Intimal hyperplasia, the obstacle in bypass grafts
Toes, Gerrit Jan

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Toes, G. J. (2002). Intimal hyperplasia, the obstacle in bypass grafts. Groningen: s.n.
CHAPTER 1

Introduction, purpose and contents of the thesis
In the Netherlands, the highest mortality and morbidity is caused by atherosclerotic obstructions. Atherosclerotic obstructions can cause severe reduction of the arterial blood flow leading to organ dysfunction. An effective tool to restore this reduced blood flow is to bypass the obstructed artery. The latest worldwide survey of coronary revascularization showed that 583,000 coronary-artery bypass operations were performed in 1995. In the Netherlands in 1995 more than 5,000 peripheral bypass operations and in 2001 more than 8,400 coronary-artery bypass operations were performed. The autologous vein is the preferred bypass graft for arterial bypass operations if the size of the recipient artery and vein are compatible and no suitable autologous arterial bypass graft is available. When the diameter of the recipient artery is at least 6 mm in diameter, also the synthetic vascular graft is an often used bypass particularly for bypassing stenotic peripheral arteries. However, half of the vein grafts are only effective for a period of 5 to 10 years due to the formation of intimal hyperplasia in these grafts. A PubMed search learned that between 1975 and 2002 more than 1950 scientific articles have been published investigating the development, and designing strategies to control intimal hyperplasia.

**Intimal hyperplasia**

The majority of vein and synthetic bypass grafts remain patent in the first 2 months after implantation into the arterial circulation. After 2 months the patency of these grafts is threatened due to development of intimal hyperplasia. Intimal hyperplasia is defined as the abnormal migration and proliferation of smooth muscle cells with associated deposition of extracellular matrix in the intimal layer of the vein graft or formation of a neointima in the synthetic graft. Intimal hyperplasia reduces the lumen of the bypass graft which leads to reduced flow and can ultimately lead to graft occlusion. Intimal hyperplasia is furthermore observed after angioplasty, endarterectomy, and in arteriovenous fistulae for haemodialysis. In the first week after operation bypass grafts usually fail because of technical factors such as technical errors induced like stenosis at the anastomoses and compression or kinking of the bypass graft. Between 2 and 24 months after operation vein and synthetic bypass grafts usually fail because of the formation of intimal hyperplasia. There is clinical and experimental evidence that intimal hyperplasia forms the basis for vein graft atherosclerosis, an important cause of late vein graft failure after 24 months after implantation. The success of a bypass graft depends furthermore on the type of bypass, and on the position of bypass graft in the arterial circulation. The success of bypass grafts is often expressed in the cumulative patency rate. For example, the ten year cumulative patency rate of vein grafts for coronary artery bypass grafting is 52-55 % in 1984 and was not improved in 1995.
The five year cumulative patency rate of vein bypass grafts and synthetic bypass grafts for femoral distal bypass grafting are 64-74% and 19-37%, respectively. Compared to the vein and synthetic bypass grafts, the arterial graft develops minimal or no intimal hyperplasia. The use of the gastroepiploic artery and internal mammary artery well known as grafts in coronary bypass grafting, resulted in a cumulative patency rate of more than 95% seven and ten years after the initial bypass graft operation, respectively. Intimal hyperplasia has an obviously important impact on the postoperative health status of patients with vein bypass grafts and synthetic bypass grafts. Occlusion of a bypass graft results often in a hospital readmission and re-operation, and forms a heavy burden for the limited resources in the health care. Therefore, studies to elucidate the events leading to intimal hyperplasia and potential reduction of intimal hyperplasia have a high priority. Important cellular events in the development of intimal hyperplasia are migration and proliferation of smooth muscle cells. Both migration and proliferation of smooth muscle cells are driven by growth factors. Currently, the pathophysiological triggers for intimal hyperplasia in vein and synthetic grafts have been classified as injury, inflammation, and haemodynamic factors.

**Injury.** During operation endothelium and smooth muscle cells of the recipient artery and autologous bypass graft are injured in different ways. Grasping of the forceps or other instruments necessary to harvest the graft, routinely applied high intraluminal pressure to check for leakage of the graft, and the construction of the anastomoses causes damage of endothelium and smooth muscle cells. Moreover, immediately after implantation of the vein graft in the arterial circulation, the vein is exposed to the high pressures and high blood flows causing further damage to the venous endothelium. This injury leads to the early cellular events in the autologous graft in the first minutes after implantation. Immediate deposition of circulating platelets is followed by deposition of leucocytes onto the luminal side of the bypass. These platelets and leucocytes are activated and release prothrombotic factors such as vonWillebrand factor and growth factors such as platelet derived growth factor or macrophage derived growth factor. In this way platelets and leucocytes have the ability to contribute to early thrombosis as well as to the formation of intimal hyperplasia. Besides the loss of antithrombotic capacity there is also loss of antiproliferative capacity in the recipient artery and bypass graft. The injured endothelium is less capable of producing antiproliferative products like heparan sulfates, nitric oxide, and prostacyclin. The physiological balance in the vessel wall is further disturbed by the release of intracellular growth factors from injured medial smooth muscle cells.
have, besides the direct release of growth factors, more pathways to contribute in the intimal hyperplastic wound response. One of the pathways is the release of lysosomal enzymes capable of degrading the extracellular matrix including the basement membrane. This degradation allows smooth muscle cells to migrate to the intima.\textsuperscript{3,5-8} The magnitude of the injury caused by activated leucocytes to the vessel wall is increased by the release of oxygen free radicals capable to detach remaining “defensive” endothelial cells. Furthermore, oxygen free radicals also inhibit the growth of endothelial cells.\textsuperscript{6,7}

**Haemodynamics.** Another phenomenon responsible for the development of intimal hyperplasia are haemodynamic factors like arterial blood flow and pressure. Low flow is cited to be an important trigger for the development of intimal hyperplasia in vein grafts.\textsuperscript{2,4,6} Flow velocity is directly related to blood-vessel wall shear stress. Shear stress is a factor determining the probability and duration of adhesion of blood-borne elements to the luminal surface of the bypass graft. It is likely that shear stress at the blood-bypass graft wall is the mechanical factor that induces the adhesion of circulating cells onto the luminal side of the bypass graft. Release of mitogenic factors of adhered platelets and leucocytes are capable to stimulate smooth muscle cell proliferation. Also in prosthetic vascular grafts, low flow and low shear stress are cited to be responsible for the development of intimal hyperplasia.\textsuperscript{16}

**The purpose of this thesis:**

The purpose of this thesis was to design new strategies to improve the patency of small diameter bypass grafts in the arterial circulation by reducing the formation of intimal hyperplasia. The following goals were formulated to evaluate the efficacy of these new strategies:

1. To inventory the factors responsible for, and the strategies designed to control the formation of intimal hyperplasia in vein grafts in the arterial circulation.
2. To introduce a model to quantify early platelet and leucocyte deposition onto synthetic bypass grafts in vitro.
3. To evaluate the effect of periadventitial application of a sulfated carbohydrate polymer on the formation of intimal hyperplasia in autologous vein graft in rabbits.
4. To evaluate the effect of superhydrophobic modification of small diameter expanded polytetrafluoroethylene vascular graft on platelet deposition and on the formation of intimal hyperplasia both in vivo and in vitro.
5. To evaluate the gastroepiploic artery as autologous bypass graft for peripheral bypass grafting in pigs.

**Contents of the thesis:**

In chapter 2 the cellular and molecular pathways leading to intimal hyperplasia in autologous vein bypass grafts and their pathological triggers are reviewed. Current strategies to control intimal hyper-
plasia in vein bypass grafts are discussed. The role of platelets in early occlusion in vein graft and in synthetic graft is evident, the role of platelets in the formation of intimal hyperplasia in these bypass grafts is uncertain. Another reason to study early platelet deposition after graft implantation beside its role in thrombosis is the capacity of activated platelets to release growth factors contributing to the intimal wound response. Leucocytes contribute to the formation of intimal hyperplasia in at least two separate pathways. One is the direct release of growth factors by activated leucocytes. Another pathway is the release of products who disturb the integrity of the recipient artery and bypass graft. This further disturbance of the vessel wall besides the surgical manipulation leads to release of intracellular and in the matrix arrested growth factors. These observations encourage the development of a model to study platelet and leucocyte deposition. In chapter 3 the fluorescence label Europium is used to study early platelet and leucocyte deposition onto synthetic vascular grafts in vitro. This in vitro method can be used to screen the impact of new biomaterials on platelet and leucocyte deposition. The majority of strategies to improve the patency of autologous vein and prosthetic bypass grafts have focussed on systemic therapies and engineering to attach endothelial cells onto the luminal side. Local therapy in vein grafts has the strong advantage of achieving high concentrations onto the target side with most likely less side effects.

Furthermore, the current type of engineering of synthetic grafts using autologous endothelial cells is costly, logistically difficult and bears the risk of loosing these cells under high arterial pressure and flow. These problems stimulated us to study the effects of a new local therapy and a lasting physiochemical modification of the luminal graft side on the development of intimal hyperplasia in vein and synthetic grafts, respectively. Thus, in chapter 4 we introduced and studied the effect of periaventitial treatment of a novel heparin mimic on the development of intimal hyperplasia in vein bypass grafts. Another way to reduce intimal hyperplasia is to repel platelets and leucocytes from the surface of synthetic grafts, in order to reduce local release of growth factors and inflammatory components. Increased hydrophobicity could potentially contribute to reduced platelet and leucocyte adhesion. In chapter 5 the effect of superhydrophobic modification of the luminal side of expanded polytetrafluoroethylene grafts on the development of intimal hyperplasia is studied. The absence of intimal hyperplasia in the gastroepiploic artery as arterial bypass for coronary revascularization stimulated us to investigate the formation of intimal hyperplasia in gastroepiploic artery as arterial bypass for peripheral revascularization. In chapter 6 this new arterial bypass graft for peripheral bypass grafting is compared with an autologous
venous bypass graft in a pig model. In chapter 7 the results of all previous studies are summarized and integrated providing future prospectives.

References


