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The iatrogenic pathology of percutaneous interventions in coronary arteries

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Chapter 10

Abstract

Acute coronary syndromes (ACS) represent the clinical manifestations of sudden flow limiting coronary artery disease leading to acute myocardial ischemia or necrosis. Treatment of progressive coronary stenosis or acute thrombotic occlusion by means of percutaneous coronary intervention (PCI) with balloon dilatation and stent placement aims to reduce the risk of myocardial ischemia or necrosis by restoring coronary flow. But, being an invasive technique, it is associated with a periprocedural and also eventually longterm risk of complications. Pathological examination of atherosclerotic coronary arteries after PCI treatment has been shown to be very helpful in providing insights in this iatrogenic pathology. Importantly, the pathological substrate of the treated coronary artery segment in patients with ACS differs significantly from coronary artery segments in patients with stable coronary artery disease. Such studies have shown that besides the physical trauma induced by a balloon or a stent also the specific histomorphological and biological properties of the treated coronary plaques play an important role in the risk of PCI related vascular complications. Major complications, which are thrombosis and restenosis, have reduced significantly over the past years. Still, late stent thrombosis remains a small but clinically important problem after placement of drug eluting stents DES, mainly related to delayed in stent wound healing and early withdrawal of antiplatelet therapy. Moreover, restenosis remains a problem in the still large group of patients treated with bare metal stents (BMS) worldwide. Both in case of BMS and DES emerging evidence from recent histopathological studies on coronary resected stents shows that the outcome of PCI can be influenced by the occurrence of in stent neo-atherosclerosis, in DES more frequently than in BMS, which in turn may stimulate both thrombosis and restenosis on the very longterm.
Introduction

Acute coronary syndromes (ACS) represent the clinical manifestations of obliterative coronary artery disease leading to acute myocardial ischemia or necrosis. These syndromes include the various types of unstable angina, non ST segment myocardial infarction (NSTEMI), ST-segment myocardial infarction (STEMI) and also sudden (coronary) cardiac death. In the USA more than 400,000 individuals die annually of coronary artery disease, and more than 1,000,000 present with ACS. Primary goals of acute management of ACS are to prevent death, to relieve the symptoms of patients and to prevent the progression of disease by minimizing the loss of myocardial muscle and cardiac function. Coronary stents in combination with balloon angioplasty (PTCA) are presently first choice for the treatment of patients with ACS. At present, stent implants in coronary arteries numbers in the millions world wide, and these numbers increase also rapidly in developing countries. Numerous clinical follow-up studies, including meta analyses, indicate on the average a highly favourable outcome of such approaches, also on the longterm (several years). However, being an invasive technique, it is associated with a low but still significant risk of periprocedural and longterm complications. Much lower numbers of studies are devoted to unravel the pathological backgrounds of such complications, the iatrogenic pathology of PCI, which are carried out on autopsy derived materials, but also with the use of PCI materials form living patients. These studies have shown that specific histomorphological and biophysical properties of the treated coronary plaques determine not only the risk of PCI related vascular complications, but also the type of complications that may occur. Current insights are reviewed in this article.

Coronary atherosclerotic plaque morphology and ACS: Atherothrombosis

Coronary atherosclerotic plaque with superimposed thrombus is the underlying cause of ACS in by far the most cases, with few rare exceptions like coronary vasculitis, dissection, arterial dysplasia or vasospasm without fixed. Two different atherothrombotic plaque complications are associated with the onset of ACS: disruptions of the fibrous cap of a plaque (plaque rupture) and significant endothelial denudation of the plaque surface (plaque erosion). Most plaque ruptures occur in so called high risk or vulnerable plaques which have a high propensity to develop thrombotic complications. They have the characteristic tissue composition of a large lipid core covered by a thin fibrous cap, high inflammatory activity orchestrated by macrophages, T-cells and mast cells, a paucity of smooth muscle cells in the fibrous cap, abundant neovascularisation and also frequently intraplaque haemorrhages (figure 1). It has been shown convincingly in pathologic studies that this type of plaque composition and the biologic
(inflammatory) activity of the coronary plaque have a greater impact on the risk of a plaque to initiate ACS than the plaque volume or degree of stenosis. Lipid related inflammation leads to degradation and weakening of the fibrous cap of the plaque, a process in which inflammatory cytokines, reactive oxygen species and proteolytic enzymes such as matrix metalloproteinases (MMP) are involved.\textsuperscript{6-8}

Autopsy studies have shown that plaque ruptures cause 75% of fatal myocardial infarction and plaque erosions account for the remaining 25%.\textsuperscript{5} Mural platelet rich thrombi (white thrombus), that lead to critical flow reduction but still allow some degree of antegrade flow through the acutely stenosed segment, are the underlying lesion in most cases of unstable angina or NSTEMI. Erythrocyte and fibrin rich thrombi (red thrombus) can develop on top of white thrombus and causes acute total occlusion, which is the characteristic lesion of STEMI patients. Especially non occluding mural thrombi bear the risk of distal embolization, especially in the first days after initiation of plaque disruption when the platelet-rich thrombus is very friable.\textsuperscript{3} Later, the organized mural thrombus will be incorporated in the plaque volume, but they this can also progress towards the more dangerous type of total occluding thrombus.\textsuperscript{3, 9,10} Spontaneous distal embolization of thrombus in the arterial bed distal may complicate every coronary thrombotic event, but the risk and also the extent of embolization increases drastically during balloon dilatation and/or vascular stenting procedures.

\textit{Figure 1.} Example of a vulnerable (high grade) coronary atherosclerotic plaque. The lesion, which protrudes into the lumen (L) of the artery, has a very thin fibrous cap (indicated by asterisks) and a large lipid core containing red staining (foamcell type) macrophages. Smooth muscle cells (stained blue) can be noticed in the media but are nearly absent in the fibrous cap of the plaque. CD68(red)/SMA-1(blue) immunodouble stain. Magnification 25x.
when thrombus material is dislodged and plaques are cracked mechanically.\textsuperscript{11, 12} The amount of atherothombotic material at the site of the intervention, and also the extent and severity of the arterial damage are risk factors: coronary stenting causes more distal embolisation than balloon dilatation alone.\textsuperscript{11} Also at high risk for distal embolization are the interventions in coronary vein bypass grafts which frequently have a large burden of soft lipid rich plaques. Distal embolic protection devices are now frequently used in these situations, which may indeed contain large amounts of lipid rich plaque materials in the collecting filter at histopathological examination\textsuperscript{13} (figure 2).

**The myocardium after coronary occlusion**

After coronary occlusion, myocardial necrosis develops from the endocardium to the epicardium in a wavelike pattern (wave front) and with a more or less well defined time course, albeit dependent on situations like ischemic preconditioning, oxygen demand of the heart and collateral blood flow in the area at risk. As such, large parts of the jeopardized myocardium can be salvaged if reperfusion of the occluded artery is accomplished as early as possible but preferably within 6-12 hours.\textsuperscript{14-16} Spontaneous thrombolysis of significant thrombus is probably rare, but early therapeutic reopening

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**Figure 2. Distal Embolic Protection Device.** Detail of the tip of the device showing the filter basket which contained 25 mm\textsuperscript{3} yellow-white atheromatous and calcified gruel (this was confirmed by histology, not shown). The PCI procedure was performed in a coronary saphenous vein bypass graft of a patient with recurrent angina due to graft stenosis.
of the infarct-related artery by interventional cardiologists has been clearly shown to limit infarct size (according to the principle “time is muscle”). This “open artery approach” can reduce drastically the risk of the life-threatening complications that are related to transmural extension of the infarction, like massive ventricular dilatation, aneurysm formation, cardiac rupture or pericarditis. As such this wave front pattern can be seen as the conceptual basis for the application of percutaneous coronary interventions (PCI). Later attempts to open the artery, when a large part of the myocardium at risk has already become irreversibly damaged, may result in so called ‘reperfusion injury’ with development of large hemorrhages in the infarcted area, no reflow phenomena, onset of arrhythmias and even increased risk of cardiac rupture (figure 3).17

Percutaneous intervention coronary techniques: balloons and stents
Since the introduction of PCI for the treatment of atherosclerotic coronary artery stenosis in 1977,18 initially by means of percutaneous transluminal coronary angioplasty (PTCA) alone, tremendous technical improvements have been made, and indications for PCI are now extended to more complex lesions, small vessel disease and thrombotic lesions underlying the various types of ACS. Application of coronary stents preceded by balloon angioplasty and in combination with dual antiplatelet therapy is presently considered first choice for the treatment of patients with ACS. In some centers stent placement is also preceded by percutaneous thrombectomy (thromboscuc-
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... but the overall beneficial effect of this procedure is still controversial at this time. And, although technical success in terms of longterm vessel patency can now be accomplished in most of the patients, the major drawbacks still remain the risk of thrombosis and restenosis respectively. Insights in the pathophysiological backgrounds of such complications stem from several pathological studies in different institutes that have been carried out since the first procedure was performed in 1997 by Gruentzig et al.

The mechanism of PTCA-induced luminal enlargement

Initially it was supposed by Dotter et al that balloon dilation increases lumen diameter at the site of stenosing plaques by compression and remodeling of the atherosclerotic plaque, but later observational studies have demonstrated that tearing or (over-)stretching of the arterial wall and fracture of plaques underlies luminal enlargement. During angioplasty, the inflated balloon causes endothelial injury and splitting of the intimal plaque at its weakest point. Once the intima has separated from the underlying media, the media and even the adventitia will be overstretched by the further expansion, which results in enlargement of the arterial outer diameter. Since often the plaque is incompressible, it moves outward together with the dilated vessel wall, which leads to formation of an iatrogenic aneurysm. Thus, there must be some degree of overstretching of media and even adventitia to produce a significant and permanent increase of lumen area.

Obviously, plaque morphology is important in this scenario. The morphology of atherosclerotic plaques varies greatly from segment to segment in the coronary arterial bed, and the distinct histological characteristics of plaques, being either fibroatheromatous or calcified (considered as stable plaques) or inflamed and lipid rich (vulnerable plaques) clearly influence the results of balloon dilatation. Most atherosclerotic plaques are located eccentrically within the vessel wall, and on cross section bordered by a disease free segment. Pathological studies have demonstrated that successful dilatation can be observed more frequently in arteries with eccentric plaques than in arteries with concentric plaques. This probably relates to the mode of splitting of the plaque, since in arteries with eccentric lesions, splitting tends to occur in the disease-free wall or in the border zone between the plaque and the plaque free wall which results in separation of the media from the intima, leading to disruption of the media and lumen gain.

Procedural success also varies with the degree of calcification of coronary plaques. Intravascular ultrasound (IVUS) coronary imaging studies have revealed that calcified plaques fracture more easily in response to balloon dilatation than non calcified plaque...
(P < 0.01). In the same study, clinical and angiographic restenosis occurred in 13 of 66 lesions (20%), of which most lesions resulted from initially concentric plaques without a fracture or dissection, compared with a mean restenosis rate of 12% in the remaining morphological patterns (p = 0.053).

The mechanism of PTCA induced restenosis

Coronary restenosis is defined clinically as the recurrence of angina symptoms and/or objective evidence for ischemia, and angiographically as more than 50% diameter stenosis of the treated segment. It is observed in about 20-40% of all the interventions after initial successful full balloon dilatation without use of stents.\(^{36-38}\) The majority of the restenosis after balloon dilatation occurs within the first 6 months after PTCA,\(^{38, 39}\) but late restenosis has also been reported even 5 years after the procedure.\(^{40, 41}\) The pathophysiological mechanisms have been largely unraveled in numerous studies, and can be considered as the response of the vascular wall (which includes the variable components of plaques to physical injury underlies the decrease of lumen area after balloon dilatation. The complex cascade of events that is inflicted in this response includes, acute thrombus formation, early passive recoil of the vessel, late passive recoil, negative vascular remodeling, cellular proliferation and extracellular matrix deposition.\(^{42-44}\)

Elastic recoil occurs within hours after the PTCA and may account for up to 50% immediately lumen loss after the balloon dilatation without use of stent.\(^{43, 44}\) Negative remodeling also changes the luminal geometry after balloon dilatation, but on the longterm. Negative remodeling is an active process characterized by increased synthesis of alpha-smooth muscle actin in the adventitial cells which may subsequently constrict the injured vessel and contribute to late lumen loss after angioplasty. These data indicate that constrictive remodeling an important determinant of the long-term outcome of PTCA.\(^{45, 46}\)

Intimal hyperplasia

The traumatically injured endothelial layer and dissection of the underlying plaque and media of the artery allows exposure to circulating mitogens such as angiotensin II and plasmin, and local tissue factor which is followed by platelet aggregation and initial thrombus formation. Platelets, leukocytes and smooth muscle cells release growth factors and cytokines that initiate a process of smooth muscle cell migration and proliferation.\(^{47}\) The extent of proliferation and matrix proliferation depends on the extent of injury. A detailed postmortem study by Nobuyoshi et al\(^ {48}\) revealed the sequential histopathological features of PTCA treated lesions. The interval between coronary angioplasty and death ranged from several hours to 4 years. Neointimal
proliferation of smooth muscle cells was observed in 83% to 100% of 28 lesions examined 11 days to 2 years after coronary angioplasty. In 20 lesions examined within 6 months, smooth muscle cells were predominantly of the proliferative type and there was abundant extracellular matrix substance mainly composed of proteoglycans. In the 8 lesions examined between 6 months and 2 years after PTCA, smooth muscle cells were mainly of the contractile phenotype and the extracellular matrix was composed chiefly of mature collagen. In 3 lesions examined 2 years after PTCA, there was hardly any evidence of antemortem coronary angioplasty and these lesions were almost indistinguishable from conventional atherosclerotic plaques. These temporal changes in histologic patterns, which grosso modo resemble the woundhealing responses at many other sites in the human body, provide a pathologic background for clinical reports that progressive restenosis is predominantly found within 6 months after coronary angioplasty. Morphometric analysis also revealed that the extent of neointimal proliferation was significantly greater in lesions with evidence of medial or adventitial tears than in lesions with no or only intimal tears.48

Coronary stent: bare metal or drug eluting
Clinical studies have shown that placement of a metal stent adjunctive to balloon dilatation is superior to PTCA alone, and the majority of PCI procedures now involve a coronary stent.49,50 Coronary stenting, if compared with PTCA alone, increases the procedural safety by preventing acute coronary occlusion and coronary dissection, and bears a lower risk on the need of emergent revascularization of the original coronary lesion (due to absence of the arterial recoil that can be seen after balloon dilatation). Moreover, also neointimal type of restenosis development is significantly lower.49,50 In practice, approximately 85% of the percutaneous interventions now involve stent implantation, and both coated (drug eluting, DES) and non-coated (bare metal, BMS) stents are widely used.2 DES are coated stents that are capable of releasing single or multiple bioactive agents specifically designed to inhibit the process of restenosis. The newest generation of stents that are not yet widely used in clinical practice include biodegradable stents, stents with biodegradable polymers, self expanding stents, stents with new type of coatings51 and are not further discussed here.
Drug eluting stents (DES) have indeed reduced the rate of restenosis development over time from 30-40% with PTCA alone down to roughly 5%, which includes also the treatment of complex lesion, lesions over longer segments and at sites of bifurcations. And in addition to that, there are also robust data on the restenosis benefit of DES over BMS.52-56 Various drugs and coatings have been tested to cover the struts of stents, including anti-mitotic, anti-inflammatory, anti-coagulant and immunosuppressive agents.
Currently, a major interest is focused on the limus family of drugs, of which Sirolimus (rapamycin) and Everolimus, both having mTOR inhibitory capability, appear the most effective because of anti inflammatory effect and durable inhibitory effect on the migration and proliferation of vascular smooth muscle cells underlying the process of in stent restenosis. However, a major drawback of these agents is the recent notion that late instant thrombosis may develop, albeit in a low percentage of patients. This can be largely attributed to the impaired healing responses in DES which leads to incomplete embedding of the stent and lack of re-endothelialization. Such cases of late stent thrombus have been reported even more than a year after insertion of the coated stent. Detailed pathological studies on stented arteries have revealed several local factors that predispose to the onset of restenosis and thrombosis in the various types of stents.

Processing of stented arteries for histopathological analysis

For studies as alluded to above, special techniques to handle the stent bearing arterial segments are required. In routine autopsy pathology practice, it is customary to remove the stents carefully from the opened artery, and the remaining arterial wall tissue can then be processed for conventional histology. This method is indeed useful to evaluate the presence or absence of stent thrombosis or arterial dissections, or to investigate the plaque mass underneath the stent. However ideally, the stent containing arteries are cross sectioned with a diamond saw in 3mm segments. Segments of interest for further histopathological examination must be embedded in hard plastics, such as methyl metacrylate; glycidil methacrylate co-polymers (GMA/MMA) and then further processed for (immune) histology. Using this technique, the exact location of stent struts in relation to vessel wall, thrombus and/or plaque tissue can be visualized in most instances. This is of importance to evaluate situations like malapposition of the stent struts, peri stent inflammation and impaired or absent wound healing, which can be helpful to explain the onset of symptomatic stent complications in patients. Post mortem radiographs and postmortem angiography can be particularly helpful to locate (multiple) stents in hearts and to evaluate the presence of in-stent thrombosis, restenosis and also stent fractures.

In-stent thrombosis

Meta analyses of randomized trials have shown that there are no significant differences in thrombosis risk between BMS and DES types of stents at 1 year implantation, and in both types less than 0,5%. Impaired wound healing, which can be appreciated from lack of complete endothelialization, persistent fibrin coating and deficient intimal covering, is the principal pathological substrate that underlies the
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**Figure 4a.** Example of 2 cross sections of thrombosed coronary artery segment containing DES stent. The stent struts are visible as white glistening dots surrounding the red thrombus mass in the artery. Histological section of the same plastic embedded material showing detail of the arterial wall, with 3 rectangular spaces at the intima – thrombus interface representing the location of stent struts. Stent material is still present in the right sided space (black). The stent struts are positioned correctly, with slight impression of the underlying thickened intima of the coronary artery. Haematoxylin & Eosin stain, x100.

**Figure 5.** Example of postmortem coronary angiography followed by cross sectioning of the stented arteries. The X-ray of the heart before contrast infusion shows multiple long stents placed in the Left Anterior Descending (LAD) artery, and one stent in the proximal circumflex artery (Fig 5a). Cross section through one of the stents reveals a concentric rim of compact white material representing in-stent neointimal formation, but no stenosis (Fig 5b). Fig 5c shows magnification of stent indicated by arrow in fig 5a, after contrast inflation. Note also the multiple minute stent fractures (arrows).
onset of late (> 1 year post implantation) stent thrombosis in a small but significant percentage of patients receiving DES. Factors that interfere (additionally to the effect of the eluted anti proliferative drugs) with the impaired healing response are: malapposition of a significant number of stent struts, stent strut fractures and allergic reactions provoked by the DES stent materials.

* Stent strut fractures have been reported in 1-2% of patients at follow up angiograms, and became of interest in the analysis of possible contributors to in-stent restenosis and thrombosis. Nakazawa et al\textsuperscript{62} found a much higher incidence of 29% autopsy in 117 lesions at autopsy. This is obviously much higher than clinically reported, but the authors used high contrast based radiography with much higher detection rate than clinical angiography or intravascular ultrasound. Moreover, they graded the fractures into 5 degrees of severity, and found that the highest grade (grade V fracture) was associated with adverse pathological findings at the fracture sites. Long stent length and longer duration of implant and specific type of DES were independent risk factors of stent fracture (see also figure 5c).

* Allergic responses to stent struts have been observed both in animal studies\textsuperscript{63} and in humans.\textsuperscript{64-66} They can be attributed to hyperstitivity to the stent material but also to the specific coatings, and they have been reported in BMS and in DES. For example, Nakazawa et al found that hypersensitivity as potential underlying mechanism of late and very late stent thrombosis occurs in Sirolimus coated stents only.\textsuperscript{67} Rittersma et al\textsuperscript{64} compared the inflammatory features of restenotic tissues after balloon

\textbf{Figure 6.} Example of delayed healing response in DES stent 1.5 years after insertion. Stent struts (asterisks) are seen near to the thrombus (T) and plaque (P) indicating that there was almost no intimal formation despite long implantation time. There is also incomplete endothelial lining of the surface (brown colored cells). Anti-CD34 immunostain, x100. Fig 7b. Same area stained with anti SMA-1 immunostain showing there are almost no smooth muscle cells (brown cells) that cover the stent struts. Magnification x80.
angioplasty and after stent (BMS) placement to evaluate the type of immune response in both situations. They investigated coronary atherectomy specimens of 32 patients, of which 16 had clinical restenosis after PTCA alone, and 16 BMS in-stent restenosis. This study revealed involvement of inflammatory responses in both types of restenosis, but significantly more eosinophilic infiltration in the cases of in-stent restenosis, and clustering of the inflammatory infiltrates around the stent struts, indicating a specific response towards the bare metal struts. Such allergic reactions are thought to be potentially implicated in late stent thrombosis and in stent restenosis.

*Malapposition of stent struts, leading to incomplete or absent endothelial coverage has been described complex procedures such as long or partially overlapping stents, stents at sites of bifurcations, stent struts that have penetrated into lipid cores of plaques and coronary aneurysms. Malapposition can also occur when stent placement in the thrombosed coronary segments of STEMI patients may lead to malapposition of struts when the thrombus mass dissolves over time. In addition, also patient related factors such as diabetes, low left ventricular ejection fraction and, recurrence of (vulnerable) plaques inside the implanted stent have been shown to be associated with increased risk on in stent thrombosis. These latter situations imply that late thrombus may also occur in some patients treated with BMS. An interesting observation derived from studies on patients who died after coronary stenting is that patients who received DES for acute coronary syndromes have more complications and significant delayed arterial healing than those treated for stable angina. This suggests that underlying plaque morphology (stable versus complicated types of plaques) is important for final outcome. And indeed, a clear link between insertion of DES on thrombosed vulnerable types of lesions and high percentage of uncovered stent struts after 9 months also emerged from imaging studies. All together, these findings support the concept that vulnerable type of atherosclerotic plaques are a major risk factor for onset of coronary thrombotic events not only as the novo coronary lesions but also, and specifically on the longterm, in stented coronary segments. Obviously, in future such data need to be confirmed in larger series of patients.

In stent-restenosis (ISR)

Intravascular ultrasound studies suggest that stenting of stenosed coronary segments virtually eliminates vessel elastic recoil and negative remodelling and that ISR is largely a result of neointima formation alone. Late luminal loss, defined as the difference in minimal lumen diameter between follow angiography and immediately after stent placement.
implantation, is often used to estimate the degree of neointimal hyperplasia, and 50% diameter stenosis at follow up angiogram is taken as a cut off point for ISR. Morphologic studies in the early phase of coronary stent implantation have demonstrated that early thrombus formation and an acute inflammatory response precedes neointimal growth. Abundant infiltration of inflammatory cells, predominantly T lymphocytes, macrophages and foreign body type giant cells around the stent struts has been observed both in animal and in human studies. Inflammation gradually diminishes and disappears after 2-3 months, but small numbers of macrophages and occasional giant cells can still be observed also on the longterm. Stent related inflammatory response can be particularly excessive when there is extensive medial injury, and also in those cases were the lipid core of the lesion was penetrated by stent struts.

The latter observation suggests that plaque morphology, especially the lipid rich variants of plaque may increase local inflammatory activity, which in turn stimulates neointimal growth through the local regulatory role of inflammatory cytokines on the migration and proliferation of smooth muscle cells. Neointimal hyperplasia is, similar to the response to balloon injury, composed principally of large numbers of proliferating SMC and proteoglycan rich extracellular matrix (figure 7). During the first year after stent implantation, the occurrence of ischemic symptoms due to progressive narrowing caused by neointimal hyperplasia can be predicted from the type of stent that has been implanted (DES or BMS), but also by systemic risk factors of the patient. Patient characteristics like diabetes mellitus, male gender, hypertension and

Figure 7. In-stent restenosis. Macroscopic image of cross section through a BMS stented artery (fig 6A) showing subtotal occlusion due to formation of white restenosis tissue bordered by the black dots of the stent. Fig 6B and 6C show the corresponding histology in sections stained with Haematoxylin and Eosin (B) and SMA-1 immuostain (C) respectively. The brown areas surrounding the vascular lumen in fig C represent large numbers of smooth muscle cells which make up the restenosis tissue. Magnification x15.
smoking are associated with increased risk of ISR, although the underlying mechanisms are not always understood.

Drug-eluting stents (DES) have dramatically reduced restenosis, but not eliminated.\textsuperscript{80, 81} Moreover, large clinical trials have not shown the benefit of DES over BMS in reducing the mortality rates of patients.\textsuperscript{81, 82}

**Multiple stents associated with increased risk of complications**

The implantation of multiple stents (3 or more) within a single coronary artery is increasing in frequency. In Matthew et al investigated the clinical and angiographic characteristics of 45 of such patients. The procedural success rate was 91.1%; with early stent occlusion in four patients (8.9%). Death, myocardial infarction (MI), CABG, repeat target vessel intervention or severe angina occurred in 10 (23.3%) patients at 6-month follow-up. At 1 year, the frequency of death, NSTEMI, CABG and severe angina was the same as in a matched group of patients who underwent CABG for a failed angioplasty procedure, but the need for repeat percutaneous intervention was more common in the stent group (25% vs. 0%). Adverse events at 6 months of follow-up were more frequent than previously reported for elective single-stent implantation; however, adverse angiographic characteristics such as dissection and thrombus were frequent in this group.\textsuperscript{83}

**Pathological Findings at Bifurcation Lesions**

Bifurcation lesions are common, and account for 15-20% of all PCI procedures. Compared with non bifurcation lesions, they are associated with more complications, both early and late thrombosis and restenosis, and lower procedural success rates. In case of BMS are even up to 60% in some series. Neointimal growth after DES implantation is reported to be significantly less at the flow divider versus the lateral wall of the artery. A higher prevalence of late stent thrombosis in DES compared with BMS was associated with greater uncovered struts at also at flow divider sites, apparently related to impaired wound healing, and likely due to local flow disturbances.\textsuperscript{84} See also figure 8.

**New insights: In-stent neoatherosclerosis**

ISR after BMS stent implantation peaks in the early phase (between 6 months and 1 year, but very late ISR can also occasionally be observed after several years post intervention. Kimura et al\textsuperscript{85} identified a triphasic neointimal response in the longtem follow up of BMS, which consisted of early onset restenosis, followed by an intermediate period of regression or maturation, and a final stage after 4 years of late luminal narrowing with features of atherosclerosis. Habara et al compared the morphological characteristics of very late cases of ISR (>5 years, n=43) with the morphology of early
ISR (<1 year, n=39) using optical coherence tomography (OCT). These authors found that restenotic tissue in late restenosis clearly differs from early restenosis, and has more similarities with native atherosclerotic plaque tissue. Also in DES, the onset of late neo intimal growth has been clearly documented in animal studies and in humans. Nakazawa et al. recently investigated a large series of autopsy cases from the CVPath institute (Gaitersburg, Maryland) stent registry containing 66 sirolimus type of DES stents and 77 BMS stents. They found that neo-atherosclerotic intimal lesions were more frequently found in DES than in BMS stents (35% versus 10%). Moreover, in

**Figure 8.** Postmortem rontgen image of complex stent procedure. Fig 8a shows a network of 4 stents at the branching site of the proximal left coronary artery. The curled stent is in the circumflex artery. Fig 8b, shows same stent complex after contrast dye inflation showing multiple sites of in-stent restenosis.

**Figure 9.** In-stent neoatherosclerosis. Histology of part of a coronary artery segment containing DES stent several years after insertion. There is a compact fibrous fibrous tissue visible within the stent (black fragments represent stent struts), and near the luminal surface an area containing foam cell macrophages. Around the stent struts there are many micro vessels present.
the same study the onset of atherosclerotic changes, typified by infiltration of lipid laden foam cells, began much earlier in DES (at 4 months) than in BMS (only after 2-4 years). An example from our own series is shown in figure 9. Necrotic core formation started in DES at 9 months, but in BMS only after 5 years. The same group of investigators also reviewed the histology of 229 autopsy cases with implanted stents (with 197 BMS and 209 DES) which revealed an incidence of 31% neo-atherosclerosis in DES versus 16% in BMS, and again with a much shorter median implantation interval after implantation for DES compared with DES. And, also unstable plaque features such as thin cap fibroatheromas and plaque ruptures occurred much earlier in DES than in BMS treated artery segments. The authors concluded that neoatherosclerosis likely plays a role as an indicator for late stent thrombosis and also for in-stent restenosis in both DES and in BMS.\textsuperscript{86}

**Conclusions**

Treatment of progressive coronary stenosis or acute thrombotic occlusion by means of percutaneous coronary intervention strategies aims to reduce the risk of myocardial ischemia or necrosis. But, being an invasive technique, it is associated with a periprocedural and also eventually longterm risk of complications. These are mainly in-stent thrombosis and in-stent restenosis, but the pathophysiological backgrounds of these complications are very variable and depend not only on the type of stent that is used, but also clinical presentation and on systemic factors in the patient such as pre-existent cardiovascular disease. Pathological examination of atherosclerotic coronary arteries has provided insights in the iatrogenic pathology induced by PCI. For example, not only the physical trauma induced by a balloon or a stent but underlies the risk of PCI related vascular complications, but also the specific histomorphological and biological properties of the treated coronary plaques. Importantly, tissue responses and wound healing after stent placement in stable or in unstable plaques differ significantly. The incidence of thrombosis and restenosis after PCI has reduced drastically over the past years. Still, late stent thrombosis remains an small but clinically important problem in drug eluting stents DES), mainly due to delayed in stent wound healing and early withdrawal of antiplatelet therapy. And, restenosis remains a problem in the larger cohorts of patients that are still treated with bare metal stents (BMS) worldwide. Both in case of BMS and DES there is emerging evidence from recent histopathological studies on resected stents that the outcome of PCI can be influenced by the occurrence of in-stent neo-atherosclerosis. The occurrence of neo-atherosclerosis and the timing of events differs after DES placement compared to BMS, which in turn may be associated with both thrombosis and restenosis on the very long term.
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