ARTIGO DE REVISÃO REVIEW ARTICLE

NEOINTIMAL HYPERPLASIA

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Abstract

Neointimal hyperplasia is a physiologic healing response to injury to the blood vessel wall, involving all the three arterial layers and it occurs in the presence of internal (endovascular) or external (surgical) injury.

It is a highly complex process involving several tissues (perivascular, vessel wall, and blood) and numerous cell lineages with multiple molecular signaling networks. So, there is a number of possible targets for inhibition of this process. There are known risk factors for Intimal Hyperplasia, such as diabetes, female gender, presence of systemic inflammation, type of arteries treated, types of surgical and endovascular materials, presence of turbulent flow and genetic status.

The present paper discusses the pathophysiology of neointimal hyperplasia and the strategies to prevention and treatment of it.

INTRODUCTION

In vascular surgery, just like in our lives, everything we do has consequences. Newton said so when he first described his third laws of motion, published in 1687. The translation of this principle for vascular surgery is called neointimal hyperplasia. Neointimal hyperplasia is a physiologic healing response to injury to the blood vessel wall, in a process analogous to scar formation.

When there is an aggression (surgery, angioplasty, stenting, altered flow pattern), endothelium stimulation occurs, with platelet activation and aggregation and leucocyte adhesion and infiltration – this is the beginning of the thrombotic and inflammatory process. At the site of injury, endothelial cells are denuded, and the subendothelial matrix is exposed to flowing blood. Platelets and fibrinogen immediately adhere to the surface of the injured vessel. A multistep cascade of platelet and leukocyte adhesion and activation promotes secretion of inflammatory signaling molecules and growth factors that promote smooth muscle cells migration from the media to the intima.[1] The smooth muscle cells proliferate in the intima and deposit extracellular matrix, release degrading enzymes with basement membrane destruction and then transmigrate into the extraluminal tissue, causing stenosis.[1]

The adventitia plays a critical role in this process. The adventitia is considered an "injury sensing tissue", due to its capability to respond to different stimuli in an outside-in manner, toward the intima and leading to vessel remodeling. Adventitial fibroblasts when stimulated, undergo phenotypical changes to myofibroblasts, which are specialized cells with contractile as well as migratory properties. Myofibroblasts can undergo proliferation and migration to form neointimal tissue.

All the three arterial layers are involved in the pathophysiology of neointimal hyperplasia and why it occurs in the presence of internal (endovascular) or external (surgical) injury. It is a highly complex process involving several tissues (perivascular, vessel wall, and blood) and numerous cell lineages with multiple molecular signaling networks. So, there are an amount of possible targets for inhibition of this process, currently under investigation.

The aim or this review is to give insight into the process of intimal hyperplasia focusing on risk factors and strategies developed so far to fight against in vascular intervention.

RISK FACTORS

There are known risk factors for Intimal Hyperplasia, such as diabetes, female gender, presence of systemic inflammation, type of arteries treated, surgical and endovascular materials, presence of turbulent flow and genetic status (IL-10 gene, chromosome 12). Diabetes is associated with increased endothelial dysfunction, increased platelet activity and more aggressive cellular response to injury. Female patients generally have smaller vessels and there may be some hormone contribution to their higher risk of development of intimal hyperplasia. Systemic inflammation, measured with C reactive protein, lipoprotein (a), postprocedural von Willebrand factor, and plasminogen activator inhibitor-1 antigen also correlate with unfavorable outcomes. Muscular (distributing) arteries, with high

vascular smooth muscle content in their media have higher restenosis rate than elastic (conductance) arteries. Iliac arteries are conductance vessels (elastic) with a high elastin content in their media. Consequently, the rate of restenosis is expected to be relatively low. Profunda femoral, popliteal, and tibial arteries are muscular (distributing) arteries, with high rates of restenosis. One of the most powerful predictors of restenosis is the vessel diameter, as we see that smaller vessels are at greater risk of restenosis. Stents and prosthetic grafts cause more inflammatory stimulus, with consequently more restenosis due to intimal hyperplasia.

Hemodynamic forces, specifically shear stress and wall tensile stress, are well-established initiators and modulators of intimal hyperplasia. Under physiologic conditions, the steady laminar blood flow generates shear stress in arteries. Endothelial cells sense this physiologic shear force, releasing mediators such as nitric oxide (NO) maintain a quiescent state for smooth muscle cells and homeostasis of the whole vessel wall.[2,3] Vascular reconstructions such as vein bypass grafts, stented diseased arteries, and arteriovenous fistulas not only alter the rate of the local blood flow but also frequently induce a disordered flow pattern. In normal and increased wall shear stress protective pathways are induced, particularly anti-inflammatory and antioxidant pathways.[3] This explains how an exercise training program is specially effective in claudicants.[3] Both clinical and experimental observations have demonstrated that disturbed flow and/or low wall shear stress accelerate development of intimal hyperplasia. Endothelial cells respond to these particular hemodynamic conditions by elaborating adhesion molecules and proinflammatory cytokines that in turn enhance cell proliferation and matrix accumulation, leading to robust intimal growth.[4] On the other hand, laminar, high blood flow (uniform high shear stress) generally exhibits an opposing effect on intimal growth. Furthermore, augmentation of blood flow in vessels with established intimal hyperplasia induces intimal regression. This knowledge has been translated to clinical application, so that creation of a distal fistula to boost the blood flow has led to improvement in the patency rate of lower extremity grafts in selected circumstances. We know the nature of the flow through the vessel will have a major effect. High flow resulting in high wall shear stress in a unidirectional uniform laminar pattern will push the vessel towards maturation or healthy re-modelling, whereas low wall shear stress with chaotic turbulent and oscillating flow will encourage the vessel to remodel inwards.[2]

TREATMENT

So how can this knowledge be used in terms prevention and treatment of intimal hyperplasia? We can prevent intimal hyperplasia by limiting the extent of endothelial injury, minimizing trauma to the adjacent normal vessel, with selective use of stents and prosthetic devices and gentle and careful handling of tissues (particularly the adventitia) during surgical procedures and during endovascular procedures. We can induce healthy flow patterns with grafts and avoid pathological flow, using adequate graft designs and anastomotic angles. Also, there are some drugs that claim to improve overall flow. We are yet to develop an agent which makes the endothelium more protected to these stimuli, to switch the endothelial cells to atheroprotective phenotype, witch makes this is an important area for study. Attempts have been made to block the effect of factors on the cells with antiproliferative agents and more excitingly with allogeneic cells.

Remembering the process of neointimal hyperplasia formation, we can inhibit each step of the cascade with endothelial protective agents, antiplatelet therapy, anticoagulants, anti-inflammatory drugs, antiproliferative agents and by the use of radiation and brachytherapy. In what concerns blockade of the cellular response to the signals, these are some of the possible targets for inhibition of intimal hyperplasia under investigation, such as selectins, integrins, ICAM, VCAM; interleukins,[1,6,9,10,19] TNF-β, MMP[2,9] and the Renin-Angiotensin System. Biologic therapy can be delivered via three platforms: drug-eluting stents (DES), drug-coated balloons (DCB) and via direct drug delivery. DES and DCB normally use drugs as paclitaxel and sirolimus, which are immunosuppressants, antiproliferative, anti-inflammatory and antimitotic drugs. Paclitaxel binds to the beta subunit of tubulin, leading to the inhibition of microtubule disassembly. By blocking microtubule disassembly, paclitaxel prevents cell progression from G2 to M, interferes with the mitotic spindle apparatus, inhibits smooth muscle cell migration, and signal transduction. Sirolimus is a weak antibiotic but a powerful immunosuppressant and antimitotic. It blocks the cell cycle from progressing from G1 to the S phase.

Drug-eluting stents

DES are excellent therapies in vessels with significant elastic recoil and/or flow limiting dissections. They improved primary patency and reduced target lesion revascularization when compared to balloon angioplasty for femoropopliteal lesions as demonstrated by some studies as the ZILVER PTX (primary patency of 66.4% with Zilver PTX DES compared to 43.4% with PTA alone at 5 years)[5] and the MAJESTIC Trial (primary patency of 83.5% with Eluvia DES at 3 years).[6] DES major disadvantages are that they lose their anti-neoproliferative over time and become a bare stent which may elicit a long-term inflammatory response and predispose a patient to develop restenosis of the vessel segment. Also, DES impairs re-endothelization and exacerbate life-threatening stent thrombosis because of endothelium damage caused by both drug and stenting.

Drug-coated balloons

DCB overcome the limitation of leaving a permanent prosthesis. They have also shown beneficial long-term outcomes above the knee compared to PTA alone as demonstrated by the IN.PACT SFA (primary patency of 82.2% vs. 52.4% with PTA alone at 1 year),[7] the Lutonix

Trial (24% Target lesion revascularization rate at 2 years)[8] and the ILLUMENATE study (primary patency of 76.3% for DCB compared to 57.6% for PTA alone).[9]

Drug coated balloons (DCB) designed to release antimitogenic agents to the site of the blockage are aimed at reducing artery restenosis after intervention. However, first generation DCB utilize mainly direct application of the chemotherapy drugs along with hydrophilic excipients to facilitate uptake into the tissue, and the majority of drug is released from the DCB systemically. Unfortunately, only a smaller fraction (~20%) of the anti-neoproliferative on the balloon is delivered to the vessel wall and the downstream shedding of anti-neoproliferative could be deleterious.

Recently, some concern has been raised with a positive mortality signal related to the use of paclitaxel.[10] In the three RCTs composed of 863 patients with longer-term follow-up of 4 years (IN.PACT SFA, presented but not yet published) and 5 years (Zilver PTX, THUNDER), the all-cause death increased further with paclitaxel (14.7% vs 8.1%, crude risk of death; RR, 1.93; 95% CI, 1.27–2.93; number needed to harm, 14 patients [95% CI, 9–32]). The absolute risk difference was 7.2% (95% CI, 3.1–11.3%). There was no statistically significant heterogeneity between studies (P = .92).[10]

There is limited data for the use of DCB below the knee. The IN.PACT DEEP trial was stopped early because it did not meet its primary endpoint and there were signals suggestive of an increased rate of major amputation in the DCB arm.[11] The BIOLUX study demonstrated similar primary patency loss between PTA and DCB (17.1% patency loss in DCB vs. 26.1% in PTA, p =0.298).[8]

An important problems related to the use of DES and DCB is that there we are dozens of sponsored trials, all of them with excellent procedure success rates, measured as TLR (target lesion revascularization), but with no differences in terms of clinical important outcomes. For instance, if we are treating claudicants, as the majority of the patients treated with this devices, the adequate outcome should be quality of life measured by validated questionnaires. Amputation rate as an outcome in claudication is not a significant endpoint. So far, drug-eluting balloons in below-the-knee disease have shown no superiority over plain balloon angioplasty besides surrogate endpoints.

The 2017 ESC/ESVS Guidelines on the Diagnosis and Treatment of PADs don't attribute strong evidence to their use (class IIb recommendation) and recognize that there are some gaps in this field.[12]

To overcome the limitations of the sponsored trials, some independent trials are ongoing. The SWEDEPAD Trial is a multicenter, prospective Randomized Controlled Clinical Trial based on the Swedish Vascular Registry (SWEDVASC) Platform (governmental sponsor), with relevant clinical outcomes. It tests the hypothesis that drug eluting (DE) technology is superior to conventional endovascular treatment (no-DE) in terms of important clinical outcomes, when applied on infrainguinal (femoropopliteal and/or infrapopliteal) obstructive vascular lesions. The Study started by November 2014, estimates to enroll 3800 participants and the estimated study completion date is June 2021. The primary endpoint for patients with critical limb ischemia (SWEDEPAD 1 -NCT02051088) is amputation rate during follow-up and the primary endpoint for patients with intermittent claudication (SWEDEPAD 2 - NCT02051088) is health-related quality of life after one year.

Direct drug delivery

Direct drug delivery can be achieved via the *"bullfrog"* micro infusion catheter, currently, the only device in the market under the category of a direct drug delivery system. This micro infusion catheter comprises of a microneedle folded within a balloon. The device is deployed by expanding the balloon against the wall of the vessel and extending the needle into the vessel wall with penetration into the adventitial layer. Pharmacotherapies can be deployed in the vessel segment of interest, presently, dexamethasone, but in the future, other pharmaceutical agents, biologics, biosimilar, and even stem-cell therapies can be deployed in this fashion.[13]

The DANCE Trial (Dexamethasone to the Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization) is a single arm multicenter study designed to evaluate the safety and efficacy of the Bullfrog device in the treatment of femoropopliteal lesions ≤15 cm in length. 262 patients were enrolled with symptomatic PAD and received either PTA or atherectomy with dexamethasone infusion.[13] No major adverse events at 30 days and no device or drug related deaths at 12-months were reported, thus concluding safe use of the device in this vascular bed. At 12 months, the primary patency in the PTA + dexamethasone group and atherectomy + dexamethasone group were 75.5% and 78.4% respectively both of which exceeded the historical comparator of 72.3% determined by the authors. A limitation of this study is that it did not compare dexamethasone infusion to the other drug-eluting technologies.[13]

LIMBO trial (NCT02479555) applies the bullfrog device in lesions below the knee and has recently finished enrollment.

The advantages of direct drug delivery technology leads to an increased efficiency and precisions allowing for lower therapeutic concentrations of drugs to be used and smaller discreet segments (around 20mm each) to be treated. Since the therapy is delivered directly into the desired location, the risk of downstream washing of the agent is virtually non-existent. The micro-infusion catheter is a versatile device because the platform can be used to deliver any combination of drugs. However, the device is designed for use in treatment of heterogeneous and restenotic plaque but it is not suited for use in the treatment of homogenous and calcific plaque.

Covered stents

Covered stents are another strategy aimed to reduce restenosis, as it provides a mechanical barrier against tissue ingrowth. Nevertheless, edge stenosis limits this treatment option.[14] To overcome this problem, a combined technique

of preparation of the landing zones of the stent graft with DBC to prevent edge stenosis was proposed, although raising important cost issues.[15]

Bioresorbable stents

Another promising devices are the bioresorbable stents. The use of absorb everolimus-eluting stent used in infrapopliteal arteries showed promising three-years results, but further studies are warranted.[16] This was an industry sponsored trial with some limitations: single--center study, only 48 symptomatic patients (Rutherford category 3–6) with 27% of claudicants and treatment of infrapopliteal arteries, which is at least highly debatable. They treated small lesions ≤5 cm long (2 cm average). There were no control group, comparing results with other studies, but treating smaller lesions and different patients. Complete bioresorption occurs within 3 years, the results thereafter would be very newsworthy, yet in the meanwhile the results are similar to standard DES.[16]

Other

Many other strategies have been attempt both in animal studies and through innovative devices applied in humans.

There are agents abled to inhibit neointimal hyperplasia in animal models. Cinnamic aldehyde has anti--inflamatory properties, with a 61% reduction in vessel occlusion(17). The nontoxic red wine polyphenols loaded in a drug-eluting nanoparticle delivery system, highly specific for endothelial cells, showed to reduce smooth muscle cell proliferation and inflammatory cell and platelet activation, while promoting re-endothelization of the injured artery.[18] Honokiol is a natural bioactive product with anti tumor, anti inflammatory, anti oxidative, anti angio¬genic and neuroprotective properties.[19] This study determined that perivascular honokiol appli-cation reduced intimal thickening in rabbits 14 days after carotid artery injury, it may inhibit vascular smooth muscle cell (VSMCs) proliferation and reduce collagen deposition in local arteries.[19]

Owing to the rapidly dividing cells in the developing neointima, radiation therapy stands as an attractive approach to prevent intimal hyperplasia, especially when delivered locally via catheter as brachytherapy. The Randomized PARIS (Peripheral Arterial Radiation Investigational Study) failed to demonstrate a significant reduction in restenosis after PTA of femoropopliteal lesions.[20]

Combination of cold therapy with angioplasty (cryoplasty) is being considered for pilot tests in lower extremity arterial interventions on the basis of several reported small series and trials.[21] However, evidence that such therapy enhances efficacy and durability of angioplasty remains limited.[22]

Finally, Wang and co-authors generated a biomimetic delivery system using nanoclusters coated with platelet membranes to target the injured arterial wall. This technology makes the delivery system so specific for endothelial cells that it can be given intravenously.[23] These nanoclusters were loaded with an endothelium-protective epigenetic inhibitor (JQ1) or sirolimus and compared for their ability to mitigate restenosis without compromising the process of re-endothelization. JQ1/nanoclusters preserved the ability of the endothelium to recover while mitigating IH and appear to be a promising EC-protective candidate drug, suitable for next-generation anti-restenosis therapy.[23]

CONCLUSION

In conclusion, one might say that nowadays we are able to do great things, amazing procedures to our patients and it would be great if we could make them last. The complete understanding and control of intimal might be the answer.

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