CHAPTER 17

General summary

The aim of this thesis entitled: ‘The heart of the matter: Exploring the interaction between the coronary artery and the downstream microcirculation’, was to unravel the interplay between the coronary artery and the downstream myocardial microcirculation in the presence of ischemic heart disease. Because ischemic heart disease is manifested by two major pathophysiological entities: acute myocardial infarction and stable coronary artery disease, both manifestations are investigated separately the first and second part of the thesis. The final part of the thesis examines how measurements of coronary microcirculatory dysfunction can be implemented in clinical practice by comparing and validating various methods to assess the coronary microcirculation.

Part 1 – Microcirculatory changes after acute myocardial infarction

In the first part of this thesis, the impact of an acute myocardial infarction on the coronary microcirculation was investigated. This part starts with a comprehensive overview of intramyocardial hemorrhage presented in Chapter 2. Decades ago, it was observed that even after successful revascularization of an acute myocardial infarction, hypoperfusion at the core of the infarcted myocardium could still occur. It was thought this happened because the microcirculation was obstructed by clumps of thromboembolic debris and inflammatory cells. However, animal experiments and observations from non-invasive imaging work suggest that hypoperfusion at the core of the infarction in fact represents severe microvascular injury and intramyocardial hemorrhage. Multiple cohort studies have demonstrated that the occurrence of microvascular injury or intramyocardial hemorrhage is associated with an adverse clinical outcome. Based upon the literature review of Chapter 2, we hypothesized that the cascade leading up to microvascular injury commences with ischemia, subsequently requires reperfusion (so-called reperfusion injury) and ultimately results in microcirculatory destruction with intramyocardial hemorrhage. This hypothesis was investigated in Chapter 3, in which an experimental study was conducted, using a rodent model of myocardial ischemia by coronary ligation with subsequent reperfusion after terminating the ligation. Using a Langendorff heart setup and immunohistochemistry as well as electron microscopy, we discovered that ischemia alone resulted in mild microcirculatory injury irrespective of whether it was given during a short duration or over
a prolonged period. However, if a short bout of ischemia was followed up by reperfusion, severe damage to the microcirculation ensued. These findings imply that a therapeutic window exists that coincides either before or immediately after reperfusion is established. During this window, an intervention can be applied to potentially rescue the coronary microcirculation from lethal reperfusion injury. In Chapter 4, a prospective study was done in patients with an ST segment elevation myocardial infarction in whom swift reperfusion by primary percutaneous intervention was accomplished. Immediately following reperfusion, intracoronary measurements of pressure and flow were taken in the culprit artery and an unobstructed reference artery. The aim of this study was to establish whether hemodynamic markers could predict the occurrence of microvascular injury at an early stage. Indeed, we found that patients with an elevated hyperemic microvascular resistance in the coronary circulation, were at increased risk of exhibiting microvascular injury on cardiac magnetic resonance imaging acquired several days later. As such, we concluded that hyperemic microvascular resistance is capable of accurately selecting patients at increased risk of developing microvascular injury who may be eligible for immediate adjunctive intervention. Chapter 5 addressed a logical follow-up question of whether the finding of an elevated hyperemic microvascular resistance in the culprit artery of an acute myocardial infarction translates to a worse long-term clinical outcome. To answer this question, a pooled multicenter study was undertaken involving all combined intracoronary pressure and flow velocity measurements in patients who suffered an acute myocardial infarction published in the literature to date. Indeed, an elevated hyperemic microvascular resistance at a cutoff value of 3.0 mmHg·cm⁻¹·s or greater, was found to accurately predict long-term clinical outcome. In this study, the pathophysiological rationale by which hyperemic microvascular resistance was predictive of adverse clinical outcome was found to be related to more frequent microvascular injury observed on cardiac magnetic resonance imaging. Chapter 6, the final chapter of this first part of the thesis, describes a translational study that aimed to unravel the development of coronary hemodynamics before the infarction and immediately following successful revascularization. This study asks a question that seems nigh impossible to answer given that a patient only presents to the hospital at the time he or she experiences a myocardial infarction – not before that time! In order to address this seemingly unanswerable question, we conducted two different experiments. In the first experiment, hemodynamic measurements immediately following successful reperfusion were linked to measurements in stable patients without obstructive coronary artery disease using propensity score matching. As such, each myocardial infarction patient was paired with a lookalike stable control patient that acted as a pseudo control measurement before the myocardial infarction occurred. To validate this first experiment, a second experiment was conducted in a porcine model whereby coronary hemodynamics were measured before, and immediately after acute myocardial infarction induced by coronary balloon occlusion.
Part 2 – Coronary hemodynamics in stable coronary artery disease

The second part of this thesis describes the interaction between the epicardial coronary artery and the downstream coronary microcirculation. In Chapter 7, the cellular machinery that governs myocardial perfusion is described as a review of the literature. In this chapter attention is devoted to the two innate compensation mechanisms that protect the heart from ischemia: arteriogenesis and coronary autoregulation. Understanding of these two compensation mechanisms, in particular the latter, is required to comprehend the theoretical basis for functional stenosis severity assessment without recourse to hyperemic pharmacological agents. Hitherto, descriptions of coronary autoregulation stem solely from animal experiments. Chapter 8 is a collaborative study involving four European academic hospitals. In this study, the pressure gradient across the stenosis, coronary flow velocity and microvascular resistance was measured in over five hundred coronary arteries. These measurements were stratified according to functional and anatomical stenosis severity. The results of the study indicate that as the pressure gradient across the stenosis increases, coronary flow is kept stable by reduction of microvascular resistance - thereby validating the principle of coronary autoregulation for the first time in humans. At present, various diagnostic modalities are capable of assessing myocardial ischemia without mandating maximal vasodilation induced by exercise or pharmacological agents. One of these tests is the recently developed instantaneous wave-free ratio, which is calculated from an invasive coronary pressure measurement. The instantaneous wave-free ratio is an alternative to the fractional flow reserve, which requires maximal vasodilation. Both tests are used to help guide the clinical decision to perform percutaneous coronary intervention for the treatment of stable ischemic heart disease. Chapter 9 provides an update of the collectively compiled knowledge on the instantaneous wave-free ratio and reviews the similarities and differences with the fractional flow reserve. Two massive randomized clinical trials have recently shown that guidance of percutaneous coronary intervention by instantaneous wave-free ratio is non-inferior to the use of fractional flow reserve. A key question that remains unanswered however, is how the instantaneous wave-free ratio compares to the fractional flow reserve with respect to objective identification of myocardial ischemia. This question was addressed in the study presented in Chapter 10 by comparing these indices (as well as the resting distal coronary to aortic pressure ratio) with the gold standard for quantification of myocardial perfusion: $[^{15}O]$ labeled water positron emission tomography myocardial (PET) perfusion imaging. The key finding of this study was that the instantaneous wave-free ratio and resting distal coronary to aortic pressure ratio had a similar diagnostic accuracy to
identify myocardial ischemia as the fractional flow reserve. Pharmacological vasodilatory agents may therefore not be needed for the guidance of percutaneous coronary intervention in clinical practice. In Chapter 11, a novel index to evaluate coronary microvascular resistance obtained from intracoronary pressure and flow measurements is proposed, termed the minimal microcirculatory resistance (mMR). The unique aspect of this index is that it is not influenced by the presence of upstream stenosis. In contrast, the hyperemic microvascular resistance is increased to a variable extent giving rise to uncertainty whether the elevated resistance is caused by the microcirculation or by the stenosis. In our study, mMR was equal in perfusion territories with an upstream stenosis and unobstructed coronary arteries. This was confirmed by an absence of a correlation between mMR and stenosis severity. These previous findings would suggest that microcirculatory remodeling downstream of a stable coronary stenosis does not occur. Chapter 12 describes a histopathology study conducted using myocardial tissue of deceased patients who either had coronary artery disease confirmed by pre-mortem coronary angiography or without appreciable coronary artery disease. Using a similar design as in the previous chapter, the results of this study show that microcirculatory remodeling indeed does not appear to occur. The capillary density was similar in myocardial beds with and without a coronary stenosis. Furthermore, thickening of the arteriolar wall was also not demonstrated distal to coronary stenoses. An older, less frequently used index to evaluate the functional severity of coronary stenosis is the diastolic-systolic velocity ratio (DSVR). This index represent the ratio between diastolic and systolic flow velocity in the left anterior descending artery and bears two unique features. The first is that it can be either computed using invasive intracoronary measurements, but also from non-invasive Doppler echocardiography. The second is that it is measured in the resting state, without vasodilatory medication. This second feature is remarkable since coronary flow is kept stable by coronary autoregulation, unless the occlusion is subtotal or total. Chapter 13 examines the fundamental rationale of why DSVR is capable of assessing functional stenosis severity from measurements of flow, despite omitting vasodilatory drugs. In this study, it was elucidated that the rationale by which DSVR is decreased distal to coronary stenoses is dependent on a comparatively higher influence of the increased stenosis resistance on total vascular resistance during diastole than systole.

**Part 3 – Comparing methods to measure coronary hemodynamics**

In the third and final part of this thesis, methods to measure coronary hemodynamics are studied. Chapter 14 describes a study that was conducted to compare which of the presently available guidewires to measure the coronary flow reserve invasively is the most accurate: the Doppler wire or the thermodilution wire. Patients with stable anginal symptoms were enrolled. $[^{15}O]H_2O$ PET perfusion imaging was used as the reference standard in this
study. The main finding here was that the Doppler wire was more accurate than the thermodilution wire. The flipside was that the Doppler wire was associated with a higher rate of measurement failures. Chapter 15 evaluated the same two techniques, but used a different study design. Instead, the study population consisted of patients with an acute myocardial infarction. The parameter of interest here, was microvascular resistance at maximal vasodilation. As compared to the thermodilution measurement, microvascular resistance measured with the Doppler wire had a superior agreement with cardiac magnetic resonance imaging defined microvascular injury. Chapter 16 represents a validation study of a novel technique that uses continuous infusion of saline and the measurement of the temperature of the coronary blood to quantify absolute coronary flow. This technique was proposed to overcome limitations associated with the two existing methods to measure coronary flow inside the coronary artery. \[^{15}O\]H\(_2\)O PET perfusion imaging was again used as the reference standard, given that it accurately measures myocardial perfusion. A strong correlation between the absolute flow measurements and \[^{15}O\]H\(_2\)O PET defined perfusion was found. A second key finding of this study was that the use of a pharmacological compound to achieve vasodilation was not necessary and continuous infusion of saline at room temperature was sufficient to establish maximal vasodilation. The findings of this study validate this novel technique as a useful adjunct technique to study the coronary hemodynamics in vivo.

**Future perspectives**

*Microvascular injury after acute myocardial infarction: can we identify it?*

The hypothesis that reperfusion after a period of ischemia due to a myocardial infarction is necessary for microvascular injury to occur, was confirmed by the results of the experimental rodent study. These results suggest a therapeutic window to rescue the microcirculation exists. Identification of patients at high risk for developing microvascular injury with a subsequent impaired long-term prognosis can be achieved by measuring the hyperemic microvascular resistance immediately after successful primary angioplasty. Previously, microvascular injury could only be diagnosed using cardiac magnetic resonance imaging, which is not immediately available when is treated in the catheterization laboratory. By the time a cardiac magnetic resonance imaging scan has been completed, the therapeutic window has already passed and transcatheter access has been closed. By providing confirmatory evidence for a therapeutic window as well as by identifying high risk patients, two goals in the quest to eliminate microvascular injury have been resolved. However, the most important goal has not been achieved, which is finding a therapeutic agent or treatment strategy that could prevent or attenuate microvascular injury. Future research should be dedicated towards identifying suitable therapeutic targets. It can be envisaged that if this target were to be identified, rapid primary percutaneous coronary
intervention for patients presenting with ST-segment elevation myocardial infarction, would be followed up by the measurement of hyperemic microvascular resistance to determine whether the patient is at increased risk for microvascular injury and amendable to adjunctive therapy.

**Is it primetime for the instantaneous wave-free ratio?**

Decades of research into coronary physiology, and fractional flow reserve in particular, led to the paradigm that maximal vasodilatation is required for accurate identification of functional stenosis significance. The finding that the instantaneous wave-free ratio could identify functional stenosis significance as well, came as a surprise to many researchers studying this field. In this thesis, the rationale by which the instantaneous wave-free ratio is capable of detecting the hemodynamic consequences of coronary stenoses has been clarified. In this thesis, it is postulated that the instantaneous wave-free ratio informs on the degree of compensatory microcirculatory vasodilation in response to the upstream coronary stenosis mediated by coronary autoregulation. The major benefit of using instantaneous wave-free ratio instead of the fractional flow reserve in clinical practice, is that it does not require pharmacological induction of the hyperemic state. Findings in this thesis demonstrate that the instantaneous wave-free ratio performed similarly to the fractional flow reserve in the detection of ischemic myocardial perfusion deficits on [15O] H2O PET. Similarly, large randomized clinical trials also report favorable findings for the instantaneous wave-free ratio. For these reasons, I would argue that the primetime for the instantaneous wave-free ratio has indeed arrived and moving forward, the instantaneous wave-free ratio can be implemented in clinical practice.

**Is microvascular resistance influenced by the presence of a coronary stenosis?**

A topic of intense scientific debate in the previous decades has been whether the microvascular resistance at maximal vasodilation is augmented by the presence of a coronary stenosis. This question is relevant for multiple reasons, including to the theoretical framework of the fractional flow reserve, which assumes no interaction between the coronary stenosis and the subtended microcirculation. Findings in this thesis showed that the microcirculation distal to coronary stenoses demonstrated no histopathological signs of remodeling. Secondly, in vivo measurements of intracoronary microvascular resistance showed that whole cycle resistance during maximal vasodilation is elevated distal to a coronary stenosis. However, if only mid-to-late diastole was assessed by the minimal Microvascular Resistance (mMR), microvascular resistance is not influenced by epicardial coronary artery disease. Taken together, the histopathology and mMR studies thus provide two separate lines of evidence that demonstrate an absent hemodynamic or structural interaction between the epicardial stenosis and the underlying microcirculation. It should
be kept in mind, that critical stenoses were not investigated in the aforementioned studies. Henceforth, mMR could be applied in clinical practice and research alike, to provide an estimate of coronary microcirculatory dysfunction, that is not influenced by the presence of an upstream coronary artery stenosis.

**What measurement technique should be used to measure intracoronary flow moving forward?**

At present, intracoronary flow can be measured using a coronary guidewire equipped with either a temperature sensor or a Doppler crystal. As became clear in this thesis and in many previous studies, the measurement of coronary flow can provide a wealth of data that can be used to further the mechanistic knowledge of coronary artery disease. Furthermore, intracoronary hemodynamic measurements can provide valuable diagnostic and prognostic information in both the acute and stable manifestations of coronary artery disease. Results in this thesis show that flow measurements ascertained with the Doppler crystal provided more accurate information than with the thermodilution technique. Henceforth, Doppler flow based measurements should likely be the preferred measurement of choice for evaluation of intracoronary flow and microvascular resistance. However, high fidelity measurements can not always be obtained with the Doppler wire with failure rates of approximately 20%. Moreover, flow velocity albeit indexed to vessel size, can only serve as a surrogate of true volumetric coronary blood flow. The novel methodology to determine absolute volumetric flow by continuous saline infusion, proved to be an extremely accurate and reliable measurement. Further research should ideally find a suitable way to index the volumetric flow to subtended myocardial mass. If this condition is met, diagnostic and prognostic implications of volumetric coronary flow could be investigated with the ultimate goal of integrating comprehensive coronary physiology by combined assessment of pressure and flow to the workflow of the catheterization laboratory.

**Conclusions**

The aim of this thesis entitled: ‘The heart of the matter: Exploring the interaction between the coronary artery and the downstream microcirculation’, was to elucidate the interaction between the epicardial coronary artery and the downstream microcirculation. With respect to these research questions, four key conclusions can be drawn on the basis of the results from the studies embedded in this thesis. Firstly, for microvascular injury to occur after an acute myocardial infarction, reperfusion is mandatory, suggesting that a therapeutic window exists in which adjunctive intervention could be effective. Patients at high risk of microvascular injury can be identified early by measuring the hyperemic microvascular resistance. Secondly, the functional significance of a stenosis can be reliably assessed using the instantaneous wave-free ratio. This pressure index measured under physiological
resting conditions, informs on the degree of autoregulatory compensation imposed on the coronary microcirculation by the stenosis. Thirdly, microvascular remodeling downstream of a non-critical stenosis does not occur. Unlike existing indices to quantify microcirculatory dysfunction, minimal Microvascular Resistance can be reliably assessed in the presence of a flow limiting stenosis. The fourth and final conclusion is that moving forward, intracoronary flow is most reliably assessed using a guidewire equipped with a Doppler sensor. Given the difficulty to obtain high quality signals however, the promising results observed with the novel volumetric flow assessment merit further investigation.

Taken together, measurements of intracoronary hemodynamic indices provides information on both the epicardial coronary artery as well as the microcirculation. This information is useful to identify patients at high risk for microvascular injury after acute myocardial infarction or aiding in the decision making of revascularization in stable ischemic heart disease. For this purpose, useful indices as well as the best way to accurately measure these indices have been explored and validated in this thesis.