Therapeutic and mechanistic explorations of in-stent restenosis in the rat aortic stenting model
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CHAPTER 1
INTRODUCTION AND AIMS
INTRODUCTION

Cardiovascular diseases cause millions of deaths worldwide\(^1\). In large part related to coronary heart disease (CHD)\(^2\). During the past decades the treatment and prevention of CHD has been significantly improved with the introduction of drugs which slow the development or progression of CHD or prevent the clinical manifestations of CHD (B-blockers, aspirin, statins, ACE inhibitors and AT1 receptor antagonists) and by revascularization of obstructed coronary arteries using coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI)\(^3-7\). In recent years therapeutic advances of PCI such as antiplatelet drugs given before and after the procedure, the stent and later the drug eluting-stent have improved mortality and morbidity for patients with CHD and this has led to a marked rise in the number of PCI procedures \(^8-10\). Nowadays In the Netherlands every year around thirty thousand PCI procedures are performed \(^11\). However PCI is still troubled by two major limitations: restenosis and stent thrombosis\(^12,13\).

Restenosis is the narrowing of the vessel wall after PCI and is the result of the arterial healing response after the induction of vascular injury. Restenosis usually does not lead to acute occlusion of the vessel with myocardial infarction and death. However recurrence of angina pectoris is often seen requiring revascularization of the stented vessel (target lesion revascularization). The rate of target lesion revascularization after 5 years is markedly lower with drug eluting stents 10,3%, compared to 26% in bare metal stents\(^14\). Riskfactors for restenosis are small vessels, longer lesions, restenotic lesions and importantly diabetes\(^15,16\). Diabetic coronary artery disease is characterized by multivessel involvement, diffuse disease, more significant stenoses, increased calcified disease and decreased collateral vessel formation\(^17\). These factors might influence the technical success of PCI leading to a lower final lumen diameter. Lower final lumen diameter is strongly correlated with increased restenosis\(^18\). At the molecular level these disease factors may be modulated by insulin resistance, hyperglycaemia and inflammation\(^19,20\). Therefore pharmacological intervention to improve glycaemic control and reduce insulin resistance and inflammation may be an interesting target to decrease the risk of restenosis in diabetic patients undergoing PCI\(^17\). Restenosis is more common after balloon angioplasty and is caused by both elastic recoil, negative remodeling and to a lesser extent neointimal formation\(^21\). Stenting has reduced restenosis by providing a rigid structure in the vessel wall which eliminates elastic recoil and negative remodelling. However restenosis is not eliminated because stenting induces more injury to the vessel wall. This leads to a more proliferative healing response with more neointimal formation\(^22,23\). To tackle the problem of restenosis after stenting the mechanism and pathways of the different phases of neointimal formation have been studied extensively: thrombus formation, inflammation, smooth muscle cell migration, smooth muscle cell proliferation and extracellular matrix formation. The arterial healing response leading to neointimal formation begins with platelet aggregation and platelet activation followed by infiltration of the injured vessel wall and thrombus by predominantly mononuclear and polymorphonuclear leukocytes\(^24-26\). The leukocytes and platelets produce cytokines like monocyte chemoattractant protein (MCP-1), platelet-derived growth factor (PDGF) and angiotensin II. These cytokines enhance inflammation, stimulate smooth muscle cell migration from the media of the vessel towards the lumen and stimulate smooth muscle cell proliferation \(^27-29\). After a few weeks the proliferation of smooth muscle cells in the neointima peaks and apoptosis of neointimal cells becomes more prominent \(^30,31\). The remaining neointimal cells (most of smooth muscle cell origin and some macrophages) begin production of proteoglycans and collagen creating an extracellular matrix\(^32,33\).

After insight had been gained in the pathophysiology of neointimal formation, a myriad of known and newly developed anti-thrombotic, anti-inflammatory, anti-migratory, anti-proliferative and anti-
extracellular matrix producing drugs have been tested in animal models and clinical trials in an attempt to reduce neointimal formation. Of these drugs, the two anti-proliferative drugs sirolimus and paclitaxel have shown exceptional promise in reducing in-stent restenosis. Brachytherapy by using the anti-proliferative properties of beta radiation was initially successful in reducing in-stent restenosis, but long term follow-up studies showed restenosis and late thrombosis. The strong anti-proliferative effects of sirolimus and paclitaxel make these drugs less suitable for systemic administration in patients. Local application of these drugs on a stent circumvents high systemic doses: the drug eluting stent was born. These two new drug eluting stents (paclitaxel eluting stent and sirolimus eluting stent) have been proven to be very successful in reducing in-stent restenosis in several clinical trials. However, recently drug eluting stents have been associated with an increased risk of late stent thrombosis.

Stent thrombosis is the occurrence of thrombus formation in or near the stent resulting in an acute occlusion of the vessel. The incidence of stent thrombosis after stenting with the use of dual antiplatelet therapy is around 1% after 1 year and 2% after 10 years. Although its incidence is much lower than in-stent restenosis, nevertheless it is a serious complication because in contrast with in-stent restenosis it leads more often to acute myocardial infarction and has a high mortality rate. It is commonly divided in acute (≤ 24 hours post-PCI), subacute (24 hours to 30 days post-PCI) and late (> 30 days post-PCI) stent thrombosis.

The problem of acute and subacute thrombosis was greatly reduced by preventing early thrombus formation using dual anti-platelet (acetylsalicilzuur and clopidogrel) therapy. However, late stent thrombosis is still a problem especially in drug eluting stents. Therefore, dual anti-platelet therapy post-PCI is recommended for one month for patients with bare metal stents (BMS) and six months to a year for patients with drug eluting stents (DES) according to the guidelines of the European Society of Cardiology. Some authors have suggested that triple anti-platelet (addition of cilostazol) may benefit patients with a DES. However, there are disadvantages of more intensive and longer anti-platelet therapy. An increased chance of serious bleeding exists with longer and more potent anti-platelet therapy. More importantly, patients who need surgery for other medical conditions often have to stop anti-platelet therapy and are at a high risk for developing stent thrombosis during surgery or risk serious bleeding with the continuation of anti-platelet therapy. Several large clinical trials with long follow-up are addressing the issue of stent thrombosis with DES and its clinical relevance. So the impact of stent thrombosis on the future use and development of present and new generation drug eluting stents is still unclear.

Pending these results research has focused on finding alternative drugs to treat in-stent restenosis and a renewed interest in the pathophysiology, mechanisms and risk factors (diabetes) of in-stent restenosis and stent thrombosis. In this thesis the rat aortic stenting model was used to study several new treatments to reduce in-stent restenosis and some aspects of the pathophysiology of in-stent restenosis. We also adapted our rat aortic model and developed and validated two different diabetic models for studying the effects of in-stent restenosis in diabetes. Furthermore, we tried to identify possible mechanisms of late stent thrombosis by comparing the neointima of bare metal and drug eluting stents.
AIMS

In Chapter 2 we introduce a novel type 1 diabetic model for in-stent restenosis after rat abdominal aortic stenting study. Diabetes is an important clinical risk factor for restenosis and with the future epidemic in diabetes related to overweight it will grow even further in importance. Research of the mechanisms of increased restenosis in diabetes may also lead to general anti-restenotic drugs. In Chapter 3 we study the contribution of circulating bone marrow cells to neointimal formation. The role of bone marrow cells in neointimal formation after stenting is not yet clear but it is an important issue, because it could lead to new cell based therapies for in-stent restenosis. The neointima of stented vessels is mainly composed of α-smooth muscle actin (SMA) positive cells and the paradigm states that the origin of α-smooth muscle positive cells in the neointima is from smooth muscle cells residing in the media and migrating to the lumen after stenting. However circulating bone marrow cells can differentiate in a wide variety of cell types (including smooth muscle actin positive cells) and could be involved in neointimal formation after stenting.

In Chapter 4 we describe the effect of the AT1-receptor candesartan on neointimal formation after stenting. Abundant pre-clinical evidence exists that Ang II is involved in in-stent restenosis, but in clinical trials ACE-inhibitors and AT1-receptor blockers have not been successful in reducing in-stent restenosis. We study if the conflicting results of animal research and clinical trials is related to the need of supraphysiological Ang II levels for Ang II mediated neointima formation. In Chapter 5 we test the effect of the statin rosuvastatin on neointimal formation and endothelial function after stenting. Statins have several pleiotropic effects which may reduce in-stent restenosis: reduction of platelet activation, amelioration of endothelial function lowering of inflammatory responses, reduction of oxidative stress and inhibition of smooth muscle proliferation and migration. Ang II increases oxidative stress, stimulates smooth muscle cell proliferation and detoriates endothelial function. We study if statins reduce neointimal formation in a normal and a stimulative setting (Ang II induced).

In Chapter 6 and 7 we describe quantitative and qualitative differences in neointimal formation between bare metal stents and drug eluting stents in normoglycemic (Chapter 6) and diabetic setting (Chapter 7). Incomplete endothelial healing has been associated with stent thrombosis. Differences in neointimal healing between drug eluting stents and bare metal stents may be associated with increased rates of late stent thrombosis.
INTRODUCTION

References


