Improved assessment of functional severity of coronary artery stenosis by analysis of combined intracoronary pressure and flow velocity signals
Nolte, F.

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The aim of the present thesis is to improve patient selection for percutaneous coronary intervention (PCI) by 1) proposing new clinical indices for the assessment of functional stenosis severity using combined measurements of intracoronary pressure and flow velocity, that do not require maximal vasodilation of the coronary vascular bed, and 2) by testing the hypothesis of collateral flow augmentation secondary to epicardial narrowing in relation to the presence of reversible ischemia and the potential contribution of increased minimal microvascular resistance to total myocardial ischemia.

Intracoronary pressure and flow velocity measurements obtained during cardiac catheterization form the basis of clinical indices of functional stenosis severity as well as for the determination of microvascular resistance. In addition to invasive hemodynamic measurements, diagnostics and treatment decision can be improved by non-invasive assessment of regional perfusion measurements. However, these different modalities in isolation often result in conflicting treatment recommendations. Chapter 2 reviews the role of the development of perfusion models of the heart used for the interpretation of underlying physiological mechanisms of coronary artery disease (CAD) on clinical decision making. Model development enables the integration of the information from these different modalities and can generate simulation frameworks, thereby providing better insights into the coronary physiology that may result in improved patient care. From this review we conclude that the developments in regional perfusion measurements are a major step forward in bringing physiology to the clinical arena since regional differences are induced by a stenosis. These regional differences are not only present between perfusion territories distal of obstructed and normal epicardial arteries but also within these territories, especially between subepicardial and subendocardial regions. Model developments allow the integration of all of these measurements at the epicardial level, from pressure and flow data, and regional information, provided by whole organ myocardial perfusion imaging. In addition to integrating data, simulation frameworks enable the simulation of individual entities such as coronary occlusion or microvascular disease as well as analysis of physiological mechanisms such as the role that contraction or ventricular pressure play on regional distribution of coronary flow. In chapter 3, a review is given on the basic characteristics of coronary hemodynamics as described by pressure-flow relations, coronary microvascular resistance and myocardial perfusion distribution in the normal and diseased heart. These basic characteristics are important to properly interpretate functional stenosis severity and resistances derived from these hemodynamic signals.

Current practice guidelines specify that sensor-equipped guide wires used to obtain hemodynamic signals for the derivation of clinical indices of functional stenosis severity should be positioned at least 2–3 cm beyond the lesion. However, for flow velocity measurements the branching and tapering vessels may form a problem when a decrease in cross-sectional area is not matched by a reduction in perfusion
territory, while pressure along a vessel is likely to decrease due to viscous losses. It can therefore be expected that choosing a more distal axial measurement location affects these hemodynamic signals. In chapter 4 we assess whether intracoronary pressure, flow velocity and derived indices of functional stenosis severity and microvascular resistance are affected by differences in axial measurement location distal to the lesion. We show that clinical indices of functional stenosis severity and microvascular resistance are not affected by measurement location. However, an inter-patient variability between flow velocities at different locations in reference vessels suggests a stronger influence of patient-specific vascular network morphology at proximal measurement locations. More distal locations are therefore advised for obtaining velocity or velocity-derived indices to assess epicardial obstructions.

The next two chapters are dedicated to overcome an important shortcoming in functional assessment of epicardial stenosis severity. Currently accepted clinical indices of functional stenosis severity critically depend on the achievement of maximal vasodilation, usually obtained by injecting adenosine. However, there is a current ongoing debate regarding the dose of adenosine required to obtain this maximal hyperemia. Furthermore, adenosine is not readily available in every catheterization laboratory. Chapters 5 and 6 propose new indices that do not have this requirement. In chapter 5, the diagnostic performance of a new, vasodilator-free functional index of stenosis severity, the baseline stenosis resistance (BSR) index, obtained during resting conditions, is compared to that of the presently available indices against non-invasive assessment of reversible ischemia detected by myocardial perfusion scintigraphy (MPS). This study demonstrates that BSR is as accurate to predict reversible myocardial ischemia as the most frequently used index, i.e. fractional flow reserve (FFR). However, the accuracy of the hyperemic stenosis resistance (HSR), known to be less dependent on the achievement of maximal hyperemia compared to FFR, was still higher than the accuracy of BSR. Despite the promising result of BSR, this index is obtained at rest. In this circumstance, coronary blood flow is kept constant despite changes in perfusion pressure, which might complicate the assessment of BSR. Since the flow limiting properties of a stenosis become more prone at a higher degree of vasodilation, discrimination between functional significant and insignificant lesions may improve at higher flow rates. Therefore, in chapter 6, we propose another index of functional stenosis severity, the pressure gradient at a fixed flow velocity of 30 cm/s (dPv30), calculated from the curve fit of the stenosis pressure gradient-flow velocity (ΔP-v) relationship, which does not require the achievement of maximal hyperemia. Since contrast medium is known to induce submaximal reactive hyperemia, this study tests if adenosine and contrast medium result in similar ΔP-v relationships, allowing the derivation of dPv30 by using contrast medium, thereby circumventing both the requirement of maximal hyperemia and the need of adenosine to functionally assess stenosis severity. Since MPS is not performed in this study, we define the diagnostic accuracy of dPv30 derived with adenosine and contrast medium against both FFR and HSR. This study shows that dPv30 obtained with adenosine has an excellent diagnostic performance against FFR and HSR. Additionally, we demonstrate that the adenosine and contrast medium obtained ΔP-v relationships are remarkably similar, and that dPv30 obtained during submaximal hyperemia induced by contrast medium results in an approximately similar diagnostic performance compared to dPv30 obtained with adenosine.
In the literature, controversial results have been reported on the influence of epicardial coronary artery disease on hyperemic microvascular resistance (HMR). This dispute is related to correction for collateral contribution to total myocardial flow in the calculation of HMR, and has become of interest since it relates to important assumptions underlying the model of the FFR. In chapter 7, we test the hypothesis of collateral flow augmentation secondary to epicardial narrowing by comparing the results of HSR and HMR in relation to the presence of reversible ischemia determined by MPS. This study shows an increased presence of reversible myocardial ischemia in patients with a high value of HMR in addition to a functionally significant stenosis, which supports the hypothesis that HMR does not require correction for collateral flow contribution. The finding of this chapter is not only important for fundamental reasons, but has also important consequences for adequate patient selection for PCI. Guidelines recommend hemodynamic-derived indices of functional stenosis severity as surrogate for non-invasive detection of myocardial ischemia to select patients for PCI. However, myocardial ischemia as detected by non-invasive techniques of myocardial perfusion are the result of flow limiting contributions of both epicardial narrowing and microvascular dysfunction, while hemodynamically derived clinical indices of functional stenosis severity only represent the epicardial contribution to myocardial ischemia. In chapter 8, the impact of the magnitude of HMR for the presence, and FFR-guided identification, of reversible myocardial ischemia on non-invasive stress testing is evaluated. It shows that HMR is an important determinant of treatment decision, as revascularization of an epicardial stenosis in patients with a high HMR is likely beneficial at higher FFR values, while revascularization of coronary lesions in patients with a low HMR may likely be deferred to FFR-values well below currently adopted fixed cut-off of 0.8. The results of both chapter 7 and 8 demonstrate the importance of incorporating microvascular dysfunction into patient selection for PCI, as it may affect the interpretation of clinical indices of functional stenosis severity as predictors of reversible myocardial ischemia, the target of revascularization therapy, which form the basis of treatment decisions.

In chapter 9 the results from the thesis are discussed based on their relevance to improvement of functional stenosis severity assessment and the contribution of microvascular resistance to myocardial ischemia, followed by an overview of recommendations and finally a future perspective is given.

In summary, this thesis recommends the combined assessment of intracoronary pressure and flow velocity in daily clinical practice enabling 1) the derivation of clinical indices of functional stenosis severity that do not require maximal vasodilation of the coronary microcirculation and 2) the assessment of HMR for optimal decision making of revascularization therapy. Additionally, diagnostics and treatment decision stand to benefit from the development of models that integrate information obtained from invasive and non-invasive methods to assess myocardial perfusion and predict treatment outcomes. Such developments can yield further insights into the coronary physiology of patients. Ultimately, these developments bear great potential to lead to improved, personalized patient care.