Improved assessment of functional severity of coronary artery stenosis by analysis of combined intracoronary pressure and flow velocity signals
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Chapter 9

General discussion
Chapter 9

Physiological basis underlying clinical decision making for revascularization

Coronary artery disease (CAD) accounts for almost 2 million deaths per year within the EU. CAD is often characterized by focal narrowing of epicardial arteries, limiting coronary arterial flow and myocardial perfusion. As discussed in Chapter 2, revascularization therapy of CAD started approximately 50 years ago by open heart bypass surgery, later followed by catheter based balloon and stent dilatation of the stenosis denoted as percutaneous coronary intervention (PCI). Initially, coronary angiography was used to evaluate coronary lumen reduction as basis for treatment decision during PCI. Later, guide wires were equipped with a pressure sensor or a Doppler flow velocity probe at the tip allowing the determination of the hemodynamic effect of a stenosis. From those hemodynamic signals, clinical indices of functional stenosis severity were derived based on either flow velocity, such as the coronary flow velocity reserve (CFVR), or pressure, such as the fractional flow reserve (FFR). These indices improved the prediction of reversible ischemia and more recently it was demonstrated that FFR guided PCI improved clinical outcome compared to the use of angiography (1, 2). However, there is still room for improvement, since CFVR and FFR were shown to result in conflicting treatment advice in approximately 30% of patients (3). More recently, dual sensor-equipped guide wires were introduced, enabling the simultaneous assessment of coronary pressure and flow velocity. With the use of those simultaneously assessed hemodynamic signals, the stenosis pressure gradient-flow velocity (∆P-v) relationship can be measured as illustrated in Chapters 2, 3 and 6. Moreover, indices of the resistance to flow from a stenosis and that of the coronary microcirculation can be defined. The hyperemic stenosis resistance (HSR) index was shown to improve treatment decision in daily clinical practice compared to sole pressure- or flow velocity-derived functional indices of stenosis severity (4). The hyperemic microvascular resistance (HMR) index can be useful to identify coronary microvascular disease as discussed in Chapters 7 and 8. In addition to the invasive assessment of intracoronary hemodynamics to assess the epicardial and microvascular status of the diseased coronary bed, also non-invasive methods can be used for diagnostics purposes by the assessment of myocardial perfusion deficits, such as magnetic resonance imaging (MRI) or myocardial perfusion scintigraphy (MPS) as discussed in Chapter 2. Integration of all these techniques will in the end allow for a more personalized diagnosis and treatment planning. In this chapter, we will summarize the most important findings of this thesis, which can contribute to this improvement, and recommendations with respect to both future research and applicability of our findings into daily clinical practice will be discussed.

Clinical indices of functional stenosis severity not requiring maximal hyperemia

The assessment of functional coronary lesion severity using intracoronary physiological parameters such as CFVR, and the more widely used FFR, relies critically on the establishment of maximal hyperemia, usually obtained by an intracoronary dose of adenosine. Although to a smaller degree than FFR and CFVR, also HSR depends on the achievement of maximal hyperemia. However, adenosine
is not readily available in every catheterization laboratory, and presently there is no consensus on the intracoronary dose of adenosine that is required to obtain this maximal hyperemic condition (5). The use of a vasodilator free evaluation of stenosis severity may overcome these issues. Recently, the instantaneous wave free ratio (iFR), defined as the ratio of coronary distal to aortic pressure during a specific mid-diastolic, wave-free period, was introduced as such a drug free index to assess coronary lesion severity (6), as it was shown to correlate closely to FFR and yielded an excellent diagnostic performance. However, simulations work by Johnson et al. (7, 8) as well as a study by van t Veer et al. (8) showed that iFR is a weak predictor of FFR and concluded that iFR is not useful for clinical decision making. Yet several patient studies are underway to validate its usefulness.

At the same time, we introduced the baseline stenosis resistance (BSR) index (Chapter 5) as a vasodilator free index of functional stenosis severity. For BSR, discrimination of lesion severity is facilitated by high-fidelity measurements of both pressure and flow velocity, whereas iFR is based on sole pressure measurements. Both indices however do not require any vasodilation at all and are therefore relatively easy to obtain in daily clinical practice. We demonstrated that the diagnostic performance of BSR (area under the receiver operating characteristic curve (AUC) of 0.77) was as accurate as FFR and CFVR (AUC of 0.77 and 0.75, respectively) with the use of MPS outcome on reversible perfusion defects as gold standard. However, HSR was still superior (AUC of 0.81) to all other investigated parameters, highlighting the importance of reducing microvascular resistance of the coronary bed to accurately assess functional stenosis severity.

One of the reasons that BSR performs less than HSR may be to the result of relative measurement uncertainties due to the smaller values of flow velocity and pressure gradient at resting flow. This also holds for iFR. Another reason for the lower diagnostic performance of BSR may be that the slope of the pressure drop-flow velocity relationship of a specific stenosis depends on the non-linear part of the pressure drop due to acceleration losses, meaning the pressure drop-flow velocity relationship of different stenoses can cross at higher flow rates, i.e. a stenosis that is less severe at baseline flow can become more severe at hyperemia. Finally, partially compliant lesions (25–30% diameter stenosis) can collapse at higher flow rates (i.e. lower intra-stenotic pressure), which will be missed at resting flow.

An alternative method was developed in Chapter 6, requiring some but not full vasodilation. This method is based on the stenosis pressure gradient obtained, c.q. predicted at a fixed flow velocity of 30 cm/s (dP \_v30). With a best cut-off value of 21.2 mmHg to define functionally significant lesions, dP \_v30 yielded an AUC of 0.96 with the use of FFR<0.8 as gold standard, 0.94 with FFR<0.75 and 1.00 with HSR as gold standard, respectively. This method was validated using adenosine for vasodilation, however the (submaximal) hyperemic response to a vasodilatory agent other than adenosine can be used to assess dP \_v30. Importantly, the submaximal reactive hyperemic response as consequence of contrast medium injection used to visualise the interrogated artery provides sufficient increase in coronary flow velocity to determine dP \_v30.
Since both BSR and $dP_{\text{st}}$ do not require the use of adenosine to induce maximal hyperemia, these indices can improve the adoption of functional lesion assessment in daily clinical practice in these situations.

**Association between hyperemic microvascular resistance and myocardial ischemia**

Evidence has been gathered that in addition to the extent of epicardial disease, coronary microvascular dysfunction importantly contributes to (9, 10), or may even be the sole origin of (11) reversible myocardial ischemia. Abnormalities in microvascular function are likely associated with alterations in hyperemic coronary microvascular resistance (12). Despite the increasing evidence that CAD not only results in the narrowing of epicardial vessels but also extends into the microcirculation (9, 10), there is controversy regarding the quantification of an elevated minimal microvascular resistance distal to a coronary artery stenosis.

This controversy relates to the possible role of the collateral circulation in the calculation of microvascular resistance. As discussed in Chapter 3, the hyperemic coronary pressure-flow relationship within the physiological pressure range is not proportional but incremental-linear. This means that this relation does not pass through its origin (i.e. pressure=0 at flow=0), but has a non-zero pressure intercept at a value higher than venous pressure ($P_v$). There are two paradigms for the incremental-linear nature of the pressure-flow relationship. The first paradigm is that resistance of the dilated coronary vascular bed is dependent on pressure and heart contraction since microvessels are distensible and compressible and hence requires that microvascular resistance at maximal vasodilation is quantified by $HMR = \frac{P_d - P_v}{v}$, where $P_d$ represents the coronary distal pressure and $v$ coronary flow velocity. This implies that HMR increases with decreasing intraluminal pressure, i.e. with increasing stenosis severity. There is ample physiological evidence to support this paradigm (13, 14). Direct observations demonstrate changes in diameter of resistance vessels with pressure (15) and heart contraction (16). The compression effect on HMR, also referred to as extravascular resistance, has been well documented by demonstrating that coronary arterial flow increases with cardiac arrest but maintenance of coronary pressure (17). The extravascular resistance is especially noticeable at the subendocardium as demonstrated by microsphere studies (18–20). The second paradigm is that coronary resistance is constant and collateral flow is linearly increasing with decreasing $P_d$. The intercept with the pressure axis then reflects the maximal collateral flow (21). Based on that assumption hyperemic microvascular resistance is quantified by subtracting the coronary wedge pressure from intracoronary pressure, as is done for the index of microcirculatory resistance (IMR), calculated as $\frac{P_d - P_w}{v}$ (22). The evidence presented for this paradigm is, however, lacking support from independent measurement of collateral flow.

It is clinically important to resolve this controversy since analysis with HMR leads to the conclusion that revascularization results in a decrease of hyperemic microvascular resistance (23, 24), while analysis accounting for an assumed collateral contribution with IMR lead to the conclusion that this is not the case. Importantly, clinically $P_w$ is
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used as a measure reflecting the presence of collateral flow, while Pw is commonly within a range where its value can be better explained by myocardial wall stress (25). Both paradigms were extensively discussed in Chapter 3. A more pragmatic approach of this discussion has been performed in Chapter 7. The definition most likely to be correct is the one with the highest prognostic value for reversible myocardial ischemia for a given stenosis as detected by an independent method such as MPS. We showed a significantly higher risk for reversible myocardial ischemia for lesions associated with high compared to low HMR, especially in functionally significant lesions (HSR>0.8 mmHg/cm/s). In Chapter 7, no Pw was measured and hence IMR could not be determined. However, adjusting HMR for collateral flow according to a correlative formula presented in the literature (26) demonstrated a loss of predictive power for ischemia. The discriminative value for the presence of reversible myocardial ischemia, assessed by the area under the receiver-operating-characteristics curve (AUC), was significantly higher for minimal microvascular resistance uncorrected for collateral flow (AUC of 0.67) compared to that of minimal microvascular resistance after Pw-based correction for collateral flow (AUC of 0.55) (data not shown in Chapter 7). In case a higher HMR would be artificial and thus the result of neglecting collateral flow, the high predictive value for HMR would be quite unlikely. Hence, from these results we conclude that HMR allows for the identification of alterations in microvascular resistance that are associated with an increased risk of associated pathology and may be considered as a useful tool to quantify the functional status of the coronary microvasculature in clinical practice.

Since FFR is proposed as the index of choice for clinical decision making (27), it is important to know how this index is influenced by microvascular resistance. As demonstrated in Chapter 7, an increased risk for reversible myocardial ischemia was found for lesions associated with high compared to low HMR. Importantly, in chapter 8 it was shown that the optimal FFR cut-off value was distinctly lower when HMR was low (optimal FFR cut-off 0.65) compared with when HMR was high (optimal FFR cut-off 0.76). Currently, a fixed cut-off value of 0.8 is used in clinical practice to identify functionally significant lesions. These results, however, imply that HMR is an important determinant of treatment decision in patients with stable coronary artery disease. Revascularization of an epicardial stenosis in patients with a high HMR is likely beneficial at higher FFR values due to the effects of perfusion pressure on resistance of the distal coronary vasculature. Conversely, revascularization of coronary lesions in patients with a low HMR may likely be deferred to FFR-values well below currently adopted cut-off thresholds in order to avoid inadvertent treatment of functionally non-significant coronary stenoses.

The results of both Chapter 7 and 8 provide novel insights into the consequences of an unaccounted extent of microvascular involvement of coronary artery disease in the contemporary revascularization strategy adopted in clinical practice, which relies on a coronary pressure-only and in essence sole assessment of the epicardial contribution to flow limitation to the myocardium. As such, appraising the magnitude of minimal microvascular resistance may benefit proper lesion selection for percutaneous coronary intervention, and thereby further improve outcomes of physiologically-guided coronary intervention.
Effect of axial measurement location on clinical indices

To avoid effects of disturbed flow on the assessment of hemodynamic signals, current practice guidelines recommend to position a sensor-equipped guide wire at least 2 cm beyond the stenosis (28), but no upper limit is specified. However, in clinical practice the distance between the actual measurement location and the throat of the stenosis may vary substantially in order to find an optimal and stable blood flow velocity signal. For a good interpretation of clinical indices derived from such measurements, it is therefore relevant to know to what extent intracoronary pressure and velocity signals are affected by the axial measurement location at which they are obtained. This location dependency was studied in Chapter 4, and it was found that based on group means, flow velocity is not affected by axial location, either in reference or distal to a stenosis in diseased vessels. Importantly for functional lesion assessment and quantification of microvascular status of diseased vessels, indices of stenosis and microvascular resistance were also not affected by axial location.

Another important issue is the use of flow velocity as a surrogate for coronary flow, based on the assumption that a decrease in cross-sectional area of the coronary bed is matched by a reduction in perfusion territory, thereby rendering flow velocity to be rather constant throughout the epicardial coronary vascular tree. The data of Chapter 4 supported the Square model, implying that flow velocity is indeed independent of changes in lumen diameter across branches and thus, rather constant throughout the epicardial vascular bed. However, when considering individual patient data rather than group averaged data, an inter-patient variability on flow velocity was found for reference vessels, which points to the influence of a patient-specific vascular morphology that was more pronounced at proximal than at distal measurement locations. Hence, the use of a more distal location to obtain flow velocity measurements may further reduce inter-patient variability of flow velocity or flow velocity-derived indices. The data presented in the other chapters were acquired rather distally, since the experience at our institution is that more stable signals can be obtained at that location.

Use of multiscale modeling to improve insights into understanding coronary physiology

Multiscale modelling aims at integrating physiological and biophysical mechanisms in predictive models than can be used in personalization of diagnosis. Although this thesis did not aim to develop such models of the coronary circulation, this research provided information for validating multiscale modelling as discussed in Chapter 2. Findings from either invasive or non-invasive studies can sometimes result in conflicting treatment recommendations, while integration of information gained by these modalities via multiscale modelling may provide comprehensive insights into reasons why these differences occur and generate a more complete picture of the coronary physiology in health and disease. A typical example is the integration of information gathered by FFR, HMR and MPS, which clearly can yield an improvement in diagnosis. Additionally, models enable the simulation of pathologies such as
epicardial narrowing or microvascular disease as well as investigation of physiological mechanisms such as the role of cardiac contraction or left ventricular pressure in the regional distribution of coronary flow (29, 30). Integration of individual pathologies by simulations may reveal the nature of mutual interactions under different conditions, and may therefore enhance differentiation and personalization for diagnostic purposes.

Recommendations for clinical practice and future research

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 do not require maximal vasodilation of the coronary microcirculation and 2) the assessment of HMR for optimal decision making of revascularization therapy.

Future research should incorporate the simultaneous assessment of intracoronary pressure and flow (velocity) for improvement and validation of indices of functional stenosis severity such as BSR and $dP_{v30}$. The latter index requires more extensive research in a larger patient cohort with non-invasive assessment of myocardial ischemia as a gold standard to validate its diagnostic and prognostic value. Future research work should also involve a comparison of the diagnostic accuracy of these two newly proposed indices with currently used (hyperemic) indices of functional lesion severity and other recently introduced indices to assess functional lesion severity not requiring maximal hyperemia, such as iFR.

Furthermore, combined measurements of intracoronary pressure and flow velocity can be used to advance the understanding of coronary (patho-) physiology in humans. 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 who - in contrast to most large animal models - present with multiple risk factors, co-morbidities and medications. Ultimately, these developments bear great potential to lead to improved, personalized patient care.
References


