

# Solutions for hemodialysis vascular access dysfunction: Thinking out of the box!!

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Hemodialysis vascular access dysfunction is currently a major cause of hospitalization and clinical morbidity in the hemodialysis population. There are two main forms of permanent hemodialysis vascular access; the native arteriovenous fistula and the synthetic PTFE graft. Despite their unfortunate increasing prevalence, cuffed double lumen silicone catheters should ideally not be considered as a permanent form of dialysis access and will not be considered further in this editorial. Both forms of permanent dialysis vascular access are associated with their own unique complications, the overall sum of which results in the huge clinical morbidity and economic costs that currently characterize hemodialysis vascular access dysfunction.

Despite the magnitude of the clinical problem, however, there has been a paucity of novel therapeutic interventions in this field. This is in marked contrast to (a) the recent plethora of targeted interventions for the treatment of arterial neointimal hyperplasia following coronary angioplasty and (b) the many advances in biomedical engineering and local drug delivery. This is particularly unfortunate since many of these novel therapies, especially local drug delivery could be ideally suited to the treatment of hemodialysis vascular access dysfunction, because of (i) the superficial position of dialysis access grafts and fistulae and (ii) the presence of synthetic material in PTFE grafts, which could serve as a scaffold for the polymeric delivery of a variety of anti-infective, anti-thrombotic and anti-proliferative agents.

This editorial review will (a) briefly summarize the main problems currently associated with the two permanent forms of dialysis access and (b) identify potential novel solutions and approaches to tackle these problems. The emphasis will be to try and apply recent scientific advances in molecular and cell biology and biomedical engineering to the clinical problem of hemodialysis vascular access dysfunction.

## A. THE PROBLEM

**(i) Native arteriovenous fistulae:** Although arteriovenous fistulae are the preferred mode of dialysis access they are far from perfect. The current primary failure rate varies from 15-40% (1, 2), following which the one and two year survival rates are 85% and 75% respectively (3). Arteriovenous fistulae are plagued by two major problems. The first is an initial failure to mature adequately to support hemodialysis. The exact reasons for this remain unclear but are probably due to a combination of factors which include poor arterial inflow, inadequate venous substrate due to previous placement of intravenous cannulas, excessive surgical manipulation and possibly genetic polymorphisms (4). These factors could combine to result in a combination of inadequate dilatation together with aggressive early neointimal hyperplasia. The second is a later venous stenosis as a result of venous neointimal hyperplasia (see the section on PTFE grafts below for current thoughts on the pathogenesis and pathology of venous neointimal hyperplasia in the setting of arteriovenous grafts and fistulae). It is likely that the incidence of both these complications could rise (particularly in the United States), as an attempt is made to create more arteriovenous fistulae in patients with inadequate veins (5).

**(ii) PTFE dialysis access grafts:** In contrast to arteriovenous fistulae, PTFE dialysis access grafts do not have any major problems with initial maturation. Their Achilles heel is an aggressive venous stenosis due to venous neointimal hyperplasia that occurs at the graft-vein anastomosis, as a result of which the primary patency rate of PTFE grafts is only 50% at one year and 25% at 2 years (3). Their cumulative patency (with aggressive monitoring and intervention), however, can be elevated to the level of arteriovenous fistulae (85% and 75% at 1 and 2 years),

albeit with a six fold greater intervention rate! At a pathogenetic level, venous stenosis (in PTFE grafts and probably in the setting of late arteriovenous fistula stenosis), is thought to be due to endothelial and smooth muscle damage at the graft-vein anastomosis due to mechanical (surgery and angioplasty), hemodynamic (turbulence and low shear stress) and inflammatory (PTFE promotes the chemotaxis of macrophages) stressors (6). The traditional view on the pathogenesis of neointimal hyperplasia and vascular stenosis emphasizes the fact that neointimal hyperplasia is due to a migration of smooth muscle cells from the media into the intima where these cells proliferate and form the lesion of venous neointimal hyperplasia. Recent studies, however, have demonstrated that neointimal cell types originate from diverse sources, which include adventitial fibroblasts (which migrate from the adventitia, through the media into the intima) and circulating bone marrow derived cells (7, 8). In many cases these cells acquire the phenotype of smooth muscle cells and myofibroblasts and contribute to total neointimal volume. At a histological level, venous neointimal hyperplasia is characterized by smooth muscle cell migration/proliferation with matrix accumulation, the presence of microvessels within the neointima and a perigraft macrophage layer (9-11). It is also important to emphasize that the final degree of luminal stenosis is dependent not just on the amount of neointimal hyperplasia, but also on the pattern of adventitial or vascular remodeling (12). Thus the same neointimal volume could result in either significant luminal stenosis (in the setting of adverse remodeling or vasoconstriction) or alternatively, minimal stenosis (in the setting of beneficial vascular remodeling or vasodilatation).

## B. NOVEL THERAPEUTIC OPTIONS AND OPPORTUNITIES

**(i) Improving arteriovenous fistula maturation:** Primary non function of arteriovenous fistulae is a poorly understood and multifactorial problem. As discussed above vasoconstriction (inability to dilate appropriately) and neointimal hyperplasia could both be involved. Conventional measures that need to be strictly adhered to in an attempt to reduce maturation failure include early referral to a nephrologist, appropriate selection of arteries and veins, optimization of cardiac function, avoidance of central catheters, minimization of surgical manipulation (personal communication; Dr Klaus Konner) and aggressive post placement radiological and surgical intervention (13-20). Because of

the multifactorial character of primary non-function in arteriovenous fistulae, it has been extremely difficult to identify any single factor that could be the focus of a targeted intervention that could prevent this problem. An innovative way to bypass this problem has been suggested by Nugent et al (21) who placed gel foam cuffs loaded with porcine aortic endothelial cells around the arteriovenous anastomosis in a pig arteriovenous fistula model. The rationale behind this approach was that endothelial cells were likely to be able to produce the *entire* slew of mediators required for both appropriate vasodilatation and a minimization of neointimal hyperplasia. Animals treated with the endothelial cell loaded cuffs had a significant decrease in neointimal hyperplasia at two months as compared to control animals.

**(ii) Drug eluting stents and other mechanical interventions:** Initial studies on the placement of bare metal stents following angioplasty of stenotic lesions associated with PTFE dialysis access grafts were unable to demonstrate any benefit of stent placement (22, 23). This was probably because any benefits from a reduction in vascular constriction were probably negated by an aggressive in stent restenosis. The development of drug eluting stents that could significantly reduce in stent restenosis has revolutionized the treatment of coronary atherosclerosis and has reduced the binary stenosis rate at 6-9 months to under 10% (24, 25). There are currently two drug eluting stents available for coronary placement that have been shown to be effective in controlled randomized studies (a sirolimus eluting stent manufactured by Cordis and a paclitaxel eluting stent manufactured by Boston Scientific). Both sirolimus and paclitaxel are small molecule inhibitors of the cell cycle and so are able to block the cellular proliferation and migration that characterizes neointimal hyperplasia. In both instances these molecules are loaded into a polymer which is then coated around the stent surface. The results of a recent trial which compared these two drug eluting stents has just been released and appears to demonstrate a superior result for the sirolimus eluting stents with regard to quantitative coronary angiography and thrombotic events, although there were no differences in the clinical end points (26). There is unfortunately no clinical information available on the use of drug eluting stents in the setting of hemodialysis vascular access dysfunction. A recent study by Rotmans et al (27) in a pig model of arteriovenous graft stenosis, however, was able to demonstrate an improvement in luminal area in animals treated with the sirolimus eluting stents. More

recently it has been shown that the placement of stent-grafts following balloon angioplasty of stenotic lesions in the setting of hemodialysis PTFE graft dysfunction results in superior results as compared to balloon angioplasty alone. Fifty-three percent of patients treated with the stent grafts had a functioning access at 6 months as compared to only 29% of patients treated with balloon angioplasty alone (28). The introduction of drug eluting stents for coronary restenosis represents an excellent example of the combined application of biomedical engineering (polymer coating of stents) and molecular and cell biology (identification of potent anti-proliferative agents) to develop an effective novel therapy for a significant clinical problem (coronary restenosis). One hopes that this and other innovative approaches to reduce vascular stenosis will also be applied/developed for hemodialysis vascular access dysfunction.

**(iii) Perivascular polymers:** Since the process of neointima formation has been shown to involve a migration of fibroblasts from the adventitia, through the media and into the intima, it seems appropriate to try and deliver therapeutic agents directly to the adventitia of the vessel wall through the use of perivascular polymers loaded with the appropriate therapeutic agents. Such an approach could be ideally suited to dialysis access grafts and fistulae since the polymers could be easily placed at the time of surgery. Alternatively, the superficial position of dialysis access grafts and fistulae could lend themselves to repeated percutaneous therapy with injected drug loaded polymers or microspheres. The validity of such an approach has been documented in a number of experimental arterial angioplasty models using agents such as nitric oxide, paclitaxel and tyrphostins (29-37). More recently we have been able to demonstrate an almost complete absence of luminal stenosis in animals treated with paclitaxel loaded perivascular polymers in our pig model of arteriovenous stenosis (38). Similar results have also been obtained by Masaki et al using injectable polymers loaded with paclitaxel (39).

**(iv) Circulating vascular progenitor cells:**

*(a) Smooth muscle progenitor cells:* It has been recently shown by a number of authors that upto 60% of the cells within the lesion of neointimal hyperplasia following experimental angioplasty are circulating or bone marrow derived smooth muscle progenitor cells that have attached to the region of vascular injury and then changed their phenotype to that of smooth muscle cells or myofibroblasts (8, 40). In-

terventions that reduce the number of these circulating or bone marrow derived cells, could therefore be extremely effective therapies for neointimal hyperplasia. In this regard, a recent paper demonstrates a potent inhibitory effect of sirolimus on circulating smooth muscle progenitor cells (41).

*(b) Endothelial progenitor cells:* There has also been tremendous interest recently in the role of endothelial progenitor cells (EPCs) in the repair of vascular injury (angioplasty, surgery, atherosclerosis) (45). EPCs are circulating cells that express both the hematopoietic stem cell marker CD34 and one or more endothelial cell markers (42). A number of researchers have demonstrated that an infusion of EPCs following angioplasty injury results in enhanced endothelialization which then translates into a reduction in neointimal hyperplasia (43, 44). An alternative approach is to try and mobilize EPCs from the bone marrow using agents such as GCSF, erythropoietin or statins (45). For example, the administration of GCSF in a mouse angioplasty model resulted in increased endothelialization of the region of vascular injury, together with a decrease in neointimal hyperplasia (46). EPCs have also been used to try and endothelialize prosthetic grafts and stents. Most of these approaches involve the *ex-vivo* culture of EPCs and so are expensive, time consuming and labor intensive (47-49). An alternative approach by Ong et al involves the coating of prosthetic stents with an antibody to CD34 (50). When these stents are placed in the circulation, circulating CD34+ve cells bind the stents, resulting in complete endothelialization within one hour of deployment!

How could the above research findings on circulating vascular progenitor cells have a clinical impact in the setting of hemodialysis vascular access dysfunction? One approach could be to try and maximize the mobilization of EPCs within the circulation while at the same time using interventions which would decrease the number of smooth muscle progenitor cells. Unfortunately, both cell types may have a common precursor which could make this an extremely difficult proposition! An alternative approach could be to try and coat PTFE graft material with the CD34 antibody.

**(v) Using the PTFE graft as a conduit for drug delivery:** Despite the aggressive stenosis and poor survival of PTFE dialysis access grafts, they do have one advantage over arteriovenous fistulae, which is the ability to use the actual graft material as a conduit for drug delivery. This could become especially relevant, since current state of the art polymer technology allows the adhesion of a variety of molecules

to PTFE graft material. An exciting example, is the ability to coat PTFE dialysis access grafts with a range of polymers that release nitric oxide (which has both anti platelet and smooth muscle cell activity) (51). Other potential coatings could include a variety of anti-proliferative and anti-infective agents.

In summary, we live in exciting times with regard to the development of novel therapeutic options for vascular stenosis in general. This is mainly due to a combination of advances in biomaterial technology linked to a better understanding of the pathogenesis of neointimal hyperplasia. The fusion between these two fields has resulted in a variety of novel *local* therapeutic interventions for neointimal hyperplasia. This is particularly relevant for hemodialysis vascular access dysfunction since dialysis access grafts and fistulae could be the *ideal clinical model* for testing out novel local therapeutic interventions, due to their superficial location, the aggressiveness of the venous stenosis which could result in

smaller clinical trials with fewer patients, and the fact that the dialysis needles could be used for multiple repeat local applications of appropriate therapies.

What is desperately needed, however is a concerted attempt to translate some of these exciting advances in biomaterials and molecular biology to the clinical setting of hemodialysis vascular access dysfunction, in order to reduce the very significant morbidity and financial cost, currently associated with hemodialysis vascular access dysfunction.

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