Intimal hyperplasia, the obstacle in bypass grafts

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CHAPTER 7

Future Perspectives

Vein grafts and synthetic grafts develop intimal hyperplasia after implantation into the arterial circulation. Nearly all arterialized vein grafts demonstrate a significant decrease in lumen size due to intimal thickening already within 4 to 6 weeks after implantation.[1] Although intimal hyperplasia may be a natural reaction of these bypass materials to adapt to the new flow and pressure forces induced in the arterial circulation, it may also result in pathologic narrowing of the lumen finally resulting in graft failure.[2] Graft failure leads often to hospital re-admission and re-intervention forming a heavy burden for the limited resources in the expensive health care.

Despite tremendous efforts of many researchers, no effective treatment has been developed to prevent intimal hyperplasia in man.[3] In this chapter future perspectives are discussed which might further improve the patency of vein grafts and synthetic grafts in the arterial circulation in man. Because arterial bypass grafts are less susceptible to intimal hyperplasia new developments in the use of arterial grafts are also discussed. Therefore, this chapter first focuses on autologous graft, veins and arteries, where after synthetic grafts are discussed.

Vein grafts

The formation of intimal hyperplasia in arterialized vein grafts depends on pre, per and post operative factors. A combination of measures targeting these factors is likely to be the most effective strategy to control intimal hyperplasia in vein grafts.

Pre operative measures

Intimal hyperplasia in arterialized vein grafts *increases* significantly in conditions of hyperlipidemia.[4,5] Smoking, another important risk factor for the development of atherosclerosis, is also an evident risk factor for the development of intimal hyperplasia.[6,7] Increased awareness of the importance of reducing the risk factors for atherosclerosis might also reduce the development of intimal hyperplasia.

Per operative measures

Intimal hyperplasia in vein grafts *decreases* when the vein graft is taken out the arterial circulation and implanted back into the venous circulation.[8-10] This reversal of intimal hyperplasia occurs only when a vein graft does not stay longer than 2 weeks in the arterial circulation. This indicates that successful strategies to reduce intimal hyperplasia must at least begin in the first 2 weeks after operation. The formation of intimal hyperplasia in a vein graft strongly depends on the depth of injury inflicted upon the arterialized vein graft. The injury to the vein graft wall will disturb the balance of antiproliferation and proliferation in favour of proliferation. The more damage, the more intimal hyperplasia will be

formed.[12]
Especially vein grafts will suffer some injury due to the surgical handling and by the high pressure and flow of the arterial circulation.[11] Due to this injury growth factors are released from vein graft smooth muscle cells and endothelial cells, activated platelets and leucocytes. These growth factors are responsible for the initiation of smooth muscle cell proliferation, the key factor in the formation of intimal hyperplasia.

Development of new operative techniques like minimal invasive harvesting reduces the injury by surgical handling. Preventing overstretching of the vein before implantation into the arterial circulation will reduce damage to the vein graft wall. Furthermore the "no touch,, technique of the vein should be used during harvesting avoiding grasping the vein graft by means of a forceps[13] Good candidates to protect the integrity of the vein graft wall are furthermore; a storage medium using a physiological buffer containing papaverine or a Hank's balanced salt sodium solution modified with glutathione, ascorbic acid and L-arginine.[14]

Many experimental studies reported successful control of intimal hyperplasia in vein grafts. Most of these studies used systemic therapies leading to possible unwanted side effects.[3] Local therapy delivering the pharmacologic compound directly to the target, the vein graft is an interesting future perspective. We designed a novel heparin mimic, insoluble sulfated polymer of ß-cyclodextrin (chapter 3) capable of tightly binding heparin binding growth factors. ß-cyclodextrin inhibits proliferation and migration of smooth muscle cells in vitro. Periadventitial application of this polymer resulted in an important reduction of intimal hyperplasia in arterialized vein grafts that were studied in rabbits.

After publication of our results, 2 studies were published which demonstrated that also smooth muscle cells from the adventitia participate in the formation of intimal hyperplasia.[15,16] Inhibition of these periadventitial smooth muscle cells may be an explanation of the success of this type local treatment.
The polymer in this study was tested during experiments in young experimental animals that had no pre existing atherosclerotic vascular changes. Therefore, our study results can not directly be extrapolated to the clinical setting. Moreover, the polymer was added onto the adventitia of the vein graft and makes also contact with the direct surrounding tissue like subcutaneous fat and muscles. The long term toxic effect of this polymer on human tissues is not known. The introduction of this polymer in the clinical setting depends obviously also on the results of its toxic effects on human tissues.
The vein graft is a very suitable target for local therapy. Local therapies allow high

drug concentrations on and in the vascular graft and minimize systemic side effects. The polymer of ß-cyclodextrin sulfate might be a new perspective for the control of vein graft intimal hyperplasia in man. However, to our knowledge no attempt has been made as yet to introduce this polymer of American Maize, Inc (Hammonton, Ind) in a clinical setting.

Genetic engineering of vein grafts.

New local drug application strategies designed to control intimal hyperplasia have focussed on blockade of the cell cycle or the introduction of genetic material in the cells of the vein graft.
In 1995, the first study was published using gene therapy to control vein graft intimal hyperplasia in rabbits. Mann et al used antisense to block the expression of genes for two cell cycle regulatory protein, proliferating cell nuclear antigen and cell division cycle 2 kinase.[17] Although this study showed very promising results, only vein graft media hypertrophy without the formation of intimal hyperplasia, till now no clinical continuation has been reported. Another approach of genetic engineering is the incorporation of enzymes in cells of the vein graft, that are capable to inhibit smooth muscle cell proliferation. Human inducible nitric oxide synthase is an example of such an enzyme. Transfer of human inducible nitric oxide synthase gene leads to overproduction of nitric oxide. The production of nitric oxide by nitric oxide synthase incorporated in porcine vein grafts lead to inhibition of smooth muscle cell proliferation and intimal hyperplasia.[18]

Postoperative factors

Ongoing atherosclerosis of the native arteries and the development of atherosclerosis in the vein graft itself will further undermine the blood flow to the organs. Therefore strict analysis of all risk factors and follow up if necessary treatment is started, is mandatory.

Arterial grafts

Compared to saphenous veins, use of internal mammary arteries as coronary bypass grafts has resulted in excellent patency rates. The capability of the internal mammary artery to produce nitric oxide partly explains the limited development of intimal hyperplasia in this graft. Due to its position, the internal mammary artery is so far only used for coronary artery bypass surgery. Founded upon the success of the internal mammary artery the clinical use of other arterial grafts as bypass grafts has also gained increasingly popularity. Examples of other arterial grafts are the gastro epiploic artery, radial artery, inferior epigastric artery, ulnar artery, descending branch of lateral circumflex femoral artery, and intercostal artery.[19] Like internal mammary arteries, also gastro epiploic arteries have excellent patency rates as coronary bypass graft. Internal mammary arteries and

gastro epiploic arteries have comparable characteristics.[19] The gastro epiploic artery might be a good perspective for patients needing peripheral arterial reconstructions. The gastro epiploic artery looks especially applicable for patients needing both a central and a peripheral arterial reconstruction.

The radial artery is easier accessible than the internal mammary artery and gastro epiploic artery. The radial artery is, supported by the use of antispastic therapy like papaverine or calcium antagonist[20] nowadays increasingly used as coronary bypass graft. The radial artery with the use of adequate antispastic therapy might also be a good perspective for peripheral reconstruction.

The number of diabetic patients needing bypass grafting will increase due to the rising incidence of diabetes mellitus.[21] Diabetes decreases endothelial production of nitric oxide and stimulates proliferation of vascular smooth muscle cells and plasminogen activator inhibitor. Hyperglycaemia itself also inhibits the production of nitric oxide in endothelial cells.[22] Arterial grafts remain their capacity to produce nitric oxide and are likely better prepared to resist the factors that stimulate intimal hyperplasia in the presence of a hyperglycaemic environment. So, diabetic patients are likely to benefit especially from arterial grafts instead of vein grafts.

Synthetic vascular grafts

Autologous blood vessels are the materials of choice for reconstruction of small diameter obstructed arteries. Autologous blood vessels cannot always be used for bypass grafting due to pre-existing disease or previous use. In these cases synthetic grafts are used as bypass graft material. The long term success rate of synthetic grafts with a diameter of less than 6 mm is far from satisfactory and drops as the diameter becomes smaller.[23,24] The most common cause of long term failure in these small synthetic grafts is the formation of intimal hyperplasia at the anastomotic site.

The morphological sequence of the development of intimal hyperplasia in synthetic grafts is described by Clowes and Watastase.[24,25] They described in chronological order the following phases: early thrombosis, appearance and proliferation of fibroblasts in the pseudo intima, appearance of endothelial and smooth muscle cells, and intimal hyperplasia by proliferation of fibroblasts and production of extracellular matrix

Intimal hyperplasia in synthetic grafts occurs under the endothelial layer.[26] It is suggested that endothelial cells in the synthetic graft provide growth factors for the development of intimal hyperplasia.[27]

Expanded polytetrafluoroethylene (ePTFE) grafts are often used for the re-

construction of small diameter arteries in the extremities and as AV fistulas. The presence of synthetic graft material like ePTFE can induce the production of growth factors necessary for the development of intimal hyperplasia in different ways: uncovered PTFE activates platelets which will release growth factors, foreign body response activates macrophages capable to secrete growth factors, compliance mismatch at the anastomosis PTFE graft – blood vessel may lead to stretching of smooth muscle cells causing smooth muscle cell proliferation. The mismatch PTFE graft – blood vessel will lead to turbulence causing endothelial damage and platelet activation with subsequent release of growth factors.[2]

Some strategies designed to improve the patency of small diameter synthetic vascular grafts are endothelial seeding and tissue engineering of new blood vessels using biodegradable polymers.

Endothelial seeding of ePTFE grafts

Endothelial seeding of ePTFE grafts is now for a long period of time an area of intensive research. Endothelial seeding of ePTFE requires the following steps. Before bypass operation subcutaneous blood vessels are obtained from the patient to harvest autologous endothelial cells. The endothelial cells are brought into culture to obtain enough endothelial cells to cover the lumen of the graft. Endothelial cells are seeded onto a precoated lumen of the synthetic graft and are allowed to settle to the surface.[28]

In 1994, a clinical study using endothelial seeded ePTFE grafts to improve graft patency showed no improvements compared to untreated ePTFE grafts.[28] The results of latest clinical studies using endothelial seeding to improve the patency of ePTFE grafts are hopeful. The cumulative 9 year patency rate of endothelial seeded ePTFE grafts was 65% versus a patency rate of 16% for the untreated ePTFE grafts in the femoropopliteal circulation.[29] The patency rate of endothelial seeding of 4 mm ePTFE bypass grafts for coronary artery bypass grafting was 90,5%.[30]

Endothelial seeding results in a lesser thrombogenic surface of the ePTFE graft, possibly accounting for the higher patency rates compared to the untreated ePTFE grafts. Although the patency rates of endothelial seeded PTFE grafts are increasing there is still room for improvement. Despite an endothelial lining the modified ePTFE graft does not behave like an artery. For example the compliance mismatch at the level of anastomosis between ePTFE graft and blood vessel is still existing causing disturbance of the normal blood flow leading to activation of endothelium and platelets. The persisting mismatch of the synthetic graft and blood vessel is not going to be resolved with the use of only an endothelial lining.

From a practical point of view endothe-

lial seeding is limited to a category of patients having stable ischemic complaints allowing postponement of a bypass operation. Also the specific requirements necessary for endothelial seeding limit the use of these techniques. When these limitations can be improved endothelial seeding of ePTFE grafts might be a hopeful perspective for the reconstruction of small diameter arteries.

Tissue engineering of new blood vessels using biodegradable polymers

Tissue engineering of new blood vessels using biodegradable polymers is the latest technique in an attempt to make lasting alternative blood vessels. In this technique, a scaffold made of biodegradable polymer is fabricated and then seeded with vascular endothelial and smooth muscle cells which are stimulated to grow in sterile culture medium.[31] The time needed to make tissue engineered biological grafts is usually weeks to months.

The preliminary results of animal studies demonstrate that the concept of tissue engineering is viable. New blood vessels resembling biological characteristics of native blood vessels were engineered while the biomaterial scaffold was degraded. Control scaffolds without a seeded mixture of endothelial cells, smooth muscle cells, and fibroblasts occluded early after implantation into the abdominal aorta of ovine.[32]

A tissue engineered graft existing of a viable endothelial layer and media may overcome the important draw backs of the synthetic vascular graft, graft thrombosis and extensive formation of intimal hyperplasia. To overcome these draw backs both the tissue engineered endothelial layer and media have to be full grown soon after implantation.

Furthermore, when problems such as aneurysm formation in the tissue engineered blood vessels are overcome[33] tissue engineered blood vessels may be a promising perspective for reconstruction of small diameter diseased arteries.

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