

## ENGLISH SUMMARY

Patients presenting with ST-segment elevation myocardial infarction (STEMI) should receive reperfusion therapy as soon as possible. Percutaneous coronary intervention (PCI) is the gold standard for treatment in these patients. PCI is performed at the catheterization laboratory and is aimed at restoring epicardial flow by balloon angioplasty, sometimes preceded by removal of the occlusive thrombus by thrombosuction, and in most cases combined with implantation of a coronary stent. The introduction of this form of mechanical revascularization, together with pharmacological therapies such as beta blockers, angiotensin-converting-enzyme-inhibitors and statins, has led to an immense improvement in outcome for patients. In-hospital mortality of STEMI patients is nowadays below 5%. However, besides benefits the introduction of PCI has also lead to the creation of a new problem. Between 40 and 50% of STEMI patients develop cardiovascular magnetic resonance-defined microvascular injury (MVI), despite successful treatment with primary PCI. The occurrence of MVI is associated with negative remodeling and left ventricular dysfunction, leading to decreased long-term survival, increased morbidity and reduced quality of life. MVI, also referred to as no-reflow, has therefore been designated the next challenge in interventional cardiology. *Part II* of this thesis addresses the assessment of coronary microvascular resistance, the prediction of MVI, the histopathological correlate of CMR-defined MVI, evolution of coronary vasomotor function in STEMI patients, assessment of myocardial viability after STEMI, kinetics of coagulation in STEMI patients and a potential treatment strategy for no-reflow.

Besides patients suffering from acute myocardial infarction, there is also a group of patients with ischemic cardiomyopathy in which mechanical revascularization has either already been performed, or is not possible due to co-morbidity or coronary anatomy. Despite maximal pharmacological therapy, their anginal complaints persist. These so called “no-option patients” have a poor outlook because currently no therapy is available to them. Arteriogenesis is a natural mechanism aimed to restore obstructed blood flow by remodeling of small, pre-existing collateral arterioles. Through arteriogenesis a circulatory system arises that bypasses arterial occlusions, reducing symptoms of ischemia and the extent of myocardial infarction. *Part III* of this thesis discusses the coronary collateral circulation in experimental models and humans, clinical parameters associated with collateral development in patients and an experimental approach to stimulate arteriogenesis.

### **Part II. Microvascular injury following primary percutaneous coronary intervention**

Currently available methods and parameters for assessing coronary microvascular resistance are discussed in *Chapter 1*. In patients presenting with acute myocardial infarction, thermodilution based index of microcirculatory resistance and

Doppler-flow derived hyperemic microvascular resistance (HMR) are parameters that can be measured invasively at the catheterization laboratory immediately after revascularization. Anatomical and functional aspects of the coronary microcirculation can be assessed by non-invasive techniques. Cardiovascular magnetic resonance (CMR) imaging with late gadolinium enhancement and positron emission tomography (PET) are gold standard techniques for respectively assessment of microvascular injury and quantification of myocardial blood flow. In *Chapter 2*, we present a prospective clinical study of 60 patients presenting with ST-elevation myocardial infarction (STEMI). HMR, measured immediately following angiographically successful percutaneous coronary intervention (PCI), predicts MVI as assessed by CMR and reduced myocardial blood flow as quantified by PET. Furthermore, we established a cut-off for HMR (2.5 mmHg / cm · s) for predicting extensive microvascular injury. In *Chapter 3*, we combined data from our clinical study with preclinical data in order to investigate the histopathological correlate of CMR findings of microvascular injury. Using this translational approach, we were able to show that areas of CMR-defined areas of microvascular obstruction after acute myocardial infarction actually represent microvascular destruction and intramyocardial hemorrhage. *Chapter 4* details the temporal evolution of coronary vasomotor function in STEMI patients as assessed by PET in infarcted as well as remote myocardium from the acute phase to 3 months after successful PCI. We describe the assessment of myocardial viability after acute myocardial infarction by PET-derived perfusable tissue index, in comparison to contrast enhanced CMR, in *Chapter 5*. The kinetics of important coagulation markers in PCI-treated STEMI patients over a period of 90 days are discussed in *Chapter 6*. We show that a disbalance between 'a disintegrin-like and metalloprotease with thrombospondin type motif no. 13' (ADAMTS13) and von Willebrand factor towards a hypercoagulable state occurs. In *Chapter 7*, we report a preclinical study investigating the benefits of treatment with recombinant ADAMTS13 in myocardial ischemia-reperfusion. In a translational approach, results from the porcine study as well as from the clinical cohort of STEMI patients were used to determine the role of ADAMTS13 in acute myocardial infarction.

### **Part III. Restoration of perfusion through collateral development**

Patients with coronary artery disease show a large heterogeneity in their arteriogenic response upon coronary obstruction. These significant differences in the capacity to develop a collateral circulation is also found between and even within animal species. In *Chapter 8*, we present an overview of genetic as well as environmental determinants of the coronary collateral circulation in experimental models and in humans. *Chapter 9* shows a typical example of the clinical importance of arteriogenesis. This case supports the notion that arteriogenesis is the prevailing mechanism to restore blood flow to hypoperfused myocardium. The identification of clinical parameters associated with collateral artery growth in patients is discussed

in *Chapter 10*. High serum leucocytes and high diastolic blood pressure are related to poorly developed collaterals whereas use of beta-blockers is associated with well-developed collaterals. Finally, in *Chapter 11* we show that blocking the interferon alpha and beta receptor using monoclonal antibodies accelerates arteriogenesis in mice without influencing atherosclerosis.

### **Future perspectives**

The prognosis of patients suffering from ischemic heart disease has rapidly and greatly improved over the course of some 35 years. Microvascular injury, designated the next challenge in interventional cardiology, however remains a threat to the desirable recovery of STEMI patients following primary PCI. In this thesis, intracoronary physiology indices were shown to be valuable in predicting the occurrence of microvascular injury and microvascular perfusion deficits after angiographically successful primary percutaneous coronary intervention. These elegant techniques may well serve to identify patients at risk of developing microvascular injury immediately following primary PCI, by which means the therapeutic window is expanded and the opportunity exists to locally deliver a therapeutic compound. The next step towards improvement of outcome in these patients is to develop adjuvant therapeutic strategies aimed to reduce, or if possible eradicate, microvascular injury. Further research to the mechanism of microvascular injury is warranted to focus therapy on underlying pathophysiology.

Restoration of perfusion in response to arterial obstruction, also referred to as arteriogenesis, is potentially a lifesaving mechanism. However, due to the large heterogeneity in the arteriogenic response in humans, therapeutic strategies aimed to enhance the process of arteriogenesis are a welcome addition to the therapeutic arsenal of cardiologists treating patients with advanced ischemic cardiomyopathy. Translating promising experimental results to clinical application however, must be done with great caution. Side effects in some cases can show to be harmful, especially in the vulnerable patients such as those with advanced ischemic cardiomyopathy. The road from bench to bedside is therefore a long and winding one, which solicits for further investigation.