Novel insights into the complexity of ischaemic heart disease derived from combined coronary pressure and flow velocity measurements
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Chapter 1

General introduction and outline of the thesis
GENERAL INTRODUCTION

Ischaemic heart disease remains the principal cause of mortality and morbidity in the Western world. Its clinical manifestations may range from effort-related chest pain syndromes, to angina pectoris at rest, acute myocardial infarction, or even sudden cardiac death. Generally, ischaemic heart disease is considered a consequence of atherosclerotic plaque development in the epicardial vessel wall, which progression ultimately leads to comprise coronary blood flow and oxygen supply to the contracting cardiac muscle. The seemingly obvious and direct link between epicardial coronary obstruction and the abovementioned clinical sequelae has led to a preoccupation with coronary stenosis and its treatment over the past decades. However, large clinical trials have documented the absence of a clinical benefit of mechanical relief of angiographically severe coronary stenoses over optimizing medical treatment in stable ischaemic heart disease, raising awareness regarding the lack of life saving potential of coronary revascularization beyond the acute phase of myocardial infarction. In the setting of stable ischaemic heart disease, physicians have since struggled with identifying those patients that benefit from coronary revascularization beyond symptom-relief.

Following identification of substantial limitations of coronary angiography to assess the functional relevance of a documented epicardial coronary stenosis, several intracoronary physiology techniques that allow documenting the hemodynamic significance of coronary stenoses have been introduced. Such techniques include physiological parameters based on intracoronary measurement of coronary pressure or flow. Mainly due to practical cumbersomeness of coronary flow assessment and the limitations associated with the coronary flow reserve as a tool to identify hemodynamically severe stenoses, the coronary pressure-derived fractional flow reserve (FFR) has emerged as a routine clinical tool to evaluate functional coronary stenosis severity assessment over the past 20 years. Despite a well-documented clinical benefit of FFR-guided revascularization compared with decision-making based on visual assessment of the coronary angiogram, adoption of FFR-guidance remains limited to an estimated 7-10% of coronary revascularizations worldwide.

The limited adoption of this relatively simple technique is considered a consequence of practical and logistical ambiguities associated with the use of intracoronary physiology techniques to guide intervention, such as the required manipulation of sensor-equipped guide wires through the diseased coronary tree, its associated increment in procedure duration and radiation exposure, as well as concerns on the validity and reliability of FFR-guided intervention in general. In particular, the prerequisite of potent vasodilators for the assessment of FFR is considered an important contributor to the limited adoption of coronary physiology, since their use is associated with a large patient burden, side-effects that may adversely affect FFR reliability, additional costs, and a substantial
increment in procedure duration particularly in the setting of multi-vessel coronary artery disease. Additionally, there is a large uncertainty regarding the appropriate dosing of vasodilators.\textsuperscript{8,9} These important limitations of coronary vasodilation in clinical practice have led investigators to evaluate whether resting, non-vasodilated, conditions could allow stenosis evaluation, circumventing the ambiguities associated with these potent pharmacological agents.\textsuperscript{10,11}

The concerns regarding the validity and reliability of FFR-guided intervention that may contribute to the limited adoption of physiology-guided intervention have been fuelled by the recent FAME II trial, documenting that revascularization of stenoses deemed functionally significant by FFR remains associated with a marginal clinical benefit beyond immediate symptom relief.\textsuperscript{12,13} Importantly, more than half of patients with stenoses considered functionally significant by FFR, which are consequently considered eligible for mechanical revascularization according to contemporary revascularization guidelines,\textsuperscript{14} actually do not require revascularization up to two years after initial deferral. In addition, more than 10\% of patients with stenoses considered functionally not significant by FFR return with clinical sequelae that require immediate intervention or even result in sudden cardiac death within 2 years after initial deferral. Apparently, a stenosis-focused approach towards the diagnosis and treatment of ischaemic heart disease, whether based on visual assessment of coronary angiograms or functional assessment using coronary pressure measurements to determine FFR, does not enhance clinical outcomes. This consideration has led many to question the appropriateness of coronary revascularization in the setting of stable ischaemic heart disease,\textsuperscript{15} while others have attributed this to an inadequate selection of patients in whom mechanical revascularization may augment the benefit introduced by optimal medical therapy.\textsuperscript{16}

Over the past years, awareness has increased that stable ischaemic heart disease is a complex disease that not only affects the epicardial coronary artery, but involves all levels of the coronary vasculature, also including the coronary microvasculature and the myocardium.\textsuperscript{17} It is especially this multi-level involvement that complicates the diagnosis and treatment of stable ischaemic heart disease, since it obscures the seemingly direct relationship between epicardial stenosis and its treatment, and clinical outcomes.\textsuperscript{18,19}

This thesis first describes the diagnostic complexity of stable ischaemic heart disease governed by the involvement of the coronary microvasculature, and the diagnostic blind spot created by the sole assessment of coronary pressure. It addresses this complexity by describing the findings from a more comprehensive physiological assessment of the coronary circulation using the combination coronary pressure and flow velocity measurements to improve the diagnosis and risk-stratification in ischaemic heart disease. Second, this thesis describes the validation of a novel physiological parameter that allows functional stenosis severity assessment during resting conditions, aiming to circumvent the
practical and theoretical ambiguities associated with the use of potent vasodilators. The observations on the diagnostic pertinence of microvascular involvement in obstructed coronary arteries are extended to the prognostic relevance of the microcirculation in angiographically normal reference coronary arteries, both in the setting of stable ischaemic heart disease and the sub-acute and acute phase of acute coronary syndromes. Finally, this thesis describes the potential of innovative technology, pressure-controlled intermittent coronary sinus occlusion, which aims to protect the coronary microvasculature in the critical condition of myocardial infarction.

**THESIS OUTLINE**

**Part A. Diagnostic complexity of ischaemic heart disease**

Ultimately, the fundamental physiological basis of clinical physiological parameters, such as fractional flow reserve, is found in the coronary pressure-flow relation, as is discussed in Chapter 2 of this thesis. Fractional flow reserve, the contemporary standard in invasive assessment of functional stenosis severity finds its cornerstone in a simplified framework of the coronary circulation, and is based on several assumptions regarding the behaviour of the coronary circulation during pharmacological coronary vasodilation. Chapter 3 details the ambiguity of these fundamental assumptions underlying fractional flow reserve, and discusses the limitations of fractional flow reserve as an intracoronary physiological diagnostic test for inducible myocardial ischaemia in routine clinical practice. Chapter 4 describes the presence of pertinent discrepancies between coronary pressure and coronary flow-based assessment of stable ischaemic heart disease, by means of FFR or CFVR respectively, which originates from a concomitant involvement of the epicardial coronary artery and the coronary microcirculation. Such multi-level involvement is not considered in contemporary practice, but is documented to play a pertinent role both in the diagnosis and prognosis of stable ischaemic heart disease. Chapter 5 describes the direct impact of the resistance to coronary flow induced by the coronary microcirculation on the diagnostic characteristics of fractional flow reserve for the identification of inducible myocardial ischaemia, and Chapter 6 describes how ageing of the coronary vasculature influences the coronary microcirculation and thereby the clinically available physiological parameters. Finally, a novel diagnostic strategy is proposed in Chapter 7, which incorporates a comprehensive assessment of the flow characteristics in the coronary circulation to overcome the limitations of coronary flow reserve as a diagnostic tool in ischaemic heart disease. This concept, termed coronary flow capacity, is documented to provide incremental prognostic value over coronary flow reserve alone, and to enrich the interpretation of, amongst others, fractional flow reserve.
Part B. Hyperaemia-free assessment of physiological stenosis severity

Despite substantial clinical benefit over angiography alone, clinical decision-making based on fractional flow reserve remains poorly adopted worldwide. To date, only 7-10% of coronary revascularizations are fractional flow reserve-guided, which is mainly attributable to practical cumbersomeness of coronary pressure measurements in clinical practice, which not only requires manipulation of sensor-equipped guide wires in the diseased coronary tree, but also necessitates the use of potent vasodilators to achieve a state of maximal hyperaemia that is a prerequisite for the calculation of fractional flow reserve. Since the dosing of these vasodilators remains ambiguous, and their use complicates and lengthens cardiac catheterization procedures, a vasodilator-free approach could potentially increase adoption of physiologically guided coronary intervention. Chapter 8, 9, and 10 describe the development and clinical validation of a novel physiological parameter, basal stenosis resistance index, which is based on a combined assessment of coronary pressure and flow velocity during resting conditions, and thereby circumvents any ambiguities associated with the use or dosing of potent vasodilators in the cardiac catheterization laboratory.

Part C. Prognostic implications of, and therapeutic strategies directed towards the coronary microcirculation

Part C of this thesis extents the observations on the pertinence of the coronary microcirculation in obstructed coronary arteries with stenoses of intermediate severity to angiographically unobstructed reference coronary arteries. Chapter 11 describes the prognostic relevance of microvascular function for long-term survival in patients with stable ischaemic heart disease, while Chapter 12 focuses on the prognostic relevance of microvascular function in the acute phase of ST-segment elevation myocardial infarction, as well as the pertinence of its recovery within the first six months.

The final chapters of this thesis focus on pressure-controlled intermittent coronary sinus occlusion (PICSO), a novel therapeutic approach towards the protection of the coronary microvasculature in patients undergoing primary percutaneous intervention for ST-segment elevation myocardial infarction. Chapter 13 describes the first-in-man use and physiological effects of PICSO in experimental coronary artery occlusion, while Chapter 14 describes the first evaluation of its safety and feasibility, as well as early insight into its effectiveness, in patients with ST-segment elevation myocardial infarction.
REFERENCES