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New insights in mechanism, diagnosis and treatment of myocardial infarction

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CHAPTER

GENERAL INTRODUCTION

1

MYOCARDIAL INFARCTION

Myocardial infarction (MI) occurs when coronary blood flow decreases significantly after a total or partial occlusion of a coronary artery which, as a consequence, leads to myocardial necrosis and scarring. If not promptly treated, myocardial infarction often results in death following pump failure or malignant arrhythmias.

The annual incidence of hospital admission for any acute MI varies considerably among European countries (900-3120/million inhabitants). Based on available data from 30 European national registries, the annual incidence of circa 1900 hospital admissions for any MI per million population seems to be typical for the European population[1]. In the Netherlands 24143 people were admitted in 2008 for an acute MI among which 7% died during hospitalization[2]. In the United States, approximately 650 000 individuals experience a first MI and 450 000 a recurrent MI each year. The early mortality is around 30%, with more than half of these death occurring before hospital care could be provided[3].

Myocardial infarction is the result of a cascade of events: first a preexistent atherosclerotic plaque fissures, ruptures or ulcerates followed by uncontrolled thrombogenesis with a sufficiently large thrombus formation leading to coronary artery occlusion.

THE ROLE OF COAGULATION AND FIBRINOLYSIS

Thrombosis is initiated by platelets in the following sequence: adhesion, activation and aggregation. Initially a platelet monolayer adheres at the site of the ruptured plaque via the GP Ib receptor in conjunction with von Willebrand factor. Various agonists including collagen, ADP, epinephrine and serotonin promote platelet activation. Activated platelets produce thromboxane A₂ and vasoconstriction and further platelet activation takes place. In parallel, activated platelets display glycoprotein IIb/IIIa in a functional conformation which binds von Willebrand factor (vWF) and fibrinogen. Through vWF and fibrinogen more platelets bind resulting in cross-linking and aggregation (Figure 1).

Damaged endothelium exposes tissue factor which starts the coagulation cascade: factors VII and X are activated ultimately leading to the conversion of prothrombin to thrombin which in turn converts soluble fibrinogen to insoluble fibrin. The end-result is an occluding thrombus containing platelet aggregates and fibrin chains[4]. As mentioned, both platelets and coagulation cascade play a crucial role in coronary thrombus formation.

Although acute cardiovascular events occur throughout the day, it has been shown that acute myocardial infarction has a circadian pattern of occurrence with a peak in the morning[5-9](Figure 2). The acute myocardial infarction morning peak is seen in large cohorts of patients regardless of gender, age, previous ischemic heart disease or myocardial infarction[10].

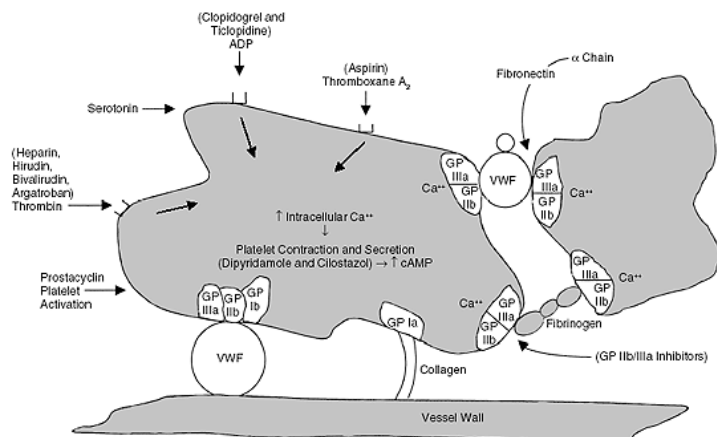


Figure 1. Platelet adhesion, activation and aggregation. Adapted from Am J Health Syst Pharm 2002.

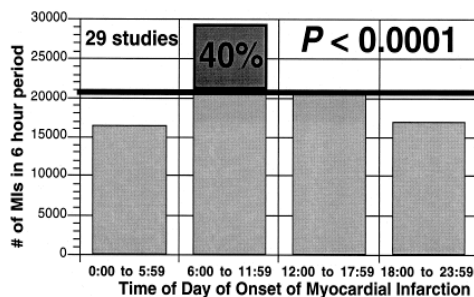


Figure 2. Meta-analysis of 29 studies including 83929 patients who were queried about when the symptoms of acute myocardial infarction began. (adapted from Am J Cardiol. 1997;79:1512-6).

THE ROLE OF ADMA

The typical morning myocardial infarction is generally considered to be triggered by factors that mechanically disrupt the vulnerable plaque, such as transitory increased blood pressure[11] and viscosity[12], coupled with increased platelet aggregability[13,14] and decreased coronary blood flow[9,15].

Asymmetric dimethylarginine (ADMA) is an endogenous amino-acid produced by virtually all human cells as a result of methylation of arginine residues in proteins. Because it is structurally similar to L-arginine (the substrate of nitric oxide (NO) synthase for the formation of NO), ADMA competitively inhibits the NO synthases in cells[16-20].

Decreased NO availability promotes platelet activation and aggregation[18,20,21]. High ADMA levels are also associated with elevated blood pressure, vasoconstriction, impaired endothelium-dependent relaxation and increased endothelial adhesiveness for monocytes[17,22-24]. The relation between the myocardial infarction morning

peak of occurrence and a possible morning peak of ADMA levels had not been investigated before. We show our results in chapter 2.

THE ROLE OF PAI-1

Unstable coronary plaques are frequent loci for non-occlusive thrombus formation. Coronary clots may resolve spontaneously and without clinical consequences due to natural fibrinolytic activity, whereas acute coronary syndromes may be triggered by imbalances between fibrinolysis and coagulation[25-28].

PAI (plasminogen activator inhibitor)-1 is the major inhibitor of fibrinolytic activity (Figure 3). PAI-1 is present in human plasma[29], platelets[30], endothelial cells[31], and various tumoral cell-lines[32-34].

Increased PAI-1 plasma concentrations reduce the efficacy of thrombolytic therapy[35] and, conversely, monoclonal antibodies that inhibit PAI-1 activity have proven their efficacy in a number of in vivo studies in which thrombus formation was prevented and lysis of platelet-rich clots was accelerated[36-40].

PAI-1 plasma concentrations show a clear circadian oscillation, with a peak in the morning[41,42]. In the PAI-1 promoter, 2 E-box elements (CACGTG) are responsible for the activation of PAI-1 by the CLOCK:CLIF complex; one of these E-boxes is located at 677 to 672. This overlaps with the sequence of a 4G/5G polymorphism in the PAI-1 promoter. This polymorphism is located 675 bp upstream of the start of transcription of the PAI-1 gene and has been associated with the circadian pattern of PAI-1 plasma concentrations[43]. Carriers of the 4G allele have a much more pronounced PAI-1 morning peak than 5G allele carriers[44,45]. Whether the PAI-1 morning peak inhibits fibrinolysis thereby contributing to the morning excess of myocardial infarction, was not known. We show our results in Chapter 3.

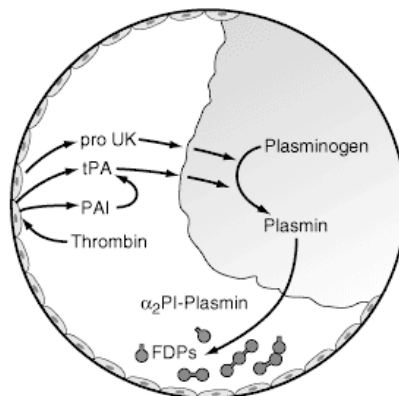


Figure 3. The role of PAI-1 in clot lysis inhibition. UK, urokinase; tPA, tissular plasminogen activator; PAI, plasminogen activator inhibitor; FDPs, fibrinogen degradation products. Adapted from Kasper et al., Harrison's Principles of Internal Medicine, 16th edition.

DIAGNOSIS OF MYOCARDIAL INFARCTION

Previous diagnosis MI criteria included a combination of 2 out of 3 criteria: clinical (chest pain), typical ECG and cardiac markers.

The current definition of MI according to ESC and ACC[46] is based upon:

Criteria for acute, evolving or recent MI:

- (1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
 - (a) ischemic symptoms;
 - (b) development of pathologic Q waves on the ECG;
 - (c) ECG changes indicative of ischemia (ST segment elevation or depression); or
 - (d) coronary artery intervention (e.g., coronary angioplasty).
- (2) Pathologic findings of an acute MI.

Criteria for established MI:

Any one of the following criteria satisfies the diagnosis for established MI:

- (1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
- (2) Pathologic findings of a healed or healing MI.

THE ROLE OF TROPONIN T IN DIAGNOSIS AND PREDICTION OF OUTCOME

As can be derived from the previous definitions, cardiac troponin T (cTnT) or I (cTnI) has become the golden standard for acute MI documentation[46,47] mainly because of its specificity: it belongs to the proteins of the contractile apparatus that are unique for cardiac muscle[48]. This characteristic makes cTnT and cTnI to have reliable prognostic properties as well. Since the beginning of the troponin era, numerous studies have linked plasma troponin (T or I) concentrations to the evolution of patients with myocardial infarction. These studies mainly assessed STEMI patients treated by thrombolysis[49-51] or combined (primary percutaneous coronary intervention (PPCI) or thrombolysis) populations[52].

However, little information is available about the prognostic role of peak cTnT in the current practice: STEMI patients treated by PPCI with stenting after having received GP IIb/IIIa blockers (abciximab). Independent predictors of peak cTnT in these patients remain to be determined. This issue we address in Chapter 4.

TREATMENT OF MYOCARDIAL INFARCTION

The current guidelines for ST-elevation myocardial infarction (STEMI) stress that PPCI should be the treatment of choice in patients presenting in a hospital with catheterization facility and an experienced team[53]. As a result, PPCI has become for many centers the first option therapy in acute myocardial infarction (MI). This is mainly the consequence of the superior outcomes of PPCI when compared to thrombolysis[54-56].

The era of percutaneous coronary intervention (PCI) began with the first balloon angioplasty performed by Andreas Gruentzig in 1977[57]. Although this technique provided impressive immediate results, mid and long term follow up was characterized by high restenosis rates and need for repeat revascularization[57,58].

Evolving our techniques, bare-metal prosthetic devices (stents) were designed to act as a barrier against intima growth and recoil, assuring long-time patency of the coronary vessel. In 1986 Sigwart and Puel implanted the first coronary stent in a human patient[59]. Although superior to balloon angioplasty alone (32-42% restenosis rate), bare-metal stent (BMS) implantation remains vulnerable to restenosis (22-32% of cases) [60,62] and often requires re-intervention. Drug-eluting stents (DES) were conceived as an answer to this problem. They, for the majority, consist of a metallic platform covered with a combination of polymer and cellular proliferation inhibitor. The antiproliferative agent is gradually released in the arterial wall at the site of stent deployment preventing restenosis. The first successful DES trials were carried out with sirolimus stents and led to their approval for use in 2002 in Europe and 2003 in USA[63,64]. Currently, other DES based upon paclitaxel, everolimus, zotarolimus, biolimus and tacrolimus are available. DES have successfully achieved their task of preventing restenosis but the experience of the last years revealed an increased incidence of stent malapposition and (very late) stent thrombosis associated with their use[65], with sometimes lethal outcomes. We systematically evaluated the frequency of these serious late problems and complications and describe them in chapter 5.

THE ROLE OF IVUS AND VH

Intravascular ultrasonography (IVUS) is an increasingly popular technique that, in contrast to angiography alone, allows cross-sectional imaging of coronary arteries and provides a comprehensive assessment of the atherosclerotic plaque. However, it cannot provide detailed data about its tissue components. Detecting changes in tissue components may increase our understanding of in vivo development of potentially vulnerable plaques. Therefore, Virtual histology (VH-) IVUS using spectral analysis of the ultrasound backscatter signals is used to analyze plaque composition and morphology. VH-IVUS allows identification of four different components of atherosclerotic plaques: fibrous, fibro-fatty, dense calcium, and necrotic core[66]. Although the implanted stent will cover the ruptured plaque, it is unclear what happens proximally and distally to the stented segments. Some studies suggested that the drug eluted from

a DES may not only have an effect on the stented segment but also on adjacent segments[63,67,68]. It is therefore of interest to study these segments during the initial procedure and during follow-up. We describe the IVUS and IVUS-VH findings and usefulness in the setting of DES in acute MI in chapters 6 and 7.

IN-STENT RESTENOSIS: INCIDENCE, CLASSIC PREDICTORS AND GENETIC RISK FACTORS.

In-stent restenosis (ISR) is defined angiographically when neo-formation tissue represents more than 50% of the lumen diameter at the site of the stented vessel. The clinical confirmation of ISR is the recurrence of angina pectoris, which further requires revascularization.

ISR is the result of in-stent cellular proliferation and migration along with extracellular matrix accumulation[69]. Classic predictors of angiographic ISR (both in BMS and DES) include diabetes, renal failure, lesion length, reference vessel diameter and post-intervention lumen area[70,71]. Inflammation plays a pivotal role in ISR and it is triggered by the vascular injury during the stent deployment and by the presence of stent struts within the vessel wall[72,73]. Besides inflammation, major contributors are smooth muscle cell migration and proliferation but the process of restenosis involves many different cell-types, among which platelets and endothelial cells, and is also characterized by thrombus formation and to a lesser extent by matrix remodelling.

Genetic risk factors for ISR include variations in thrombus formation, inflammatory factors, smooth muscle cell proliferation and matrix metalloproteinases.

STENT MALAPPOSITION: INCIDENCE, CLASSIC PREDICTORS AND GENETIC RISK FACTORS.

Stent malapposition (SM), commonly detected by intravascular ultrasonography (IVUS), represents a separation of the stent struts from the intimal surface of the arterial wall (in the absence of a side branch) with evidence of blood speckles behind the struts[74]. SM may be acute (present immediately after implantation), persistent (present both immediately after implantation and at follow-up) or late-acquired (present only at follow-up). Acute and persistent SM are mainly procedure-driven while late-acquired stent malapposition (LASM) is a consequence of positive remodelling of the vessel wall and and/or of plaque volume reduction behind the stent (including clot lysis or plaque regression)[75-79]. Independent predictors of LASM include lesion length, unstable angina, absence of diabetes and primary stenting in acute MI. The main repercussion of late SM (persistent or acquired) is stent thrombosis (ST). To date, the risk of ST in late SM patients as well as the risk of LASM in patients with DES compared to those with BMS have not been properly assessed.

Moreover no study yet scrutinized the role of genetic variations in LASM.

STENT THROMBOSIS: INCIDENCE, CLASSIC PREDICTORS AND GENETIC RISK FACTORS.

ST is a complication which occurs in 0.8-2% of patients undergoing PCI and is associated with large MI and death[81]. ST is categorized into “acute” ST (within 24 hours from stent implantation), “subacute” ST (within 1 – 30 days from stent implantation), “late” ST (within 30 days – 1 year) and “very late” ST (> 1 year after stent implantation). Subacute and acute ST are classically related to procedure parameters such as stent underdeployment (acute SM)[82,83] or procedure-related complications such as coronary dissections[84,85]. In contrast, (very) late ST appears to be an active phenomenon associated with late SM (persistent or acquired)[65,86], stent type[65], duration of dual anti-platelet therapy [81] and inflammation[75]. Gene variations in the platelet aggregation pathway, responsiveness to anti-aggregation therapy or presence of inherited thrombophilic disorders were associated with both acute and late ST.

In chapter 8 and 9 we describe in a systematic way the pathophysiology of stent restenosis, stent malapposition and stent thrombosis and we focus on potential genetic factors related to these complications. We also investigate the role of inflammatory polymorphisms on LASM in STEMI patients receiving sirolimus-eluting stents.

OUTLINE

The research work presented in this thesis was performed for a large part among patients included in the MISSION! Intervention Study and the MISSION! STEMI Protocol, both projects of the Cardiology Department – Leiden University Medical Center, Leiden, The Netherlands. Additional data are presented in 2 chapters: chapter 5 describes results from a meta-analysis and chapter 8 presents a systematic literature review. In Chapter 2 we report the results of a cross-sectional study among patients with documented MI. In total, serum ADMA levels were measured in their acute MI setting in 120 patients. The daily pattern of MI onset of symptoms, emergency coronary catheterization and the ADMA levels were compared. Chapter 3 describes the daily MI occurrence variation and difference in cardiac risk among the PAI-1 4G/5G polymorphism. We hypothesized that the circadian variation of cardiac risk is more pronounced among persons with the 4G4G genotype than among ones with 4G5G and 5G5G genotypes. We assessed the time of onset of symptoms in consecutive patients with acute MI and we genotyped the patients for the PAI-1 4G/5G polymorphism in the PAI-1 gene. We have then quantified and compared the amplitude of the circadian variation of MI based on the 3 genotypes. Chapter 4 describes the prognostic importance of early peak cardiac troponin T in patients with a first acute MI treated with primary PCI. Main outcome measures were left ventricular ejection fraction at 90 days and clinical outcomes through 1 year follow-up. Chapters 5-9 represent the main part of the thesis and describe the incidence, diagnosis and

pathology of complications occurring post-stenting. In chapter 5 we performed a meta-analysis to compare the risk of late-acquired stent malapposition in bare metal stents with drug-eluting stents and to investigate the possible association of late stent malapposition with very late stent thrombosis. In chapter 6 we underline the role of IVUS in preventing late stent thrombosis as observed in the MISSION! Intervention cohort. Chapter 7 describes the results of a Virtual Histology intravascular ultrasound analysis performed in a subset of stented patients. The aim was to investigate the impact on coronary plaque composition of sirolimus-eluting stent implantation compared to bare-metal stent implantation for acute MI. Chapter 8 is an extended review over the incidence, characteristics and potential genetic determinants of adverse outcome (restenosis, malapposition and thrombosis) after coronary stent implantation. This chapter focuses on the current results, limitations and perspectives of the genetic approach for the post-stenting complications. Chapter 9 presents the results of a study that investigates whether established inflammatory genetic polymorphisms play a role in late-acquired stent malapposition. Finally, a summary, the conclusions and future perspectives are presented both in English and Dutch.

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