenicity represented by DUS-derived GSM can be used to predict the success of primary subintimal femoral-popliteal angioplasties [68].

Overall, the sensitivity of Computed tomography arteriography (CTA) for detecting more than 50% stenosis or occlusion was 95% (95% confidence interval [CI], 92–97%) and specificity was 96% (95% CI, 93–97%). CTA correctly identified occlusions in 94% of segments, the presence of more than 50% stenosis in 87% of segments, and absence of significant stenosis in 96% of segments. Overstaging occurred in 8% of segments and understaging in 15% [69]. The diagnostic performance of multidetector CT angiography in the infrapopliteal tract is lower than but not significantly different from that in the aorto-iliac and femoropopliteal tracts. Regression analysis showed that diagnostic performance was not significantly influenced by differences in study characteristics [70]. When evaluated by TASC classification, time-resolved imaging of contrast kinetics (TRICKS) MRA correlated with digital subtraction angiography (DSA) in 83% of the popliteal and in 88% of the infrapopliteal segments. MRA correctly identified significant disease of the popliteal artery with a sensitivity of 94% and a specificity of 92%, and of the tibial arteries with a sensitivity of 100% and specificity of 84% [71]. Intra-arterial (IA) contrast-enhanced 3D-gradient-echo-MRA (CE MRA) on an open-bore MR-scanner with the detection of significant stenoses and occlusions, the overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of IA-MRA were 96, 83, 88, 94, and 90%, respectively [72]. A recent meta-analysis sought to determine the diagnostic accuracy and cost-effectiveness of duplex ultrasound (DUS), magnetic resonance angiography (MRA), and computed tomography angiography (CTA), as alternatives to contrast angiography (CA), for the assessment of lower limb peripheral arterial. The results of the review suggested that CE MRA has a better overall diagnostic accuracy than CTA or DUS, and that CE MRA is generally preferred by patients over CA. Where available, CE MRA may be a viable alternative to CA. There was insufficient evidence to evaluate the usefulness of CTA for the assessment of PAD, particularly newer techniques. The results of the economic modeling suggest that for PAD patients for whom the whole leg is evaluated by a preoperative diagnostic test, DUS dominates the other alternatives by presenting higher effectiveness at a lower cost per quality-adjusted life year (QALY). However, when the analysis of stenosis is limited to a section of the leg, either above the knee or below the knee, 2D time-of-flight (TOF) MRA appears to be the most cost-effective preoperative diagnostic strategy. Further research is needed into a number of areas including the relative clinical effectiveness of the available imaging tests, in terms of surgical planning and postoperative outcome [73].

Angiography provides information on luminal characteristics of peripheral arteries but severely underestimates the extent of atherosclerosis in patients with PAD even in "normal appearing" vessels [74]. When plaque composition in the popliteal and tibial vessels of patients with severe peripheral arterial disease was examined by intravascular ultrasound (IVUS) virtual histology, tibial vessels had more dense plaque calcium than popliteal arteries. Consequently, distal vessels had less fibro-fatty and fibrous plaque than popliteal arteries. Necrotic core plaque

composition was found to be similar when comparing tibial vs. popliteal arteries. Clinical factors including diabetes, hyperlipidemia, and chronic renal insufficiency were not associated with plaque composition differences using a univariate analysis [75].

If IVUS is used immediately after PTA, the extent of dissection, free lumen area, and diameter are predictive factors of patency [76]. Factors on IVUS that favor improved patency are the absence of calcification, dissection or plaque rupture and a residual stenosis of less than 30% [77]. IVUS predictor of failure at one and 6 months is initial residual stenosis after PTA [78]. Similarly, significant residual stenosis (>30%) on duplex ultrasound 1 day after PTA correlates with failure within 1 year; unfortunately, the converse is not true, as a normal duplex at +1 day cannot predict failure within 1 year [79]. Plaque area increase and vascular remodeling contribute to lumen area change after PTA of the femoropopliteal artery on intravascular ultrasound study [80]. Capek [81] and Hunink [82] have shown that repeat PTA has similar patency as primary PTA; in contrast, several reports have shown that repeat SFA angioplasty has a low patency (<20% at 3 years) and have suggested that bypass may be more beneficial [83–86]. Failure of PTA is not associated with worsening of the patient's clinical condition and 19% will be recannulized at a second sitting [87, 88].

The graduation of femoropopliteal stenoses by either digital subtraction angiography (DSA) or duplex sonography remains challenging, particularly after percutaneous transluminal angioplasty (PTA). The relationship between DSA, IVUS and duplex before and after femoropopliteal PTAs has been examined. Over the whole range of stenoses, peak systolic velocity (PSV) and peak velocity ratio (PVR) correlated better with DSA-stenosis ($R(2) = 0.72$ and 0.74, respectively; $P < 0.01$) than with IVUS-stenosis ($R(2) = 0.58$ and 0.50; $P < 0.01$). Within the subgroup of preinterventional (51–99%) stenoses, PVR was significantly correlated only with DSA-stenosis ($R(2) = 0.60$; $P < 0.01$). Severe dissection after PTA was associated with a disproportionate rise in PSV and large discrepancies between IVUS and DSA. Of note, it has been reported that intra-stenotic flow acceleration assessed by duplex sonography correlates better with DSA- than with IVUS-stenosis. The concordance between duplex sonography, DSA, and IVUS was particularly weak in postinterventional measurements, casting some doubt on the reliability of these methods for the assessment of residual stenosis after femoropopliteal PTA [89]. Integration of various image modalities with simulation and modeling which is then individualized to the patient is a growing area of interest. Integrated registration of the cumulative imaging a patient receives is necessary to enhance medical decision making and intervention.

Endoluminal Procedures

Since the introduction of percutaneous transluminal angioplasty in 1964 by Dotter and Judkins [90] and its refinements by Gruntzig [91], PTA has grown into a viable alternative to surgical intervention in most arterial beds. The diseased SFA may be

approached with a repertoire of techniques. The conventional approach is to access the SFA in an antegrade manner and negotiate a guide wire through the target lesion prior to performing PTA. A similar approach can be achieved in short segment occlusions. An antegrade transfemoral approach has initial technical success rates of 90–95% for stenotic lesions and of 80–95% for complete occlusions. Use of the retrograde transpopliteal approach can increase the original technical success rate by an additional 6% [92]. However, longer occlusions require additional techniques. Percutaneous intentional extraluminal recanalization (PIER) [93] or sub-intimal angioplasty or Bolia angioplasty is a technique used to recannulize chronic occlusions [94]. It intentionally achieves a dissection plane in the vessel wall to circumvent a total occlusion. Gaining luminal access into the distal target vessel remains the Achilles' heel of this approach. Results from subintimal angioplasty of superficial femoral artery occlusions were superior to the results of PTA, but calcification is associated with subintimal angioplasty failure [95]. Recently, the use of intravascular ultrasound to identify and guide a needle from the false dissected lumen into the true lumen has been shown to be effective. PIER through the retrograde popliteal approach can be achieved in up to 80% cases [96].

Outcomes

The national reporting standards for vascular procedures define three categories of clinical success: anatomic, hemodynamic, and clinical. A composite analysis of all published trials of PTA with or without stenting in the femoropopliteal arteries shows patencies of 71, 59, and 53% at 1, 3, and 5 years, respectively. Technical success was 90% and the complication rate was 10%. Endoluminal therapy for SFA occlusive disease yields lower assisted patency rates and higher restenosis rates for those patients presenting with claudication who have insulin dependent diabetes. Among those patients presenting with tissue loss, limb salvage rates are lowered for all diabetics (both noninsulin-dependent and insulin-dependent diabetes mellitus (NIDDM and IDDM)) in spite of equivalent patency and restenosis rates [97]. Insulin levels and the C-peptide/insulin ratio were associated with restenosis after femoral PTA. In nondiabetic patients, insulin levels were significantly associated with restenosis, whereas the ratio of C-peptide to insulin showed no association with restenosis. In patients with type II diabetes, in contrast, the C-peptide/insulin ratio was associated with restenosis, whereas insulin levels showed no significant association with restenosis [98]. Multiple factors may adversely affect patency; these include presenting symptoms (claudication vs. critical ischemia), type of lesion (stenosis vs. occlusion), length of lesion <10 and >10 cm) and distal runoff [81, 82, 99, 100]. Additional significant predictive factors of a good outcome are as follows: female gender, nondiabetic, at least one patent artery below the knee, AHA classification <2, no stent, treatment of an occlusion, number of dilatations <3, treatment by statins for hypercholesterolemia [101]. The IL-6 promoter polymorphism (-174)G/C seems to influence the occurrence of restenosis after PTA. Homozygous carriers of the (-174)C allele have an increased rate

of intermediate-term restenosis [102]. Plasma levels of tissue factor, prothrombin fragment 1 + 2, D-dimer, P-selectin, C-reactive protein (CRP), and fibrinogen analyzed before and after angioplasty are not related to restenosis [103]. Plasma tissue factor is a predictor for restenosis after femoropopliteal angioplasty [104].

Subintimal angioplasty for the treatment of lower extremity chronic arterial occlusions is technically feasible, results in minimal morbidity, and provides satisfactory revascularization without surgical bypass. Secondary patency is comparable to that of autologous vein bypass and is achieved with a low rate of reintervention [105, 106]. However, percutaneous SFA intervention in preparation for a distal origin graft is a useful and effective strategy in select patients. The durability appears comparable with distal origin grafts performed in the absence of an SFA intervention. This strategy provides a good option in the setting of both atherosclerotic SFA disease and limited autogenous conduit. Simultaneous performance is not associated with increased morbidity and decreases overall hospital use [107, 108]. Multivariate analysis reveals critical limb ischemia to be the only predictor of reduced primary patency [106]. Most amputations occurred in patients in whom subintmal angioplasty had been unsuccessful and were associated with long ($>$ or $=$ 10 cm) occlusions.

Pharmacotherapy After PTA

The role of pharmacotherapy after PTA in the SFA has been driven by the data derived from the coronary artery interventional literature. Heiss et al. have shown a significant benefit of aspirin compared to placebo after PTA [109], but antiplatelet drugs have not shown a consistent benefit in preventing restenosis [109, 110]. Low dose aspirin appears as effective as high dose aspirin in the prevention of restenosis [111]. The coronary literature supports the use of the combination of aspirin and clopidogrel after endoluminal intervention. No data is readily available in the periphery; however, most centers add clopidogrel prior to and after intervention. The required duration of this additional therapy has not been tested. Adjunctive abcximab, a platelet receptor inhibitor, does not appear to demonstrate any identifiable effect [112]. Statins can decrease restenosis and the reintervention rate after percutaneous intervention, independent of their lipid-lowering effect and CRP level in this study. Multivariate analysis indicated that the prescription of statins, but not LDL-C level at follow-up and % reduction of LDL-C during the follow-up period, predict the restenosis prevention [113] One small study compared changes in IVUS morphology of the lumen, vessel, and plaque in statin treated ($n = 5$) and non-statin-treated patients ($n = 5$). At follow-up, both statin-treated and nonstatin-treated patients showed a similar increase in plaque volume at the nondilated segment ($+4\%$ and $+2\%$, respectively). In statin-treated patients, the plaque volume increase was compensated by an increase in vessel volume ($+2\%$), resulting in an increase in lumen volume ($+1\%$). In non-statin-treated patients, on the other hand, the increase in plaque volume was associated with a decrease in vessel volume (-2%), resulting

in a decrease in lumen volume (−4%) [114,115]. Management of comorbidities and medication dosing reconciliation and monitoring are integral to effective electronic medical management.

Adjuvant Stenting

Four randomized studies comparing PTA alone vs. PTA plus stent placement in the SFA have all failed to demonstrate a benefit to stenting in terms of long-term patency and symptom relief [116–119]. There is little evidence to support the superiority of endovascular stents over PTA alone in the femoropopliteal arteries. Their use should be confined at present to flow limiting dissections or inadequate results from balloon angioplasty alone [117,120,121]. Cheng et al. have suggested that significant factors which impede stent patency were occlusions, stented segment length >10 cm, use of the procedure in claudicants and the use of Memotherm stents [122]. Liermann reported a primary patency rate of 82% after 18 months and noted a lower patency rate for stents placed in the distal portion of the SFA compared to the proximal portion [123]. Strecker et al. reported a 2-year patency rate of 73% for stent placement for stenosis and 32% in occlusions [124]. Use of wall stents for short lesions and stenoses reveals a 1–2-year primary patency of 67%, while for occlusions this dropped to 49% [125]. One report has suggested a high rate of early thrombosis and a restenosis rate of 77% when wallstents are placed in the SFA [126]. One report has shown that the 12-month restenosis of nitinol stents is 46%, which was not influenced by the cumulative length or the number of stents placed, but was worsened in the presence of diabetes [127]. Self-expanding stents produce acceptable outcomes for the treatment of SFA disease. Poorer patency rates are associated with TASC D lesions and poor initial runoff score; hypertension was associated with improved patency rates. Stent occlusion and in-stent stenosis were not entirely benign; one-third of patients had deterioration of their tibial artery runoff [128]. Re-occlusion rates of 32–43% in the first 12–18 months after implantation have been observed [129–132]. The Femoral Artery Stent Trial (FAST study) was designed to investigate the impact of nitinol stenting of superficial femoral artery lesions with a maximum length of 10 cm on restenosis and clinical outcomes at 1 year. There was no difference in binary restenosis at 1 year between the implantation of a single Luminex nitinol stent and stand-alone PTA [133]. The impact of nitinol stenting of superficial femoral artery (SFA) lesions with a maximum length of 10 cm (TASC-II A or B) on 1-year outcomes was compared to a historical study cohort from FAST was examined in the Femoral Artery Conformexx Trial (FACT study) [134]. Single de novo >70% SFA lesions <10 cm long treated with the self-expanding nitinol Conformexx stent had a primary endpoint of ultrasound-assessed binary restenosis which was lower vs. the historical balloon angioplasty. Reconstructive surgery in patients presenting with infrainguinal stent occlusion or restenosis appears to be associated with higher morbidity and major limb amputation rates [135]. Two recent meta-analyses suggest that stent placement in the femoropopliteal occlusive disease does not increase the patency rate when compared with angioplasty alone at 1 year [136, 137].

Drug Eluting Stents

While several drug eluting stents have been utilized in the coronary circulation, only one, the sirolimus eluting SMART stent, has data available in the periphery. The results of the SIROCCO studies show that despite excellent 6-month patency observed in the bare nitinol stent group, comparative analysis reveals a reduction in neo-intimal hyperplasia in the sirolimus eluting stents [138–140]. It does not appear that these stents had a significant clinical effect. The final report stated that the cumulative in-stent restenosis rates according to duplex ultrasound were 22% at 24 months and that no significant difference could be found between the sirolimus-eluting and the bare SMART stents [141].

Covered Stents

In a bid to counteract in-stent restenosis, covered stents have been proposed [142]. There appears to be an initial gain in patency over the first 6–12 months [143, 144]. While this strategy did prevent in-stent restenosis, it did not prevent the development of intimal hyperplasia at the ends of the device [129]. The long term patency of the Viabahn stent-graft for long Transatlantic Inter-Society Consensus class C and D lesions was 79% at 4 years and was independent of lesion length and type but was dependent on device diameter. The primary vessel patency rate in devices of at least 7 mm ($n = 21$) was 82% at 4 years. No stent fractures were observed despite the use of multiple overlapping stent-grafts [145]. Severity of lesions, rather than preoperative symptoms or runoff, is mainly to be considered before using Hemobahn/Viabahn endoprosthesis in severe SFA occlusive lesions, as primary and secondary patencies decrease as TASC severity worsens [146]. Treatment of SFA occlusive lesions (excluding TASC D lesions) with the Hemobahn covered stent yielded good results for both claudicants with good outflow and patients with critical or acute ischemia with bad outflow if concomitant outflow-improving procedures were performed [147]. Results from a prospective multicenter registry evaluting the safety, effectiveness, and patency of the aSpire self-expanding polytetrafluoroethylene covered stent showed good mid-term results, but with a number of reinterventions necessary to obtain an optimal secondary patency. Risk of patency failure was related to critical limb ischemia as an indication for the procedure. Technologic and pharmacologic improvement and longer follow-up are needed to define the indications for the aSpire stent [148].

Atherectomy

Debulking of lesions may enhance patency. Atherectomy devices and endovascular endarterectomy have been used to achieve these aims. Directional atherectomy appears to have a 75% patency at 24 months but, there is a high restenosis rate [149].

Endovascular SFA endarterectomy appears to have a 65% technical success rate and a cumulative patency of 59% in patients, in whom technical success can be achieved [150]. Directional atherectomy has a patency of 57% at 2 years with patients with diabetes, complete luminal occlusion or critical ischemia having lower patency [151]. Studies have suggested that debulking segments prior to adjunctive balloon angioplasty may offer advantages in reducing acute complications and improving long term patency [152, 153]. In addition, treatment of in-stent restenosis may be helped by debulking prior to dilation [154]. Several mechanical atherectomy devices have been used in the treatment of peripheral vascular disease. The Simpson Atherocath is commonly employed to treat focal eccentric lesions in larger vessels and bypass graft anastomoses. It is limited by its high profile and side-cutting design. The SilverHawk catheter (FoxHollow Technologies, Inc.), which is derived from the Simpson catheter, has reduced these obstacles to catheter placement and use. Case series suggest that it has short-term benefits [155–157]. Rotational atherectomy (Rotablator) uses a very high speed rotating diamond coated burr to abrade lesions into microparticles which are dispersed down stream; it is very useful for heavily calcified lesions, but the consequences of distal embolization remains a significant concern. The TEC catheter uses aspiration to collect debris shaved by a rotating cutting head and appears more effective in treating soft or thrombus containing obstructions. In a retrospective analysis of 35 SFAs treated with the TEC device, the initial success rate was 100%, but the 5-year patency was 0% [158]. Both the pullback atherectomy catheter and the Redha-Cut catheter rely on first passing the obstruction with the entire device then removing the material as the catheter's cutting blades are pulled back across the lesion. In three prospective randomized trials, there was no difference between angioplasty and atherectomy for SFA disease [159–161]. Initial ABI, but not tibial runoff, or long occlusions, appeared to be the most predictive of patency after atherectomy. Lower extremity atherectomy procedures with the SilverHawk or Diamondback devices are a safe and effective means of improving symptoms. However, there is decreased durability, significant patency, and limb loss over time. Multivariable analysis demonstrated that tobacco use, renal disease, diabetes, and tissue loss are all predictors of patency loss, while only diabetes and tissue loss were associated with greater limb loss. There was no difference in patency rates irrespective of location, TASC classification, vessel treated (femoral vs. tibial), or degree of stenosis (occluded vs. stenotic) [162]. Several experiences suggest a very poor midterm patency of excisonal atherectomy, although a 74% limb salvage rate was maintained through secondary interventions [163].

Laser Assisted Angioplasty

Laser-assisted angioplasty increases luminal cross-sectional area by both atheroablation and vessel expansion without calcium ablation [164, 165]. Technical success with laser-assisted angioplasty is as high as 91% [166–168]. There appears to be better initial recanalization with laser-assisted angioplasty compared

to PTA, but no long-term differences between PTA and laser-assisted angioplasty have been appreciated [169, 170]. SFA lesions, including in-stent restenosis (ISR), can be treated in the majority of cases with directed laser atherectomy, significantly reducing plaque burden as measured by IVUS. Embolization was attributed to device-specific features of the prototype antegrade sheath design, which was discontinued [171]. Enclosed thrombolysis associated with PTA has no advantage over PTA alone [172].

Brachytherapy

Delivery of radiation to the injured field in a vessel has had beneficial effects. Endovascular radiotherapy can prevent intimal hyperplasia after stent implantation in femoropopliteal arteries [123] but partially prevents healing of disrupted vessel surfaces [173]. Gamma radiation induces positive vascular remodeling after balloon angioplasty, as shown in a prospective randomized IVUS scan study [174]. When doses of 12–14 Gy (gamma radiation) are applied endoluminally to the femoropopliteal segment after PTA, there is a twofold increase in 12-month patency compared to untreated controls [175–177]. Similar results were noted in the PARIS trial [178]. The Vienna-2-trial showed a significant reduction of the restenosis rate compared to controls. Subgroup analysis showed a significant decrease in restenosis rate in the subgroups with restenosis after former PTA occlusion and PTA length of greater than 10 cm. Significant reduction was not achieved in diabetes patients [179]. Endovascular brachytherapy (14 Gy) applied by an ^{192}Ir source to the vessel wall resulted in an absolute risk reduction of significant restenosis of 9%, yet in patients with totally occlusive disease this reduction was 32% [180]. Results suggest that intravascular brachytherapy is effective at improving the patency of femoropopliteal arteries undergoing PTA in the short term, particularly in nondiabetics with long occlusions (>10 cm) [181]. Restenosis and inward remodeling after PTA are delayed by intravascular brachytherapy. At 24 months, patients treated with brachytherapy have a larger lumen than those treated with PTA alone. The decrease in luminal and total vessel area between 3 and 24 months after intravascular brachytherapy indicates that the restenotic and remodeling process is not abolished but merely delayed with this therapy [182].

Cryotherapy

Cryoplasty is a novel therapy that combines conventional balloon angioplasty with application of cryotherapy (Fig. 1). Experimental data suggests that cryotherapy induces early arterial wall cell loss through apoptosis but does not alter intimal hyperplasia development or eventual lumen area compared to conventional balloon angioplasty [183]. The single system on the market at present uses a double balloon system that exerts 8 atm. on the lesion and is accompanied by cold-induced

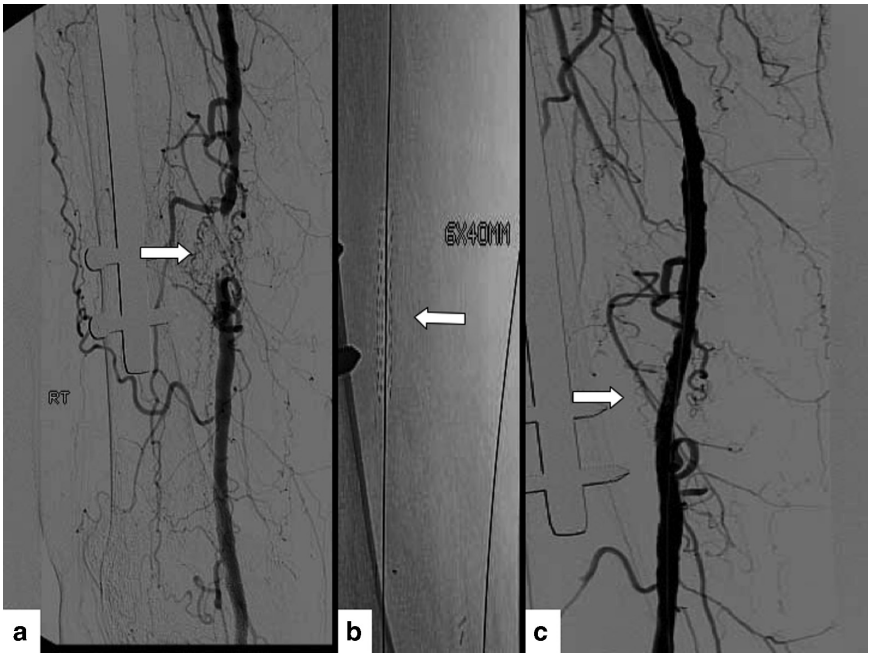

Fig. 1 Lower extremity angiogram showing in (**a**) a occlusion of the superficial femoral artery (*arrow*), (**b**) inflation of a Polarcath balloon angioplasty catheter (*arrow*), and (**c**) completion angiogram showing restoration of flow (*arrow*)

injury to the wall. The hope is that cryotherapy will allow more accurate angioplasty and induce apoptosis in the wall, thus reducing dissections and vessel response to injury. The final results of a cryovascular safety registry of 102 patients have shown a primary patency of 82% at 10 months [184, 185]. Longer-term data are required, although case series suggest that improved patency can be achieved for up to 18 months [186]. However, the mode of failure is different, with stenosis, more common than occlusion [187]. Associated costs are greater than those for conventional balloon angioplasty but lower than those for stent placement [187, 188]. The benefit of cryoplasty over conventional angioplasty has not been established, as no randomized controlled trials exist to properly evaluate this method. The technical success and primary patency rates seen in the prospective series are encouraging and may suggest a future role for cryoplasty in the treatment of PAD, but this data cannot be reliably interpreted due to the nature of the studies [189].

Cutting Balloon PTA

In a study of predominantly TASC A and B lesions, the overall technical success rate of a cutting balloon PTA (CB-PTA) was 96.3% and the complication rate was 8.9%. The 1- and 2-year results for femoropopliteal and infrapopliteal lesions in patients

with critical limb ischemia (CLI) were as follows: primary patency 64.4 and 51.9%, respectively; limb salvage 84.2 and 76.9%; survival 92.6 and 88.5%. More distal lesions and a high TASC classification were significant independent risk factors for outcome. Treatment of multiple segment lesions was an independent predictor of a favorable outcome ($P = 0.04$) [190]. Cotroneo and colleagues compared midterm results of cutting balloon angioplasty (CBA) to conventional percutaneous transluminal angioplasty (PTA) for the treatment of short femoropopliteal arterial stenosis. In the PTA group, primary and secondary patency rates, respectively, were 91.0 and 95.5% at 6 months, 83.1 and 92.4% at 12 months, and 66.6 and 76.5% at 2 years. In the CBA patients, the primary and secondary patency rates, respectively, were 93.2 and 95.9% at 6 months, 90.4% ($P < 0.001$ vs. PTA at same interval) and 94.5% at 12 months, and 79.7% ($P < 0.001$) and 85.6% ($P < 0.001$) at 2 years [191].

Complications of Intervention

In situ thrombosis appeared to occur more frequently in females, reflecting a smaller vessel size, current smokers with critical limb ischemia, and more complex procedures with longer lesions associated with poorer runoff that needed more than a simple angioplasty. While pharmaco-mechanical therapy did reopen the majority of these lesions, they did fail more frequently in follow up. In early reports, risk factors for acute thrombosis in the coronary circulation included stenting for threatened or abrupt closure, smaller vessels and longer lesions, and more recent studies have shown the risk factors to have shifted to multiple stent use, residual dissection, and smaller final lumen [192] (Fig. 2).

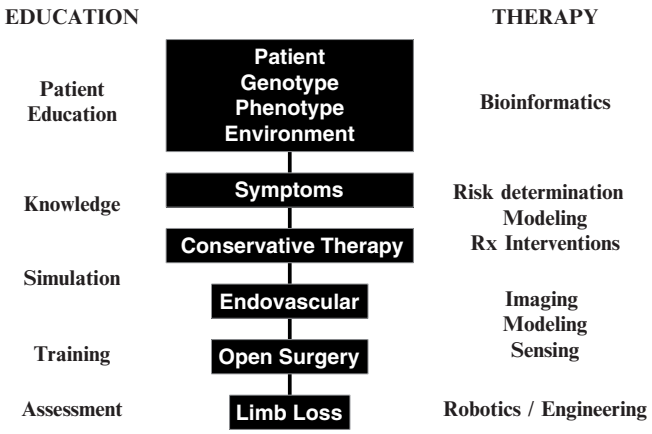

Fig. 2 Flow chart of patient care with computational interactions in the areas of education and therapy

Distal embolization has been identified during wire crossing, angioplasty, stent deployment, and atherectomy [193]. The frequency of embolization is greatest during stent deployment. The occurrences of embolic signals were particularly frequent in the 2 h after angioplasty [194]. In a single-center prospective registry (PROTECT), macro-embolization occurred in 55% of patients. Clinically significant ($\geq$2 mm in diameter) macrodebris was found in 45% of patients [195]. In the PROTECT study and in a second smaller case series study, superficial femoral and popliteal artery atherectomy was associated with debris in the filter in all cases [195, 196]. When the particles captured in embolic filters were examined, the particles were found to consist primarily of platelets and fibrin conglomerates, trapped erythrocytes, inflammatory cells, and extracellular matrix. Increased lesion length, increased reference vessel diameter, acute thromboses, and total occlusions have been positively correlated with higher amounts of captured particles ($P < 0.05$). However, by multivariate analysis, it appears that declotting procedures were the only independent predictor of increased embolic burden in the study [197].

The criteria for embolic protection device placement in the PROTECT registry, and by implication, the criteria for distal embolization were: (1) moderate or severe calcification of any length, (2) total occlusions of any length, (3) a filling defect, (4) irregular (ulcerated) lesions at least 30 mm in length, (5) smooth, non-ulcerated lesions at least 50 mm in length. Distal embolization is associated with a greater likelihood of a major amputation, but this finding can be confounded by the fact that the patients initially presented with critical ischemia, complex lesions, and poor distal runoff.

Exercise vs. Angioplasty

Various trials have compared SFA PTA to exercise therapy. They suggest that although PTA may give a short 3- to 6-month improvement in symptoms, exercise therapy has better results at 12 months. However, at the 5-year follow up, there appears to be no differences between the groups. The loss of the initial advantage of PTA was attributable to restenosis of the dilated segment, whereas those treated conservatively had a steadily increased benefit due to exercise. The later loss of the advantage of exercise was probably due to a lack of adherence to the exercise program. The best effect of exercise was found in patients with disease confined to the superficial femoral artery, in contrast to PTA, which had the best effect in iliac lesions. One study has compared PTA to exercise to no treatment and has suggested that PTA moderately but significantly improves quality of life at 1 year. All these studies lacked sufficient power and the seminal group of PTA with supervised exercise is missing in all studies. Intervention for SFA occlusive disease does not provide superior long-term benefits compared with conservative medical therapy, with adverse events were observed more frequently in the intervention group than the control group (69.1 vs. 46.2%, $P < 0.05$). This was mainly due to

a higher frequency of re-hospitalization in the intervention group than in controls (52.7 vs. 15.4%, $P < 0.001$) [198]. In a recent randomized study, there was no significant difference in effectiveness between endovascular revascularization compared to supervised hospital-based exercise during 12-month follow-up, any gains with endovascular revascularization found were non-significant, and endovascular revascularization costs more than the generally accepted threshold willingness-to-pay value, which favors exercise [199].

Surgery vs. Angioplasty

When examining the benefits of exercise in the claudicant population, a further question arises: "is there a functional benefit of surgery in the intermittent claudication population?" One study has compared peripheral bypass surgery, surgery followed by 6 months of supervised exercise training with dynamic leg exercises, and 6 months of supervised training alone in 75 patients with claudication. At 13 months of randomization, walking ability was improved in all three groups. The most effective treatment for improving functional status was exercise training plus surgery. The median changes in maximal walking distance were 173% for the surgical group, 263% for the group that received both supervised exercise and bypass, and 151% for the exercise group alone. The surgically treated patients increased their walking distance more than patients who received only exercise training; they also had a greater rate of complications than the exercise groups. Percutaneous balloon angioplasty/stenting (PTA/S) for TASC-II C lesions has a superior midterm patency to that of above the knee femoropopliteal bypass (AK-FPB) using polytetrafluoroethylene (PTFE), and AK-FPB with PTFE has better primary and assisted-primary patency than PTA/S-D [200].

Economics

In Sweden, the cost effectiveness ratio (cost per month of patency) for PTA and local open thrombo-endarterectomy appears equivalent. For a decision and cost effectiveness analysis of revascularization procedures for femoropopliteal disease (4,800 PTAs and 4,511 bypasses), six treatment strategies were analyzed: (1) no treatment, (2) initial PTA with no further revascularization, (3) initial PTA with subsequent PTA, (4) initial PTA with subsequent bypass surgery, (5) bypass surgery followed by no therapy and (6) bypass surgery followed by graft revision. The results showed that for a 65-year-old man with disabling claudication and a femoropopliteal stenosis or occlusion, an initial PTA strategy increased QALY by 2–13 months and resulted in decreased lifetime expenditures as compared with bypass surgery. Sensitivity analysis showed that when the 5-year patency of PTA exceeds

30%, PTA is the preferred initial invasive strategy in patients with disabling claudication and femoropopliteal stenosis or occlusion. Endovascular revascularization of SFA disease improves quality of life (QoL), and restenosis negatively affects QoL outcomes. After stent implantation, whether primary or secondary, QoL was significantly ameliorated compared to balloon angioplasty alone. However, it remains to be proven in larger cohorts whether primary stenting yields a QoL benefit compared to balloon angioplasty with optional secondary stenting [201].

Conclusion

The superficial femoral artery (SFA) is the longest artery in the body and experiences a unique array of biomechanical forces during daily life. While the modeling and imaging of these vessels has been restricted to healthy volunteers, there is only limited data on the biological and mechanical features of these vessels as they develop atherosclerosis, as they stenose and produce symptoms, and as they respond to intervention (drug therapy, balloon angioplasty or stent placement). There are several highly relevant potential areas of research for computational sciences including bioinformatics, modeling vessel biomechanics, enhancing image interpretation, visualizing the impact of intervention on the vessel, and predicting the patterns of restenosis, dissection and occlusion after intervention (Fig. 3). Successful integration of clinical information with imaging, modeling, and simulations of the SFA is crucial to further therapeutic advances in the treatment of lower extremity disease (Fig. 4).

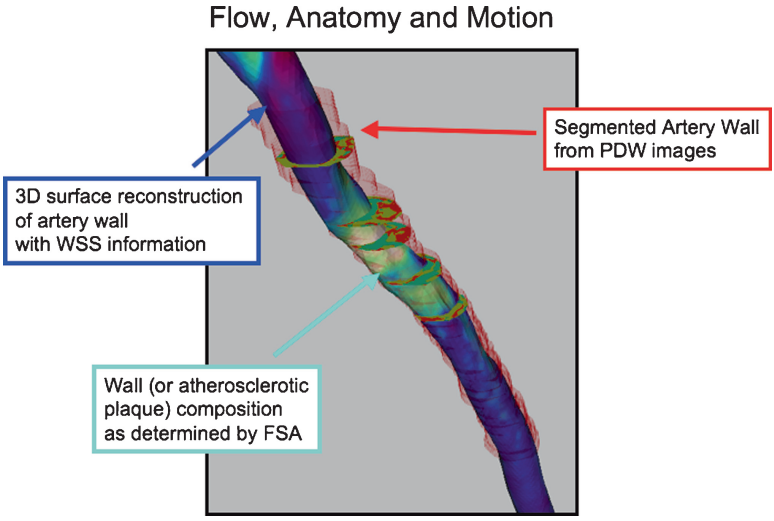

Fig. 3 Composite computational analysis of the SFA illustrating the potential of the integration of anatomy, composition and hemodynamics

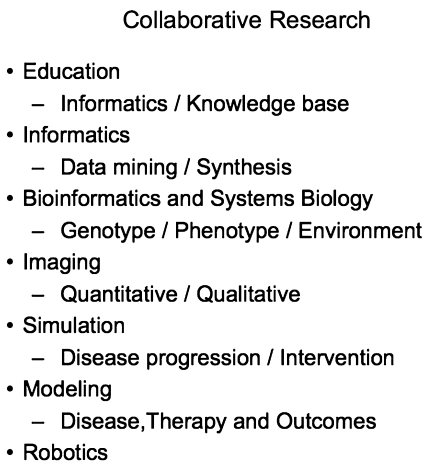

Fig. 4 Areas of collaborative research between clinical vascular surgery and computational sciences to achieve computational surgery

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