Clinical significance of the microvasculature in coronary syndromes

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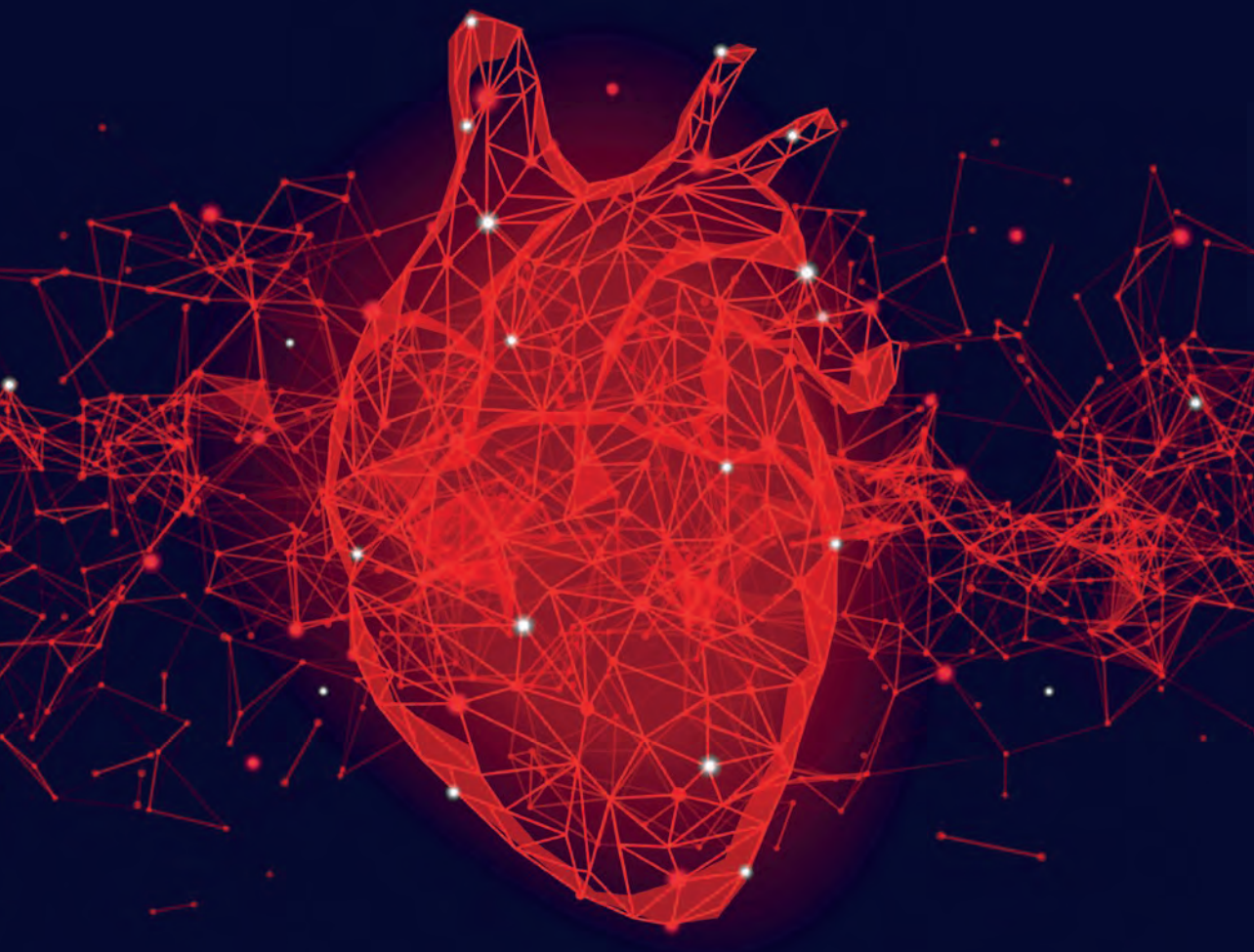

Martijn A. van Lavieren

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Clinical significance of the microvasculature in coronary syndromes

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CHAPTER 1

Introduction

The human heart is a vital organ for the systemic circulation to provide adequate flow to other organs according to their demand. It transports oxygenated blood and nutrients to all other organs through the arterial system and collects metabolic waste (e.g., carbon dioxide) that is transported through the venous system. The heart can be divided into four chambers, the left and right atria and the left and right ventricles, that contract and relax in an orchestrated manner. The heart's right side receives blood from the venous system and pumps this through the right atrium into the right ventricle to eventually flow through the lungs to be re-oxygenated. This oxygenated blood that leaves the lungs and arrives at the left atrium passes through the left ventricle to be pumped into the aorta and the systemic vasculature. The heart itself also needs to be perfused to maintain its adequate function; therefore, the coronary arteries originate just above the aortic valve. The left and right coronary arteries are responsible for myocardial perfusion. If coronary blood flow is hampered due to disease (e.g., a narrowing of the blood vessels due to plaque formation), the heart muscle may be hampered in its function and the patient may suffer from symptoms like chest pain and/or shortness of breath.

Structure and function of the coronary microcirculation

The coronary artery system handles the conductance and regulation of coronary blood flow for myocardial perfusion. From a structural perspective, the coronary vasculature branches out, starting from the epicardial arteries followed by the pre-arterioles (100 to 400 μm) and arterioles (<100 μm) and finally the coronary capillaries (<10 μm). [1][2] From a hemodynamic perspective, the coronary artery blood flow is regulated differently than many other organs' perfusion. The myocardial oxygen extraction of the heart is already near-maximal during resting conditions. Any change in its metabolic state (e.g., increased oxygen demand upon exercise) can exclusively be accommodated by changing coronary blood flow to increase myocardial oxygen delivery. Another difference to the systemic vasculature is that myocardial perfusion occurs in diastole since coronary blood flow is impeded by the cardiac muscle contracting during systole. This effect is more pronounced in the left coronary artery system than in the right coronary artery system.

The epicardial arteries' primary function is to act as conduit vessels, and they exhibit low resistance to coronary flow under normal conditions. The regulation of coronary blood flow occurs at the level of pre-arterioles and arterioles by changing their vessel diameter and thereby altering resistance to the blood flow, i.e., increasing flow by lowering resistance due to vasodilation or decreasing flow by increasing resistance through vasoconstriction. Since roughly 80% of coronary vascular resistance is located in the pre-arterioles and arterioles, they are called resistance vessels. By changing the resistance, these vessels are capable of facilitating an equilibrium between myocardial perfusion and the oxygen demand for a given metabolic state through autoregulation and metabolic adaptation. The process of autoreg-

ulation ensures constant myocardial perfusion independent of alterations in perfusion pressure, where metabolic adaptation modifies coronary blood flow to meet changes in myocardial oxygen demand. [3] Myocardial exchange occurs at the capillary vessel level, where the oxygenated blood satisfies the dynamic needs of local tissue metabolism.

Invasive functional assessment of the coronary microcirculation

The function of the coronary microcirculation can only be assessed indirectly by non-invasive and invasive diagnostic modalities. Invasive assessment of microvascular function can be performed during cardiac catheterization by inserting pressure and flow sensor-equipped guidewires into the coronary arteries. At present, there are two methods to assess coronary flow: (1) Doppler flow velocity, where a miniature ultrasound transducer is mounted on the tip of the guidewire, optionally together with a pressure sensor, and (2) by thermodilution utilizing the temperature sensitivity of the pressure sensor-equipped guidewire to measure the mean transit time after injection of a bolus of saline at room temperature. Typically, flow measurements are obtained during resting conditions as well as under a state of maximal coronary blood flow (hyperemia), which is pharmacologically induced (e.g., using adenosine, papaverine or dipyridamole) during cardiac catheterization to simulate conditions of maximal exercise. This increase in flow is primarily mediated by the vascular smooth muscle relaxation of the resistive vessels located in the (pre-)arterioles. Coronary Flow Reserve (CFR) and microvascular resistance are the diagnostic parameters derived from these invasive measurements. [4]

CFR can be calculated by using Doppler flow measurements, dividing the averaged Doppler flow velocity under hyperemia by the averaged Doppler flow velocity at rest, or by using thermodilution measurements, dividing the mean transit time at rest by the mean transit time during hyperemia. [5][6] This parameter evaluates both the status of epicardial conductance and microvascular function; hence, in the presence of obstructive epicardial artery disease, CFR will reflect both the impact of the epicardial obstruction and the distal microvascular resistance. However, in the absence of significant obstructive epicardial artery disease, CFR directly estimates distal microvascular resistance.

Microvascular resistance is calculated following Ohm's law by dividing the arterial to venous pressure gradient by the coronary flow. For the arterial to venous pressure gradient, the distal pressure (Pd) measured by the sensor-equipped guidewire is used as the inlet pressure for the coronary microcirculation. Since venous pressure is not determined routinely during cardiac catheterization and is very much lower than arterial pressure, it is assumed that the impact of venous pressure can be ignored and that the pressure gradient over the microvascular bed is represented by the distal arterial pressure value Pd. When microvascular resistance is measured using Doppler and pressure sensor-equipped guidewires, resistance

can be calculated by dividing distal pressure by Doppler flow velocity under hyperemic and baseline (resting) conditions and is referred to as Hyperemic Microvascular Resistance (HMR) and Baseline Microvascular Resistance (BMR), respectively. [7] If this parameter is measured using the thermodilution method, microvascular resistance is determined by dividing the distal pressure by the inverse of the mean transit time to calculate the Index of Microvascular Resistance (IMR). [8]

Coronary microvascular dysfunction

Coronary microvascular dysfunction can be defined as the inability of the resistance vessels' residual vasodilatory capacity to satisfy an increase in myocardial oxygen demand through structural and functional abnormalities in the arterioles and capillaries, eventually resulting in ischemia. [9] A complex interplay of numerous pathophysiological mechanisms often underlies an impaired microvascular conductance. [10]

Patients referred for diagnostic cardiac catheterization upon suspicion of a chronic coronary syndrome frequently present with a component of microvascular dysfunction in both the presence and absence of obstructive coronary artery disease. At the (pre-)arterioles, structural changes due to intimal thickening, smooth muscle cell thickening, or proliferation and perivascular fibrosis can result in impaired microvascular conductance. There can also be an impaired vasodilatory capacity due to functional abnormalities in the smooth muscle cells' arteriolar tone. Structural changes to capillaries, such as changes in capillary density and diameter or obstructions and injuries, can also contribute to this phenomenon.

Microvascular dysfunction in the setting of acute coronary syndromes is also considered the consequence of numerous pathophysiological mechanisms, including reperfusion injury, distal embolization of plaque and thrombus material, endothelial dysfunction, leucocyte plugging and external compression of the microvasculature. [11]

Importance of assessing microvascular function

Over the past decades, the diagnosis and treatment of coronary artery disease was characterized by focusing on the epicardial arteries, neglecting the rest of the coronary vasculature as a possible contributing pathophysiological mechanism. However, in patients presenting with intermediate coronary artery stenoses, in the absence of hemodynamically significant epicardial disease, an abnormal microvascular function is found in 14–24% of the patients. [12][13] In patients presenting with angina but without epicardial artery stenoses, that is, patients with so-called non-obstructive artery disease, microvascular dysfunction is found in up to 40% of the patients. This high prevalence has recently led to changes to guidelines, promoting guidewire-based CFR and/or microvascular resistance measurements from a Class IIb to a Class IIa recommendation. [14]

Microcirculatory dysfunction is associated with a worse prognosis both in patients presenting with acute and chronic coronary syndromes. In patients with stable coronary artery disease, the presence of microvascular dysfunction in reference arteries, defined as a CFR ≤2.7, results in an increase in hazard for long-term all-cause mortality. [15] Among patients deferred for revascularization, target vessel microvascular dysfunction determined by a CFR has a worse prognosis than those with a normal CFR regardless of epicardial stenosis severity. [13][16][17] Moreover, patients with a normal Fractional Flow Reserve and microvascular dysfunction are also at risk for worse clinical outcomes, including a greater risk for cardiac death or myocardial infarction at follow-up. [13]

In the setting of ST-segment Elevated Myocardial Infarction (STEMI), acute microvascular dysfunction is reported to be a pan-myocardial phenomenon that also occurs in non-ischemic regions remote of the infarcted myocardium. [18] An impaired microvascular function in a non-infarct related artery, defined as a CFR <2.1, is associated with a 4.09-fold increase in long-term cardiac mortality hazard. Persistent microvascular dysfunction at six-month follow-up was associated with a 10.7-fold increase in cardiac mortality hazard during subsequent follow-up. [19]

Advancements in microvascular function assessments

Despite the increasing interest in assessing microvascular function and the recently altered guideline recommendations, the adoption of these assessments in routine clinical practice has been rather limited. It has long been considered an assessment that only serves scientific purposes. However, the recently published CorMiCa trial represented a tipping point for the general cardiology community and paves the way for these assessments to move from research use to application in daily clinical practice. [14][20] Unfortunately, the currently available armamentarium to invasively assess microvascular function is cumbersome, thereby hampering the adoption of coronary hemodynamics.

Two novel concepts to estimate CFR from pressure measurements have emerged: the pressure-derived CFR (CFRpres) and the pressure-bounded CFR (CFRpb). [21][22] The concept of CFRpres assumes that the stenosis pressure gradient is dominantly determined by separation losses, while the contribution of viscous friction losses is considered negligible. The concept of CFRpb assumes that the stenosis pressure gradient may either be governed by friction losses alone at one end of the spectrum or by separation losses at the other end. CFRpb therefore appraises the lower and upper extremes of CFR to estimate the actual CFR. However, the degree of assumptions and simplifications applied in these methods is unknown and is investigated in this thesis.

The concept of coronary flow capacity (CFC) was introduced as a cross-modality platform for the diagnosis, risk-stratification and prognosis in ischemic heart disease. [23][24] It integrates both the CFR and hyperemic flow, thereby correcting for variation in baseline flow and providing comprehensive insight into coronary hemodynamics. Accordingly, CFC was documented to be less prone to alterations in systemic hemodynamics since it comprehensively captures all relevant flow characteristics. [25] Given the hemodynamic alterations in the setting of STEMI, CFC has the potential to assess the alterations in coronary microvasculature in the acute and chronic phases of an acute myocardial infarction.

Aim of this thesis

The overall aim of this thesis is to advance the understanding in coronary hemodynamics and the role of the coronary microcirculation in the setting of acute and chronic coronary syndromes. It will address this from a methodological, mechanistic, diagnostic and prognostic perspective.

Thesis outline

Part A of this thesis describes coronary physiology during chronic coronary syndromes. It will discuss procedural consideration and alternative approaches when assessing coronary physiology, followed by the additional diagnostic insights that can be obtained by combined pressure and flow measurements and finishing with providing a perspective on the impact of treatment given discordant pressure and flow measurements.

Although performing assessments based on resting indices seems easier than those based on hyperemic indices, it does not mean that they are not sensitive to both procedural and technical errors. In **Chapter Two**, it is emphasized that physiological assessment should always be performed in a careful and meticulous manner to ensure optimal conditions for clinical decision making. Methodological considerations around the impact of collateral flow and coronary wedge pressure during microvascular resistance measurements are described in **Chapter Three**.

Chapter Four introduces us to the diagnostic value of combined pressure and flow measurements and describes a case study of a patient with refractory angina and a single stenosis presenting with a normal FFR but abnormal CFR. By understanding the interplay between the coronary stenosis and microvascular function, the chapter explains how a patient can benefit from percutaneous coronary intervention (PCI) to alleviate symptoms. Despite the

diagnostic value of assessing CFR invasively in patients, the assessment of this parameter, using Doppler flow in particular, is cumbersome for inexperienced operators. This limits the widespread adoption of assessing coronary flow reserve in daily clinical practice. Therefore, in **Chapter Five**, novel concepts of pressure-derived CFR are evaluated against Doppler flow derived CFR for diagnostic and prognostic purposes. In **Chapter Six**, the long-term follow-up in a cohort of stable coronary artery disease patients categorizes them using both CFR and fractional flow reserve measurements.

The first part of this thesis is concluded with **Chapter Seven** looking into the impact of treatment by percutaneous coronary intervention in lesions presenting with discordant CFR and fractional flow reserve measurements by assessing the novel parameter of coronary flow capacity (CFC).

In addition to stable coronary artery disease, microvascular dysfunction plays an indispensable role in the pathophysiology of patients presenting with an acute myocardial infarction. In **Part B** of this thesis we describe the microvascular function in acute coronary syndromes.

Chapter Eight provides an overview of the currently available armamentarium for assessing microvascular function, contemporary strategies to protect the microcirculation and novel insights into the microvascular pathophysiology in the setting of primary percutaneous coronary intervention.

Chapter Nine aims to increase the understanding of the origin of the acute alterations in microvascular function in patients presenting with STEMI, examining stress-related metabolic changes. It investigates the relationship between admission glucose levels and microvascular function in non-diabetic STEMI patients. In **Chapter Ten**, the time course of microvascular function is described in the setting of STEMI using the novel parameter of coronary flow capacity (CFC) that integrates both hyperemic average peak flow velocity and CFR.

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PART A

Coronary Physiology in Chronic Coronary Syndromes

CHAPTER 2

Resting Indices of Coronary Lesion Severity: Not Always as Simple as It Seems

Martijn A. van Lavieren and Jan J. Piek

Circ Cardiovasc Interv. 2016 Apr;9(4):e003747. doi: 10.1161/CIRCINTERVENTIONS.116.003747.

Physiological guided percutaneous coronary intervention (PCI) has been demonstrated to result in a better clinical outcome compared with angiographic guidance alone. [1] Pressure and Doppler-tipped guide wires that can be used for intracoronary physiological assessment were introduced >2 decades ago. Fractional flow reserve (FFR) has emerged as the most widely used physiological index in current clinical practice. This pressure-only index estimates the functional significance of a coronary stenosis by quantifying the trans-stenotic pressure ratio under hyperemic conditions and has been well validated throughout the years.[2][3] However, the prerequisite of inducing stable hyperemia is considered the main practical limitation of FFR measurements that has hampered its embedment in clinical practice.

More recently, nonhyperemic pressure-derived indices were introduced to accommodate the need to further simplify physiological assessment; instantaneous wave-free ratio (iFR) and whole-cycle distal to proximal pressure ratio (Pd/Pa). Both indices make use of a trans-stenotic pressure gradient across a stenosis during resting conditions, obtained with conventional pressure wires and, in case of iFR, appropriate software. iFR assesses the pressure ratio in a particular part of the diastole, the wave-free period, where microvascular resistance is constant and minimal. [4] Thereby, it relies on the same theoretical framework as FFR. Both iFR and whole-cycle Pd/Pa are shown to have equivalent diagnostic accuracy for the detection of ischemia-generating coronary stenoses when compared with FFR. [5]

These non-hyperemic pressure-derived indices rely on smaller differences in trans-stenotic pressure than FFR and are thereby more vulnerable to technical and procedural errors affecting distal and aortic pressure. These errors result in pressure drift that in general becomes overt at the end of the procedure when equality of signals is verified again with the pressure sensor located just inside the guiding catheter. Drift can be observed as an absolute or relative pressure offset between both signals, which can originate from drift of the pressure wire sensor and changes in aortic pressure. It may cause stenosis misclassification, especially when indices values are close to their cutoff values.

In this issue of Circulation: Cardiovascular Interventions, Cook et al report a single-center study in which they quantify the effect of clinically tolerated levels of pressure wire drift on the rates of reclassification with FFR, iFR, and whole-cycle Pd/Pa. [6] They enrolled 447 patients (447 stenoses) who underwent physiological stenosis severity assessments and conducted the measurements in a robust and standardized fashion, that is, by fixing the aortic pressure transducer and eliminating coronary artery spasm by the administration of 300 μg nitroglycerine before the procedure. Aortic and distal pressures were recorded during resting condition and stable hyperemia, using intravenous or intracoronary administration routes for adenosine. At the end of the procedure, pressure drift was checked, and

if found to be >2 mm Hg, the entire recording was repeated. All data were analyzed off-line, and both aortic and wire pressure drifts were assessed, offsetting the pressure trace relative to its original position by 1-mm Hg increments from −2 to +2 mm Hg. FFR, iFR, and Pd/Pa were recalculated for different origins and degrees of pressure drift.

The present study shows that a pressure wire drift of ±2 mm Hg causes stenosis misclassification in all contemporary-used pressure-derived indices, in particular when close to the cutoff value. The effect of drift originating from changes in distal pressure resulted in reclassification in 21%, 25%, and 33% with FFR, iFR, and whole-cycle Pd/Pa, respectively. Both FFR and iFR had significantly lower proportions of misclassification than Pd/Pa. The effect of pressure drift originating from aortic pressure drift yielded similar results. FFR and iFR are reported to be less susceptible to drift than whole-cycle Pd/Pa. The authors further conclude that measurements need to be repeated when drift exceeds ±2 mm Hg.

The present study is the first to assess the impact of drift on stenosis misclassification in a systematic way. The authors address a relevant and important topic of the influence of pressure drift of the sensor-equipped guide wires on the assessment and classification of functional stenosis severity by pressure-only–derived indices. The present study is of particular interest in an era where physiological stenosis severity assessment is shifting toward non hyperemic indices. Several thresholds for pressure drift are proposed and used in core laboratory analyses. [7][8] Core laboratories apply a threshold of ±2 mm Hg, although the present study shows that it already causes severe reclassification. Unfortunately, data on the influence of pressure drift on physiological indices are lacking, and the present study provides valuable insight into a phenomenon frequently encountered by those performing these physiological measurements in clinical practice.

The pressure wire is not always the source of error. Pressure drift can originate from many other sources as presented by Cook et al in Table 1 of their article. Cook et al performed their measurements in a robust methodological fashion, thereby eliminating the likelihood of drift induced on the aortic pressure signal and mainly focused on the drift originating from the pressure wire. However, it is this drift on the aortic pressure signal that, because of procedural errors, should be considered the main source of the observed drift. In particular, the alteration of the pressure transducer height after normalization and not removing the needle guidewire introducer are frequently encountered errors during physiological assessment that affect the aortic pressure signal. With the introduction of nonfixed aortic pressure transducers lying loosely on top of the patient, shifting the transducer by only 3 cm in height, a pressure drift as high as 2 mm Hg is induced originating from the aortic pressure rather than from the pressure wire sensor. However, these rather small procedural errors are often not noticed.

Pressure drift is often depicted as the absolute difference between aortic and distal pressure but can also be assessed as a ratio. The impact of absolute pressure drift on stenosis reclassification may differ depending on the absolute values of mean aortic pressure. For example, in a patient with a mean arterial pressure of 120 mm Hg, the relative influence of a pressure drift of 5 mm Hg, according to the expert consensus, is less than that of a patient with a mean arterial pressure of 90 mm Hg. This effect is of particular interest when hyperemia is induced by means of continuous administration of intravenous adenosine, where often a pronounced decrease in arterial pressure is observed due to systemic vasodilation. It could be postulated that assessing the relative pressure drift is preferred to assessing an absolute drift to accommodate the relative impact of drift on the physiological measurements depending on the mean arterial pressure.

Despite the fact that the ±2 mm Hg threshold for clinically accepted drift is used in core laboratory analyses of numerous studies, the threshold for drift itself has never been a subject of extensive research. The proposed thresholds of clinically acceptable drift range widely. The present study underscores the importance of adhering to the stringent threshold also used in core laboratory analysis. This is of particular importance when the indices are close to the cutoff value, ±0.05 U of their cutoff value, in which the authors report that for iFR and whole-cycle Pd/Pa reclassification occurred in 50.1% and 62.1%, respectively. This indicates that drift cannot be tolerated using non-hyperemic indices that are close to the cutoff value and the ±2 mm Hg might already be too liberal. On the contrary, when values are far away from their cutoff value, drift is unlikely to result in stenosis misclassification.

Evidence for the usefulness of non-hyperemic indices, such as iFR and whole-cycle Pd/Pa, for the assessment of physiological stenosis severity is accumulating. It is conceivable that these indices, because of their ease of use, will be more frequently applied in daily clinical practice. However, the use of resting indices for the evaluation of coronary stenosis severity is not always as simple as it seems. They are more vulnerable for drift, resulting in a marked and clinically significant misclassification, in particular when indices are close to their cutoff value. Physiological assessment should always be performed in a careful and meticulous manner to avoid procedural and technical sources of drift and ensure optimal conditions for clinical decision making.

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CHAPTER 3

Coronary wedge pressure and collateral flow contribution: not a dichotomy!

Martijn A. van Lavieren, Tim P. van de Hoef and Jan J. Piek
Reply by: Murat Sezer

EuroIntervention 2014;9:1485-1488. DOI: 10.4244/EIJV9I12A250

LETTER TO THE EDITOR

By Martijn A. van Lavieren, Tim P. van de Hoef, Jan J. Piek

Dear Editor,

We read with great interest the report by Akdeniz et al, evaluating the impact of percutaneous coronary intervention (PCI) on distal microvascular resistance in patients presenting with non-ST-segment elevation myocardial infarction. [1] The authors are to be congratulated for their extensive effort on this timely topic, since microvascular resistance is increasingly recognised as an important element in the diagnosis and prognosis of acute coronary syndromes. [2][3]

However, since, similar to epicardial coronary arteries, microvascular resistance vessels without tone are known to be pressure-distensible, the finding that hyperaemic microvascular resistance increases upon revascularisation contradicts basic coronary physiological principles, and may well be explained by the methodology applied by the authors. [4][5]

Despite the importance of microvascular resistance as a surrogate of the functional status of the coronary microvasculature, a lively debate continues on the accurate calculation of microvascular resistance from intracoronary measurements of pressure and flow, with or without coronary wedge pressure-based correction for the assumed contribution of collateral flow. Although the authors are correct that collateral flow should optimally be accounted for when assessing an index of microvascular resistance in the presence of collateral flow, the methodology applied by the authors, using wedge pressure as an exclusive measure of collateral flow, is not compatible with its physiological origin, and largely invalidates the conclusions of the present report.

In addition to collateral flow, the magnitude of coronary wedge pressure also depends on venous pressure, heart rate, and ventricular wall stress, and its use as an exclusive measure of collateral flow by definition overestimates the magnitude of actual collateral flow. [6] Collateral flow is absent at wedge pressures below a threshold of 25 mmHg, where it is entirely determined by these chronotropic and inotropic properties of the heart. [7] Furthermore, collateral flow contribution is known to be negligible distal to stenoses with a fractional flow reserve (FFR) >0.68. Therefore, correction of an index of microvascular resistance by means of the coronary wedge pressure generally underestimates the magnitude of actual microvascular resistance, particularly in stenoses with wedge pressure <25 mmHg, and/or FFR >0.6 (Figure 1). The authors report a pre-PCI wedge pressure of 30.5±11.5 mmHg (range 14-44 mmHg), and pre-PCI FFR of 0.64±0.14. Hence, in a substantial part of their patient population, collateral flow was probably absent, for example in the case presented in Figure 1 of the paper by Akdeniz et al.

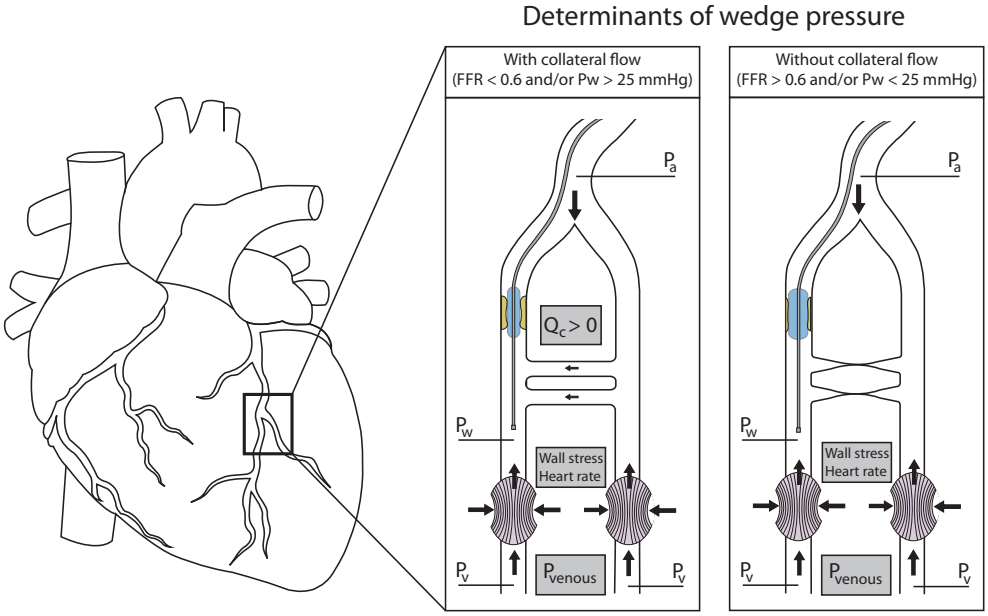

Figure 1. The magnitude of coronary wedge pressure is a result of venous pressure, heart rate, ventricular wall stress, and collateral flow. Hence, its use as an exclusive measure of collateral flow by definition overestimates the magnitude of true collateral flow. FFR: fractional flow reserve, Pa: aortic pressure, Pw: wedge pressure, Pv: venous pressure, Qc: collateral flow

Importantly, the authors applied a rather curious methodology of a coronary wedge pressure-based correction before PCI, while omitting such a correction after PCI. Although this approach was probably governed by the belief that coronary wedge pressure exclusively reflects collateral flow, and that collateral flow would be absent after PCI, the authors have concomitantly neglected the chronotropic and inotropic properties of the heart which obviously influence coronary wedge pressure similarly pre- and post-PCI. Clearly, extracting coronary wedge pressure before PCI and omitting to extract coronary wedge pressure after PCI by definition results in a higher resistance value post-PCI, even in the absence of physiological alterations in the microvasculature.

Although the report by Akdeniz et al illustrates the importance of further investigation on this subject, such investigations should apply a consistent methodology that does not iatrogenically obscure the results and lead to conclusions that are physiologically implausible. Considering the limitations of paramount magnitude associated with the use of coronary wedge pressure as an exclusive measure of collateral flow contribution, we would suggest calculating microvascular resistance without correction for assumed collateral flow, and re-evaluating the findings from a physiological perspective.

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REPLY TO THE LETTER TO THE EDITOR

By Murat Sezer

We thank Dr van Lavieren and colleagues for their interest in our work and for their precious comments. Dr van Lavieren highlights some of the potential limitations of our approach and focuses mainly on the way in which microvascular resistance was calculated in our study. [1] As they very appropriately point out, there is a lively debate going on about the accurate calculation of the microvascular resistance (MR) by using intracoronary pressure and flow measurements in the presence of epicardial stenosis. It can generally be accepted that the assumed contribution of collateral flow should be accounted for and thus coronary wedge pressure (CWP)-based correction for collaterals should be performed when assessing microvascular resistance in the presence of flow-limiting epicardial stenosis (FFR <0.80). [2] On the other hand, there are some inherent limitations in performing CWP-based correction. We agree that the magnitude of CWP not only reflects collateral flow but is also affected by the chronotropic and inotropic properties of the heart. [3] The potential contribution of collateral flow is probably overestimated by incorporating CWP, particularly in patients with elevated wall stress (such as left ventricular hypertrophy). However, these factors produce a rather small effect on CWP in non-hypertrophied (normal) hearts. [3] In particular, CWP is most probably determined by collateral flow when it is above a threshold of 25 mmHg, as the authors point out. In our patient population, while the mean value was reported as 30.5 mmHg, CWP values were above 25 mmHg in 27 of the individual cases (71%). [4] Although the author states that the collateral flow contribution was shown to be negligible distal to the stenosis with an FFR >0.6, it is elegantly reported by the same group in a recent study that there is 16.5+10% overestimation in corrected MR for stenosis with FFR between 0.6 and 0.85. Furthermore, Yong et al demonstrated that corrected MR, which incorporated collateral flow, would be routinely overestimated to some extent by the uncorrected MR when the FFR value was below 0.80. In this latter report, there was almost no difference between corrected and uncorrected MR values when FFR was >0.80. [2] In our study population, there were 13 patients with FFR <0.60, 22 with FFR between 0.60 and 0.80, and only three patients with an FFR value above 0.80. Accordingly, we thought that, before PCI, correction of MR for collaterals by incorporating CWP into the simple formula would be appropriate. Furthermore, besides the haemodynamic significance of epicardial stenosis, it is also known that many factors may affect the magnitude of collateral formation which may contribute to the wide range of CWP values which might be found in patients with an FFR value between 0.60 and 0.80. Therefore, it seems reasonable to us that incorporation of CWP while calculating MR would be appropriate in the presence of haemodynamically significant stenosis (FFR <0.80).

Another important issue raised by the authors concerns the methodology we used in the calculation of MR before (in the presence of haemodynamically significant stenosis) and after PCI (after removal of epicardial stenosis). While we took into account collateral contribution as assessed by CWP in the presence of epicardial stenosis, we did not make correction for collateral flow after PCI with the assumption that establishing antegrade flow by removal of epicardial stenosis would abolish the contribution of collaterals. In a recent paper which showed no effect of PCI on MR in patients with stable angina undergoing PCI, while pre-PCI MR had been calculated with incorporation of CWP, after PCI no correction for collaterals was performed with the same assumption. [6] In that paper, there was also no difference between mean post-PCI MR values calculated with or without CWP-based correction. The most probable reason for indifferent MR values found (corrected or uncorrected) at pre- and post-PCI phases could be the exclusion from that analysis of the patients who developed post-PCI myonecrosis. [6] However, when patients with periprocedural myonecrosis were not excluded from the trials, significant increases in mean post-PCI MR when compared to pre-PCI MR were clearly demonstrated. [7][8] These results are, indeed, in line with our paper in which we showed a significant increase in mean post-PCI MR in patients with non-ST-elevation acute coronary syndrome who developed periprocedural myocardial infarction after PCI.

It is known that post-PCI high MR values are related to higher troponin release and indicative of microvascular injury and loss of capillary integrity that is most probably caused by plaque disruption and distal embolisation following PCI. [8][9][10] Accordingly, marked plaque burden reduction achieved by stent deployment in patients with unstable lesions most likely results in embolisation of plaque contents, which could help to explain our finding that MR increases upon revascularisation of unstable plaques in patients with non-ST-elevation acute coronary syndrome who develop myonecrosis after PCI.

Invasive measurement of microvascular resistance is increasingly recognised as an indispensable tool for interrogating coronary microcirculation. Especially after its prognostic importance became apparent in acute coronary syndrome settings, resolving the continuing controversy in its calculation and applying a consistent methodology across investigations has become more important.

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CHAPTER 4

How should I treat a patient with refractory angina and a single stenosis with normal FFR but abnormal CFR?

Martijn A. van Lavieren, Tim P. van de Hoef, Krischan D. Sjauw and Jan J. Piek
Invited experts: Angela Ferrara, Bernard De Bruyne and K. Lance Gould

EuroIntervention. 2015 May;11(1):125-8. doi: 10.4244/EIJV11I1A23. PMID: 25982657.

CASE SUMMARY

Background: A 66-year-old male with crescendo angina pectoris with persisting disabling angina despite optimal medical therapy. Coronary angiography in the referral hospital showed a stenosis of intermediate severity in the first diagonal branch.

Investigation: Physical examination, electrocardiogram, exercise testing, transthoracic echocardiogram, coronary angiography, functional stenosis severity assessment.

Diagnosis: Depletion of coronary vasodilatory reserve in the presence of a focal stenosis of intermediate severity superimposed on a background of small vessel disease.

Management: Stenting of the stenosis in the diagonal branch to increase vasodilatory reserve.

PRESENTATION OF THE CASE

A 66-year-old male presented to the outpatient clinic of a referral hospital with typical crescendo angina pectoris. His angina markedly limited his physical activity, and was classified as New York Heart Association (NYHA) Class III. Risk factors for coronary artery disease included insulin-dependent diabetes mellitus, hypertension, obesity and smoking. Exercise electrocardiography was positive and showed downsloping ST segments in II, III, AvF, V5, V6. Transthoracic echocardiography demonstrated moderately dilated left and right atria, and a mildly hypertrophic left ventricle with diastolic dysfunction, but normal systolic function. Coronary angiography was performed in the referral hospital because of the positive exercise test, and persistence of disabling angina pectoris despite optimal medical therapy with aspirin 100 mg daily, pravastatin 10 mg daily, bisoprolol 5 mg daily, isosorbide mononitrate 100 mg daily and nifedipine 90 mg daily. Blood pressure at the referral hospital was found to be 194/65 mmHg at a heart rate of 64 beats per minute, his serum glucose level was 11.2 mmol/l and no information was available on total cholesterol, HDL and LDL.

At angiography, a visually intermediate stenosis (50%) in the first diagonal branch was documented. In accordance with the subsequent multidisciplinary Heart Team discussion, the patient was referred to our institution for physiological stenosis severity assessment to guide decision making on potential percutaneous coronary intervention. Cardiac catheterisation was performed according to routine procedures and, accordingly, the patient stopped caffeine intake at least eight hours prior to the procedure. Notably, at cardiac catheterisation, the patient had a blood pressure of 180/75 mmHg at a heart rate of 77 beats per minute. After intracoronary administration of nitroglycerine (200 μg), a ComboWire® (Volcano Corp., San Diego, CA, USA) was positioned distal to the stenosis in the first diagonal branch. A stable Doppler flow signal was acquired by flipping the tip of the ComboWire (Figure 1, Moving image 1), and obtaining the Doppler signal retrogradely. Intracoronary pressure and blood flow velocity were recorded during resting conditions, as well as during hyperaemia induced by the administration of an intracoronary bolus of adenosine (40-60 μg) to obtain the fractional flow reserve (FFR) as well as the coronary flow velocity reserve (CFR).

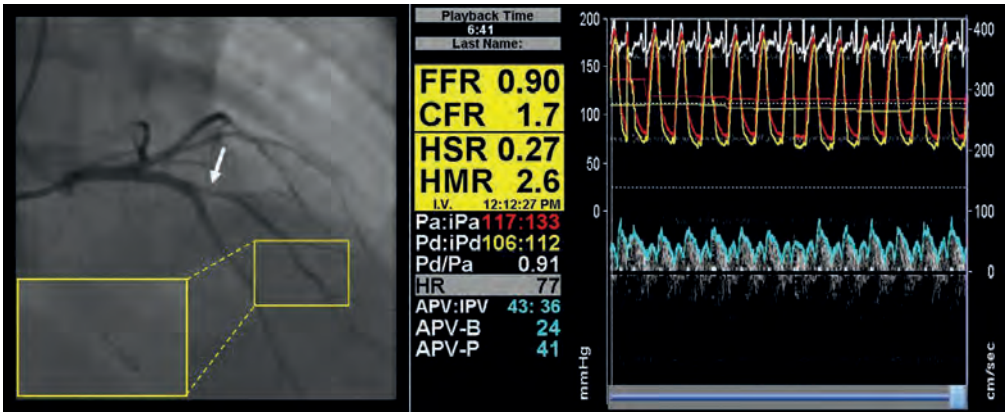

Figure 1. Coronary angiogram showing a visually intermediate stenosis (50%) in the first diagonal branch (white arrow). In addition, combined pressure and Doppler flow velocity recordings were acquired using a ComboWire® (Volcano Corp.) positioned distal to the stenosis. A stable Doppler flow signal was established by flipping the tip of the ComboWire, and obtaining the Doppler signal retrogradely.

Notably, discordant results of FFR and CFR were obtained, where FFR was normal at 0.90 (deferral threshold of >0.80), whereas CFR at 1.7 was vastly below the interventional threshold (deferral threshold of >2.0). Because of these ambiguous results in the presence of typical angina symptoms and inducible ischaemia on exercise ECG, combined pressure and flow velocity parameters, the hyperaemic stenosis resistance index (HSR), defined as the pressure gradient across the stenosis (Pa-Pd) divided by the averaged peak velocity (APV), and the hyperaemic microvascular resistance index (HMR), defined as the distal pressure (Pd) divided by the averaged peak velocity (APV), were additionally evaluated. Both HSR and HMR are readily available on the ComboMap® system (Volcano Corp., San Diego, CA, USA). HSR was found to be low, 0.27 mmHg·cm·s^{-1} (deferral threshold ≤0.8 mmHg·cm·s^{-1}), and HMR was high, 2.6 mmHg·cm·s^{-1} (reference values ranging from 1.85-2.05 mmHg·cm·s^{-1}) Figure 1, Moving image 1). [1-4]

HOW WOULD I TREAT? THE INVITED EXPERT'S OPINION

By Angela Ferrara, Bernard De Bruyne

In this 66-year-old diabetic patient with chest pain, tailored medical therapy should be advocated along with the control of all risk factors, a drastic loss of weight, regular and intense physical exercise, and reassurance of the patient and his family. While stenting of this stenosis would be particularly easy, and even though the placebo effect of "fixing a coronary blockage" cannot be excluded, revascularisation cannot be justified in this patient. The reasons are the following:

1. The truly ischaemic nature of the chest pain is questionable. The invalidating complaints (CCS III) are extremely unlikely to be related to a mild stenosis in a small diagonal branch. The complaints are reported to be "crescendo" suggesting instability of the process, while all clinical data point towards a chronic condition (left ventricular hypertrophy [LVH], diabetes, arterial hypertension [AHT], the morphology of the stenosis in the diagonal branch). The authors themselves were unsure about the nature of the complaints, otherwise one may wonder why a stress test was performed in a patient with four major risk factors and "typical crescendo angina". The results of this stress test should be considered aspecific: no chest pain occurred (while this diabetic patient is reported to have CCS III symptoms), and downsloping ST depressions were observed –a typical finding in LVH– from the inferolateral leads, when they would have been from the anterolateral leads in order to be ascribed to the diagonal branch.
2. There is certainly room to improve the medical therapy: a pressure of 180/80 mmHg and a heart rate of 77 bpm suggest insufficient beta-blockade. The association of long-acting calcium entry blockers should be considered to preclude (paradoxical) vasoconstriction.
3. Revascularisation of lesions with an FFR greater than 0.80 has no prognostic implications, especially not in a small diagonal branch.
4. A CFR value of 1.7 associated with an FFR value of 0.90 indicates largely predominant microvascular disease. The latter is not surprising in the presence of diabetes, obesity, LVH and AHT. An FFR of 0.90 means that optimal stent implantation would increase maximal flow by 10%. In this case CFR would reach 1.87, a value that is still too low to ascertain the absence of ischaemia. In contrast to a common erroneous belief, this has nothing to do with "discordant" values.
5. The long, diffuse infiltration of the stiff-looking mid and distal LAD, a vessel supplying a markedly larger myocardial mass, is actually more concerning than the mild stenosis in the small diagonal branch. Therefore, after measuring the diagonal branch, it would have been interesting to quantify the haemodynamics of the LAD. An abnormal FFR in the LAD would not be surprising, and would justify the placement of a LIMA with its well-known prognostic implications, especially in a diabetic patient.

HOW WOULD I TREAT? THE INVITED EXPERT'S OPINION

By K. Lance Gould

Several aspects of the data imply that the stenosis is physiologically mild and unlikely to be the cause of the symptoms. The pressure gradient is small at rest and during hyperaemia. Flow velocity tracings show no characteristic phasic flow damping expected from a severe stenosis. The flow velocity reserve of 1.7 is not normal but reduced due to either diffuse disease (a pullback pressure tracing is not provided) or microvascular disease, or a mixture of both, or caffeine preventing hyperaemia.

My measurements indicate a 50% diameter stenosis in a small diameter diagonal branch similar in its widest calibre to the guiding catheter, indicating mild stenosis and severe diffuse disease. Stenosis geometry is smooth without evidence of plaque rupture or clot, thereby making transient thrombosis or emboli unlikely, hence stable disease with more favourable prognosis than acute coronary syndromes.

Is the angina truly refractory? The baseline blood pressure of approximately 180/80 mmHg and heart rate of 77/minute indicate suboptimal medical therapy, but medications are not listed. Reducing the pressure-rate product by medications lowers myocardial oxygen demand and reduces symptoms. Both randomised trials and my clinical experience confirm that the vast majority of patients achieve angina relief with combined lifestyle changes plus optimal medical therapy. Additionally, a wide pulse pressure of 100 mmHg in this case warrants exploration for aortic regurgitation or myocardial disease.

Assuming true refractory angina, several mechanisms can explain angina with low flow capacity and no significant pressure gradient: first, coronary spasm superimposed on this mild stenosis; second, diffuse disease together with a mild stenosis; third, vasodilation blunted by residual caffeine; fourth, microvascular disease due to upstream atherosclerosis or primary vasomotor dysfunction.

Before going to the cathlab, I routinely perform quantitative stress PET perfusion imaging in all patients to quantify precisely either adequate or ischaemic low flow in the distribution of every coronary artery or their sub-branches and/or whether quantitative perfusion is globally reduced indicating severe diffuse disease. Caffeine levels are obtained in all my patients undergoing PET, to confirm the precise global and regional coronary flow capacity as a specific reliable indication for PCI or not, on every specific artery or branch.

In my practice, such patients rarely reach the catheterisation laboratory since I am able to distinguish among the above possibilities in the vast majority of cases. In this case, I would have stopped the diagnostic angiogram, done the quantitative PET imaging, ruled out valve disease and adequately treated the patient to lower BP to 120 and HR to 55 or lower. Only then, after review of patient preference, would I have proceeded with percutaneous coronary intervention on the grounds of: i) refractory spasm superimposed on mild structural stenosis paralleling no ischaemia by PET, or ii) mild stenosis superimposed on diffuse disease, where the combined disease may cause ischaemia with insignificant pressure gradient but relief of angina due to improving coronary flow, even modestly, in the face of diffuse disease paralleling globally reduced stress perfusion and CFR by PET.

HOW DID I TREAT? ACTUAL TREATMENT AND MANAGEMENT OF THE CASE

Despite a normal FFR, percutaneous coronary intervention of the intermediate stenosis in the first diagonal branch was performed. The decision was governed by the combination of typical crescendo angina pectoris irresponsive to optimal medical therapy, a vastly positive exercise test highly specific for inducible myocardial ischaemia, and the presence of a low CFR and high HMR, indicating a compromised coronary microvasculature operating at the limits of its vasodilatory reserve. After predilatation at 10 atmospheres, a drug-eluting endothelial progenitor cell-capturing stent (Combo™ Stent; OrbusNeich Medical, Fort Lauderdale, FL, USA) 2.5 mm×13 mm was placed and post-dilated at 14 atmospheres. Post-procedurally, physiological measurements were repeated to evaluate the result of the revascularisation. Blood pressure and heart rate remained unchanged at 190/80 mmHg and 70 beats per minute, respectively. FFR and CFR both improved and were now concordantly normal, with an FFR of 0.96 and a CFR of 2.4. HSR and HMR improved as well, with an HSR of 0.04 mmHg·cm·s^{-1}, and an HMR of 2.0 mmHg·cm·s^{-1} (Figure 2, Moving image 2). According to standard practice, clopidogrel 75 mg daily was added to the patient's medical therapy to establish DAPT.

At one month telephone follow-up, the patient reported relief of his angina symptoms, despite no material changes in his medical therapy. At one-year clinical follow-up, the patient still reported a relief of his anginal symptoms. He now received amlodipine 5 mg daily, doxazosin 4 mg daily, irbesartan 300 mg daily, and hydrochlorothiazide 12.5 mg daily. Nonetheless, his blood pressure remained elevated at 165/75 mmHg at a heart rate of 68 beats per minute. His total cholesterol was 2.6 mmol/l, HDL was 1.1 mmol/l and LDL was 0.9 mmol/l. No information on the serum glucose level was available at time of follow-up.

Discussion

The limitations of coronary angiography to document the functional significance of coronary artery disease have long been recognised, particularly in stenoses of intermediate angiographic severity. As a result, physiological indices are increasingly being used to guide revascularisation. FFR is the most widely used measure of functional stenosis severity in clinical practice, and has been proven to result in superior clinical outcomes compared to angiography-guided revascularisation. [5] FFR aims to estimate the flow-limiting effects of a coronary stenosis by means of coronary pressure measurements, and is reported to be governed by the extent of epicardial disease. Nonetheless, the pivotal FAME II study documented that over 70% of FFR-positive stenoses, e.g., stenoses that require PCI according to contemporary clinical practice guidelines (FFR ≤0.80), do not actually require PCI during the first year of follow-up if revascularisation is initially deferred. Moreover,

the FAME II investigators documented that, in stenoses with a normal FFR (FFR>0.80), although clinical outcome is favourable, a risk for major adverse cardiac events still exists. Hence, despite the notion of strict cut-off value-based FFR-guided decision making in clinical practice guidelines, functional coronary artery disease severity seems to go beyond coronary pressure.

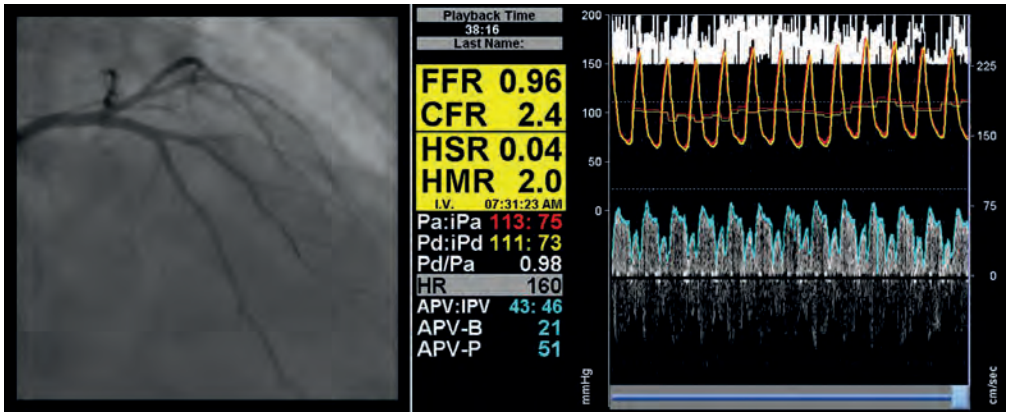

Figure 2. Coronary angiogram showing the visual result after PCI was performed of the intermediate stenosis in the first diagonal branch. In addition, combined pressure and Doppler flow velocity recordings were repeated using a ComboWire® (Volcano Corp.). A stable Doppler flow signal was established by flipping the tip of the ComboWire (Figure 1), and obtaining the Doppler signal retrogradely.

In the light of an increasing recognition of microvascular disease as an important component in the spectrum of coronary artery disease, it is important to recognise that contemporary coronary-pressure-based assessment of the coronary artery disease by means of FFR has two important limitations: 1) a pressure-only parameter such as FFR is by definition unable to identify the relative involvement of the epicardial vessel and the coronary microcirculation, and 2) coronary pressure measurements may be obscured by the effects of microvascular disease on distal coronary pressure. Despite being long neglected as a functional parameter of the coronary vasculature, CFR is increasingly reported as a measure of combined epicardial and microvascular disease severity. The combination of both FFR and CFR was recently reported to provide a comprehensive evaluation of the pathophysiology of coronary artery disease in a specific patient. In particular, the discordance between FFR and CFR is now recognised as occurring from typical pathophysiological patterns, and specifically as resulting from the relative involvement of the epicardial vessel and the coronary microcirculation. However, the interpretation of discordant results between FFR and CFR in order to guide decision making in the catheterisation laboratory may be more difficult.

The clinical relevance of CFR and FFR discordance

By definition, the pressure drop across the stenosis depends on the flow through the stenosis. The pressure drop increases with increasing coronary flow, and vice versa, and a change in flow thus induces a change in distal pressure, and FFR, in the opposite direction of the change in flow, and CFR. Since coronary flow is in turn dictated by microcirculatory resistance, a change in the latter influences CFR and FFR in opposite directions, potentially causing discordant results. Discordance between CFR and FFR is present in 30-40% of stenoses routinely assessed in clinical practice, and yields important information on the epicardial and microcirculatory contribution to blood flow impairment. [3]

Three regions of discordance can be identified by combined measurements of CFR and FFR. [6] The presence of a near normal FFR (roughly 0.95 or greater) with reduced CFR (<2.0) defines pure small vessel or microcirculatory disease. On the other hand, a reduced FFR (≤0.80) with preserved CFR (>2.0) represents a focal epicardial stenosis with adequate flow reserve above ischaemic thresholds and minimal diffuse or microcirculatory disease: a non-flow-limiting epicardial stenosis. Finally, a preserved FFR (>0.80) with reduced CFR (<2.0) represents a moderate focal epicardial stenosis superimposed on a background of severe diffuse and/or microcirculatory disease. In particular, this presence of microcirculatory disease, regardless of epicardial patency, is associated with a significant increase in fatal events at long-term follow-up. [7] The patient in the presented case had several risk factors associated with microcirculatory disease (e.g., diabetes, smoking, arterial hypertension, obesity). [8] The presence of microcirculatory disease was confirmed by advanced physiological assessment, revealing an abnormal CFR with a normal FFR, which is physiologically explained by a physiologically moderate epicardial stenosis (HSR 0.27 mmHg · cm · s^{-1}), superimposed on substantially increased coronary microcirculatory resistance (HMR 2.6 mmHg · cm · s^{-1}), in the presence of increased myocardial oxygen demand by arterial hypertension indicated by a high baseline averaged peak velocity (24 cm/sec).

Contribution of microcirculatory disease: a diagnostic and therapeutic dilemma

In patients with stable angina, microcirculatory disease may contribute to, or even exclusively determine, the occurrence of myocardial ischaemia. It is likely that microcirculatory disease not only impairs the maximal achievable blood flow, but additionally depletes the coronary vasodilatory reserve. In response to the increase in microvascular resistance, the autoregulatory resistance vessels dilate to allow an increased flow into the microvasculature to maintain adequate flow to the myocardium; ischaemia occurs when myocardial oxygen demand exceeds vasodilatory reserve. [1] The presence of epicardial stenosis in addition to microvascular disease makes an even stronger appeal to the vasodilatory reserve, thereby further impairing the ability to adjust myocardial flow to an increase in myocardial oxygen demand. Hence, a depleted vasodilatory reserve secondary to the combined functional

effects of epicardial and microcirculatory disease is likely to result in ischaemia at the slightest increase in myocardial oxygen demand.

The patient described in this case report indeed showed a depleted vasodilatory reserve in the presence of an intermediate coronary stenosis. In addition, this reserve was further compromised by the presence of arterial hypertension, increasing myocardial demand. The effect of epicardial stenosis alleviation on the magnitude of distal microvascular resistance is currently debated, and hence the applicability of mechanical revascularisation of an intermediate stenosis in the presence of predominant microvascular abnormalities can be argued. However, restoration of perfusion pressure is associated with a decrease in the minimal resistance of the microvasculature, and probably partly restores the vasodilatory reserve by alleviation of the strain on the compensatory autoregulatory vasodilation. [9] It must be noted that this area of research is evolving, and that no evidence is available which conclusively supports that reduction of microvascular resistance in this setting is associated with alleviation of myocardial ischaemia and its symptoms. Nevertheless, in this patient with evidence and symptoms of inducible myocardial ischaemia despite optimal medical therapy, hypertension, and substantially increased microvascular resistance, alleviation of an intermediate stenosis was associated with partial alleviation of microcirculatory resistance and an improvement in subjective angina complaints at one month, and one-year follow-up.

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CHAPTER 5

Pressure-derived estimations of coronary flow reserve are inferior to flow-derived coronary flow reserve as diagnostic and risk stratification tools.

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ABSTRACT

Background: Pressure-derived coronary flow reserve (CFR_{pres}) and pressure-bounded CFR (CFR_{pb}) enable simple estimation of CFR from routine pressure measurements, but have been inadequately validated. We sought to compare CFR_{pres} and CFR_{pb} against flow-derived CFR (CFR_{flow}) in terms of diagnostic accuracy, as well as regarding their comparative prognostic relevance.

Methods: We evaluated 453 intermediate coronary lesions with intracoronary pressure and flow measurements. CFR was defined as hyperemic flow/baseline flow. The lower bound (CFR_{pres}) and upper bound of CFR_{pb} were defined as $\sqrt{[(\Delta P_{hyperemia})/(\Delta P_{rest})]}$ and $[(\Delta P_{hyperemia})/(\Delta P_{rest})]$, respectively. Long-term follow-up (median: 11.8 years) was performed in 153 lesions deferred from treatment to document the occurrence of major adverse cardiac events (MACE) defined as a composite of cardiac death, myocardial infarction and target vessel revascularization. CFR<2.0 was considered abnormal.

Results: CFR_{pb} was normal or abnormal in 56.7% of stenoses, and indeterminate in 43.3% of stenoses. There was a poor diagnostic agreement between CFR_{pres} and CFR_{pb} with CFR_{flow} (overall agreement: 45.5% and 71.6% of vessels, respectively). There was equivalent risk for long-term MACE for lesions with abnormal versus normal CFR_{pres} (Breslow P=0.562), whereas vessels with abnormal CFR_{flow} were significantly associated with increased long-term MACE(Breslow P<0.001). For vessels where CFR_{pb} was abnormal or normal, there was equivalent risk for long-term MACE for vessels with abnormal versus normal CFR_{pb} (Breslow P=0.194), whereas vessels with abnormal CFR_{flow} were associated with increased MACE rates over time (Breslow P<0.001).

Conclusions: Pressure-derived estimations of CFR poorly agree with flow-derived measurements of CFR, which may explain the inferior association with long-term MACE as compared to flow-derived CFR.

INTRODUCTION

Coronary flow reserve (CFR) is an established index that interrogates the functional status of both the epicardial and microcirculatory compartments of the coronary circulation. [1] Although CFR is among the most well-studied coronary physiology parameters in terms of ischemic heart disease prognosis, its invasive assessment can be technically challenging. [2] As a result, the pressure-derived fractional flow reserve (FFR) and instantaneous-wave free ratio (iFR) are now dominantly used to guide revascularization decision-making. Nonetheless, novel insights into the multi-level origin of IHD have fueled interest in the combined assessment of FFR and CFR, which allows specific separation between epicardial and microvascular involvement in IHD. [3][4][5][6] Following the technical difficulties of invasive coronary flow assessment, the calculation of CFR from routine coronary pressure measurements has been proposed as an alternative, simpler approach for CFR estimation. [7] Two concepts to estimate CFR from pressure measurements have been studied, the pressure-derived CFR (CFR_{pres}), and the pressure-bounded CFR (CFR_{pb}). [8][9][10][11] Nonetheless, both pressure-derived estimations of CFR have only been validated in small sample sizes, and their prognostic value was not compared to CFR_{flow}. The aim of the present study was to compare CFR_{pres} and CFR_{pb} against CFR_{flow} in terms of diagnostic accuracy, as well as regarding their comparative prognostic relevance in a large cohort of patients with coronary stenoses of intermediate severity.

METHODS

Data source

Between April 1997 and December 2014, we evaluated patients with coronary artery disease (CAD) referred for intracoronary evaluation of at least one intermediate coronary stenosis (40-70% diameter stenosis) in a series of consecutive study protocols. [12][13][14][15][16] Patient and procedural characteristics were entered into a dedicated database. All patients were evaluated in the Academic Medical Center, Amsterdam, The Netherlands (AMC), and Hospital Universitario Clinico San Carlos, Madrid, Spain (HUCSC). Patients with ostial stenoses, culprit vessels of acute coronary syndromes, serial stenoses, severe renal function impairment (MDRD calculated glomerular filtration rate<30mL/min/1.73m2), significant left main coronary artery stenosis, atrial fibrillation, recent myocardial infarction (<6 weeks before screening), prior coronary artery bypass graft surgery, or visible collateral development to the perfusion territory of interest were excluded. The institutional ethics committees approved the study protocols and all patients gave written informed consent.

Cardiac Catheterization and Hemodynamic Measurements

Coronary angiography was performed in a manner suitable for quantitative coronary angiography-analysis (QCA). Intracoronary nitroglycerin (0.2 mg) was given before invasive measurements. In AMC, coronary flow and pressure was assessed sequential using Doppler sensor-equipped and pressure-sensor equipped guide-wires (Philips-Volcano, San Diego, CA). In HUCSC, coronary flow and pressure was assessed simultaneous by guide-wires equipped with temperature-sensitive pressure-sensors (Abbott-St. Jude Medical, St. Paul, MN) utilizing the thermodilution-technique. Pressure-sensors were equalized and normalized with aortic pressure, whereafter sensor-equipped guide-wires were positioned at least three vessel-diameters distal from the stenosis. At AMC, flow and pressure were determined during baseline and at peak hyperemia after intracoronary bolus injection of 20-40 μg adenosine for both the right and left coronary artery systems, and maximal values were averaged over three-heartbeats. At HUSCS, flow and pressure were determined during baseline and maximal stable hyperemia following two minutes of intravenous infusion of adenosine (140 μg/kg/min). After the procedure, sensor-equipped guide wires were pulled-back to the catheter to document pressure-drift. In the occurrence of clinical relevant pressure-drift (>2 mmHg) measurements were repeated.

Data analysis

QCA was performed offline to determine percentage diameter stenosis with the use of validated automated contour detection algorithms. Doppler-derived CFR was defined as the ratio of hyperemic average peak velocity (hAPV) to baseline average peak velocity (bAPV), and thermodilution-derived CFR was defined as the ratio of the hyperemic average mean transit time (T_{mn}-hyp) to baseline average mean transit time (T_{mn}-bas) of three intracoronary bolus injections of saline. Distal coronary and aortic pressure was matched with T_{mn} for each baseline and hyperemic saline injections, and values were averaged. Doppler flow-derived and thermodilution-derived CFR datasets were merged and the term CFR_{flow} was used. CFR_{flow}<2.0 was considered abnormal.

Theory and calculation of pressure-derived CFR and pressure-bounded CFR

The total pressure drop across a stenosis is the sum of viscous friction losses along the entrance and throat of the lesion that increase with flow linearly (Poiseuille's Law), and losses incurred by convective acceleration along the narrowed section (Bernoulli's Law) and increase with the square of flow. The relationship between the flow through a stenosis and the pressure drop over a stenosis is generally described as

$$\Delta P = f \cdot Q + s \cdot Q^2$$

where ΔP is the pressure drop across the stenosis, Q is coronary flow across the stenoses, f is the coefficient of pressure loss due to viscous friction and s is the coefficient of pressure loss due to flow separation. The coefficients f and s are a function of stenosis geometry and rheological properties of blood. [1]

The theory and calculation of pressure-derived estimations of CFR are explained in detail in the supplementary materials. The concept of CFR_{pres} assumes that the stenosis pressure gradient is dominantly determined by separation losses, while the contribution of viscous friction losses is considered negligible. [7] CFR_{pres} can then be calculated as:

$$CFR_{pres} = \sqrt{[(\Delta P_{hyperemia}) / (\Delta P_{rest})]}$$

The concept of CFR_{pb} assumes that the stenosis pressure gradient may either be governed by friction losses alone on one end of the spectrum, or by separation losses on the other end. Thereby CFR_{pb} appraises the lower and upper extreme of CFR_{pb} to bound the range of actual CFR. [10, 11] The lower bound of CFR_{pb} is reflected by the situation where pressure loss across a stenosis arises solely from separation losses and, therefore, equals CFR_{pres}.

$$\text{Lower bound } CFR_{pb} = \sqrt{[(\Delta P_{hyperemia}) / (\Delta P_{rest})]}$$

The upper bound of CFR_{pb} is reflected by the situation where pressure loss across a stenosis arises solely from friction losses. Upper bound CFR_{pb} can then be calculated as:

$$\text{Upper bound } CFR_{pb} = (\Delta P_{hyperemia}) / (\Delta P_{rest})$$

CFR_{pb} can then be bounded as:

$$\sqrt{[(\Delta P_{hyperemia}) / (\Delta P_{rest})]} \leq CFR \leq [(\Delta P_{hyperemia}) / (\Delta P_{rest})]$$

CFR_{pres}<2.0 was considered abnormal. CFR_{pb} was determinate abnormal when both the upper and lower bounds of CFR_{pb} were <2.0, whereas CFR_{pb} was determinate normal when both the upper and lower bound of CFR_{pb} were ≥2.0. In all other cases, CFR_{pb} was indeterminate.

Long-Term Follow-Up

In AMC, 3-, 6-, 12-month, and long-term follow-up was performed by a clinical visit or by telephone contact to document the occurrence of major adverse cardiac events (MACE). MACE was defined as the composite of cardiac death, acute myocardial infarction not

clearly attributable to a non-index vessel, and clinically driven (urgent) revascularization of the index vessel by means of coronary artery bypass graft surgery or PCI. All patient-reported adverse events were verified by evaluating hospital records or contacting the treating cardiologist or general practitioner.

Statistical analysis

Continuous variables are presented as mean±standard deviation (SD) or median+interquartile range and differences between groups were compared with one-way ANOVA or Kruskal-Wallis, as appropriate. Categorical variables are presented as counts(percentages), and were compared with Chi-square test. Correlation between CFR_{pres} and CFR_{flow} was tested by Spearman-Rho and continuous agreement was assessed by Bland-Altman and Passing-Bablok analyses. Classification agreement between CFR_{pres}/CFR_{pb} and CFR_{flow} ($CFR_{Doppler}$ and CFR_{thermo}) were tested by Cohen's kappa. Agreement between $CFR_{Doppler}$ or CFR_{thermo} and CRF_{pb}/CFR_{pres} are visualized in the supplementary materials. Ten-year MACE-rates for normal and abnormal CFR_{pres}/CFR_{pb} and CFR_{flow} were estimated using the Kaplan Meier (KM)-method. Statistical significance of differences in event rates was assessed with the use of the Wilcoxon-Breslow-Gehan test of equality (Breslow *P*). The prognostic value of CFR_{pres}, CFR_{pb} and CFR_{flow} for 10-year MACE was assessed using Cox-regression analyses, adjusted for the effect of relevant clinical characteristics. The best-fit model for adjustment was identified using Akaike's information criterion, where candidate covariates were clinical characteristics (Table 1) and the interrogated vessel. All Cox-proportional hazards models were preceded by verification of the proportional hazard assumption using Schoenfeld's-residuals. Results are presented as standardized-hazard ratios (sHRs) and their 95%-confidence intervals (CIs), which were estimated from the Cox-proportional hazard models by exponentiating the β-coefficient multiplied by the standard deviation (exp[β×SD]). A *P*-value below the 2-sided α-level of 0.05 was considered statistically significant. The Stata 13 (StataCorp LP, College Station, TX) software package was used for all calculations.

RESULTS

Patients

Combined pressure and flow data were obtained in 362 patients (466 stenoses). We excluded 13-stenoses (2.8%) with a resting stenosis pressure drop <1 mmHg, leaving 354 patients (453 stenoses) for analysis; 298 vessels studied with Doppler flow velocity, and 155 vessels studied with thermodilution. Baseline demographic, procedural, and physiological characteristics of the patients are depicted in Table 1. Overall, coronary stenoses were of angiographic and physiologic intermediate severity (diameter stenosis: 53.0±11.2%; FFR: 0.81 (Q1, Q3: 0.72, 0.88).

Table 1: Baseline characteristic and physiologic outcome

	Overall population	MACE analysis
Patients	N = 354	N = 153
Demographics		
Age, years	62 ± 11	61 ± 11
Male gender	264 (74.6)	109 (71.2)
Risk factors for coronary artery disease		
Hypertension	176 (49.7)	59 (38.6)
Hyperlipidemia	217 (61.3)	88 (57.5)
Positive family history	121 (34.2)	76 (49.7)
Cigarette smoking	103 (29.1)	48 (31.4)
Diabetes mellitus	70 (19.8)	24 (15.7)
Prior myocardial infarction	150 (42.4)	57 (37.3)
Prior PCI	113 (31.9)	33 (21.6)
Medication prior to admission		
Beta-blocker	273 (77.1)	119 (77.8)
Nitrates	225 (63.6)	109 (71.2)
Calcium antagonists	232 (65.5)	100 (65.4)
ACE-inhibitors	76 (21.5)	28 (18.3)
Statins	218 (61.6)	86 (56.2)
Aspirin	336 (94.9)	148 (96.7)
Lesions	N = 453	N = 153
Angiographic parameters		
Diameter stenosis (%)	53.0 ± 11.2	52.7 ± 8.3
Mean lumen diameter (mm)	1.30 ± 0.42	1.37 ± 0.39
Reference diameter (mm)	2.88 ± 0.66	2.90 ± 0.62
Physiologic outcome		
P_d/P_a	0.93 (0.88, 0.96)	0.94 (0.91, 0.97)
FFR	0.81 (0.72, 0.88)	0.82 (0.76, 0.88)
Δ*P*-hyperemia (mmHg)	16.0 (10.0, 25.0)	17.0 (11.0, 23.0)
Δ*P*-baseline (mmHg)	7.0 (3.0, 11.0)	6.0 (2.0, 9.0)
Δ-P_d/P_a	0.1 (0.06, 0.16)	0.12 (0.06, 0.16)
CFR_{flow}	2.2 (1.5, 2.7)	2.5 (2.1, 2.9)
$CFR_{pb\ upper\ bound}$	2.3 (1.6, 3.5)	2.9 (2.0, 4.7)
$CFR_{pb\ lower\ bound}$ (CFR_{pres})	1.5 (1.3, 1.9)	1.7 (1.4, 2.2)

Values are mean ± SD or N (%)
PCI = percutaneous coronary intervention, ACE = angiotensin converting enzyme , P_d/P_a = coronary distal-to-aortic pressure ratio, FFR = fractional flow reserve, $\Delta P = P_a - P_d$, Δ-P_d/P_a = (P_d/P_a-FFR), CFR_{flow} = flow-derived coronary flow reserve (CFR), CFR_{pb} = pressure-bounded CFR, CFR_{pres} = pressure-derived CFR

Relationship between CFR_{pres} and CFR_{flow}.

The relationship between CFR_{pres} and CFR_{flow} is shown in Figure 1. There was a modest correlation between CFR_{pres} and CFR_{flow} (ρ=0.44, P<0.001)(Figure 1A). Passing-Bablok analysis revealed a significant constant (Coefficient A: 0.66 (95%-CI: 0.55–0.78)) and proportional (Coefficient B: 0.43 (95%-CI: 0.36–0.50)) difference between the methods. Bland-Altman analyses revealed significant bias of -0.54±0.95 (limits of agreement: -2.41, 1.33)(Figure 1B).

CFR_{pres} was abnormal in 79.5% of stenoses (360 out of 453) and CFR_{flow} was abnormal in 41.5% of stenoses (188 out of 453). CFR_{pres} agreed with CFR_{flow} in 54.5% of stenoses (247 out of 453), of which CFR_{pres} and CFR_{flow} were concordant abnormal in 37.7% of stenosis (171 out of 453) and concordant normal in 16.8% of stenosis (76 out of 453). CFR_{pres} disagreed with CFR_{flow} in 45.5% of stenoses (206 out of 453), of which CFR_{pres} was abnormal and CFR_{flow} normal in 41.7% of stenosis (189 out of 453) and CFR_{pres} normal and CFR_{flow} abnormal in 3.8% of stenosis (17 out of 453). Accordingly, agreement between CFR_{pres} and CFR_{flow} was poor (Cohen's kappa coefficient: CFR_{flow} 0.173 ($CFR_{Doppler}$ 0.187; CFR_{thermo} 0.093)).

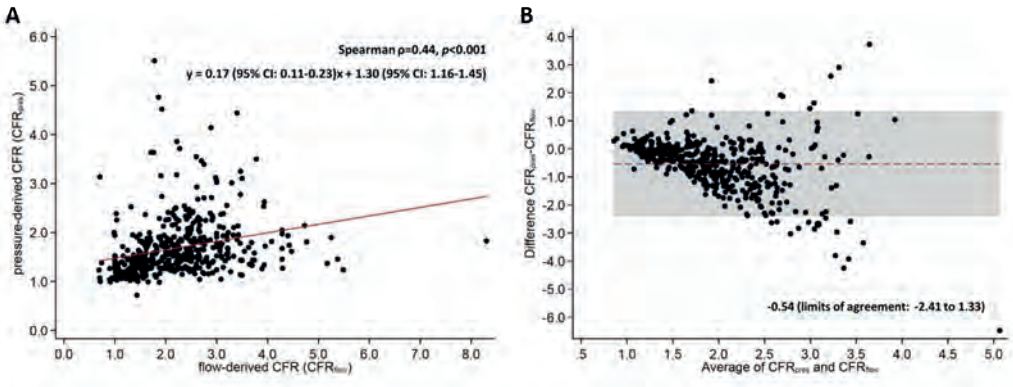

Figure 1 Relationship between pressure-derived coronary flow reserve (CFR_{pres}) and flow-derived CFR (CFR_{flow}); A) Scatterplot of CFR_{pres} and CFR_{flow}, and B) Bland-Altman analysis of agreement for CFR_{pres} and CFR_{flow}.

Relationship between CFR_{pb} and CFR_{flow}.

CFR_{flow} was within the bounds of CFR_{pb} in 44.1% of stenoses (200 out of 453), CFR_{flow} was lower than the CFR_{pb} lower bound in 22.5% of stenoses (102 out of 453), and CFR_{flow} was higher than the CFR_{pb} upper bound in 33.3% of stenoses (151 out of 453)(supplementary table 1).

CFR_{pb} was determinate in 56.7% of stenosis (257 out of 453). Of these, CFR_{pb} was abnormal in 63.8% of stenoses (164 out of 257) and CFR_{flow} was abnormal in 48.6% of stenosis (125 out of 257). CFR_{pb} agreed with CFR_{flow} in 71.6% of stenoses (184 out of 257), of which CFR_{pb} and CFR_{flow} were concordant abnormal in 42.0% of stenosis (108 out of 257) and concordant normal in 29.6% of stenosis (76 out of 257). CFR_{pb} disagreed with CFR_{flow} in 28.4% of stenoses (73 out of 257), of which CFR_{pb} was abnormal and CFR_{flow} normal in 21.8% of stenosis (56 out of 257) and CFR_{pb} normal and CFR_{flow} abnormal in 6.6% of stenosis (17 out of 257)(supplemental table 2). Accordingly, agreement between CFR_{pb} and CFR_{flow} was poor (Cohen's kappa-coefficient: CFR_{flow} 0.436 ($CFR_{Doppler}$ 0.496; CFR_{thermo} 0.242)).

Clinical outcome after deferral of revascularization stratified by CFR_{pres}, CFR_{pb} and CFR_{flow}.

Long-term clinical outcomes were available in 153 patients (182 stenoses) deferred from revascularization, which were enrolled at AMC. In patients with multiple stenoses, one was chosen at random for MACE-analyses, which consequently included 153 patients and 153 stenoses. Median follow-up was 11.8-years (Q1, Q3: 10.0, 13.3 years). Baseline characteristic for these patients are depicted in Table 1. CFR_{flow} was determined by Doppler flow velocity in all 153 patients.

CFR_{pres} was abnormal in 67% of stenoses (103 out of 153), and CFR_{flow} was abnormal in 20.3% of stenoses (31 out of 153). The KM-estimate of MACE for stenoses with abnormal CFR_{flow} was significantly higher than for stenoses with normal CFR_{flow} (CFR_{flow}<2.0: 62.3% vs. CFR_{flow}≥2.0: 32.8%, Breslow *P*<0.001: Figure 2B). Whereas, the KM-estimate of MACE was not significantly different for stenoses with abnormal versus normal CFR_{pres} (CFR_{pres}<2.0: 40.5% vs. CFR_{pres}≥2.0: 37.6%; Breslow *P*=0.562: Figure 2A).

CFR_{pb} was determinate in 55.6% of stenosis (85 out of 153). Of these, CFR_{pb} was abnormal in 41.2% of stenoses (35 out of 86) and CFR_{flow} was abnormal in 20.0% of stenoses (17 out of 85). The KM-estimate of MACE for stenoses with abnormal CFR_{flow} was significantly higher than for stenoses with normal CFR_{flow} (CFR_{flow}<2.0: 72.6% vs. CFR_{flow}≥2.0: 33.8%, Breslow *P*<0.001: Figure 2D). Whereas, the KM-estimate of MACE was not significantly different for stenoses with abnormal versus normal CFR_{pb} (CFR_{pb}<2.0: 47.2% vs. CFR_{pb}≥2.0: 37.6%; Breslow *P*=0.194: Figure 2C).

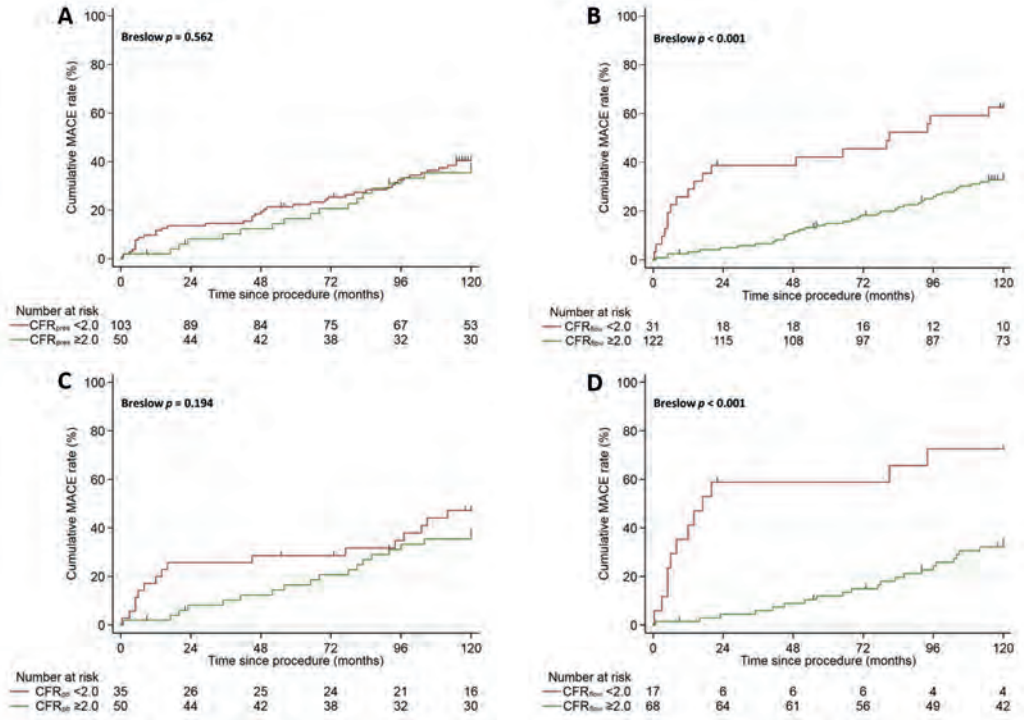

Figure 2 Kaplan Meier estimates of major adverse cardiac event (MACE) rate during 10-years of follow-up, stratified by: A) pressure-derived coronary flow reserve (CFR_{pres}), CFR_{pres} <2.0 was considered abnormal; B) flow-derived CFR (CFR_{flow}); C) pressure-bounded coronary flow reserve (CFR_{pb}); D) CFR_{flow} for vessels with abnormal or normal CFR_{pb}. CFR_{pres},CFR_{pb} and CFR_{flow} <2.0 was considered abnormal.

The best-fit model for adjustment included angiotensin-converting-enzyme inhibitor use, the presence of diabetes mellitus, and age at the time of the index procedure. Cox-proportional hazards models adjusted for these variables demonstrated that, in the overall study population, CFR_{flow} was significantly associated with long-term MACE (CFR_{flow}-sHR: 0.63 (95%-CI: 0.46-0.86), *P*=0.003), whereas lower (CFR_{pres}) and the upper bound of CFR_{pb} were not significantly associated with long-term MACE ($CFR_{pb\ lower\ bound}$ or CFR_{pres}-sHR: 0.83 (95%-CI: 0.60-1.15), *P*=0.262); $CFR_{pb\ upper\ bound}$-sHR: 0.85 (95%-CI: 0.60-1.21), *P*=0.367 (Table 2).

Table 2. Univariate and Adjusted logistic regression analyses for long-term MACE

MACE study population (N=153)				
	Univariate analysis		Adjusted analysis*	
Variable	sHR (95%CI)	*P*-value	sHR (95%CI)	*P*-value
CFR_{flow}	0.64 (0.46-0.88)	0.006	0.63 (0.46-0.86)	0.003
$CFR_{pb\ upper\ bound}$	0.85 (0.61-1.20)	0.364	0.85 (0.60-1.21)	0.367
$CFR_{pb\ lower\ bound}$ (CFR_{pres})	0.84 (0.62-1.15)	0.277	0.83 (0.60-1.15)	0.262

Data presented as standardized hazard ratio and its 95% confidence interval
*adjusted for angiotensin converting enzyme inhibitor use, the presence of diabetes mellitus, and age at the time of physiological assessment.
sHR = standardized hazard ratio; CFR_{flow} = flow-derived coronary flow reserve (CFR), CFR_{pb} = pressure-bounded CFR, CFR_{pres} = pressure-derived CFR

DISCUSSION

The present study demonstrates that pressure-derived estimations of CFR show a poor agreement with actual flow-derived CFR. In addition, both pressure-derived estimates of CFR show no association with long-term MACE, whereas actual CFR_{flow} has a potent association with long-term MACE in the same patient population.

Pressure-derived estimations of CFR: physiological basis of its unreliability

The inaccuracy of pressure-derived estimation of CFR is likely explained by basic physiology. Most importantly, both concepts of pressure-derived estimation of CFR assume that the pressure drop across a stenosis fully explains the impairment in CFR. However, coronary hemodynamics are characterized by an interplay between epicardial conduit arteries and the coronary microcirculation. [4][17] Such interplay determines that changes in coronary pressure gradients from baseline to hyperemic conditions may be induced by opposing changes in coronary flow. Taken into consideration Poiseuille's and Bernoulli's Law ($\Delta P = f \cdot Q + s \cdot Q^2$), a small increase in ΔP from baseline to hyperemic conditions may be governed by dominant microvascular dysfunction precluding an increase in coronary flow in the presence of a moderate coronary stenosis (moderate *f* and *s*; low *Q*) or by a mild stenosis with high coronary flow when microvascular function is normal (low *f* and *s;* high *Q*). *Vice versa*, a large increase in Δ*P* from baseline to hyperemic conditions may result from a large increase in coronary flow in the setting of moderate non-flow-limiting coronary stenosis with normal microvascular function (moderate *f* and *s*; high *Q*) or by a severe flow-limiting stenosis (high *f* and *s*; low *Q)*. These pathophysiological mechanisms may induce similar changes in Δ*P*, but have opposing prognostic implications, which are not reflected in pressure-derived estimations of CFR. [6][18]

Secondly, the concept of CFR_{pres} ($CFR_{pb\ lower\ bound}$) neglects energy losses due to viscous friction, which actually pose an important factor in the occurrence of a pressure drop across a coronary stenosis. Friction losses increase linearly with flow, and depend critically on stenosis diameter and length. Therefore, they play an important role particularly for tight and longer stenoses, and can easily exceed separation losses for severe lesions at low (baseline) flow rates. The theoretical derivation of CFR_{pres} is likely incorrect in such stenoses. Additionally, for mild diffuse stenoses, the baseline pressure gradient may be significant on the basis of significant friction losses, whereas the increase in pressure gradient from baseline to hyperemia may only be small due to low flow separation losses. According to the methodology of CFR_{pb}, the bounds of CFR_{pb} are assumed to be abnormal in such stenoses, while CFR_{flow} actually may be normal. Indeed, our data showed that in stenoses with abnormal CFR_{pb} and normal CFR_{flow} the baseline pressure-gradient was routinely large, whereas the increase in ΔP from baseline to hyperemia was only modest (supplemental table 2). *Vice versa*, for short severe stenoses, the baseline pressure gradient may not be significant due to mild friction losses, whereas the increase from baseline to hyperemic pressure gradient may be large due to high flow separation losses. The bounds of CFR_{pb} are assumed to be normal in such stenoses, while CFR_{flow} actually may be abnormal. Accordingly, our data showed that in stenoses with normal CFR_{pb} and abnormal CFR_{flow}, the baseline pressure-gradient was routinely small, whereas the increase in ΔP from baseline to hyperemia was large (supplemental table 2). [8] The relative contribution of viscous friction and flow separation losses on the pressure gradient and coronary flow as well as their prognostic implications warrant further studying.

Third, the poor diagnostic accuracy between $CFR_{pres,}$ CFR_{pb} and CFR_{flow} could partly be explained by changes in stenosis geometry between baseline and hyperemic conditions, as pressure-derived estimations of CFR assume that the *f* and *s* coefficients remain equal in resting and hyperemic conditions. [19] This hypothesis supports the fact that pressure-derived CFR provided a substantially better estimation of CFR_{flow} in fluid dynamic modeling with fixed stenoses than in animal studies. Changes in geometry have been attributed to paradoxical vasoconstriction distal to the stenosis, or the presence of collapsible stenoses. [20][21] Yet, although potentially clinically relevant, it remains unclear to what extent alterations in stenosis geometry affect hemodynamic indices.

Comparison with previous studies

CFR_{pres} was initially validated by computational fluid-dynamics modeling and in an in-vitro bench study, which yielded favorable relationships between CFR_{pres} and $CFR_{flow.}$[7] Subsequent in-vivo validation in an animal model (29 stenoses) and humans (34 stenoses) using Doppler flow velocity-derived CFR revealed a significant correlation between both methods. [9] However, an additional validation in humans (38 stenoses) using coronary thermodilu-

tion-derived CFR, revealed that CFR_{pres} systemically underestimated CFR. [8] Zimmermann and colleagues validated the concept of CFR_{pb} and studied the prognostic value of CFR_{pb} in lesions with normal FFR (FFR≥0.75) included in the Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis (DEFER) trial. In a small patient subset of 64 stenoses, the authors demonstrated a diagnostic agreement with CFR_{flow} of 84% with thermodilution-derived CFR, but documented no significant differences in MACE or angina burden between lesions with normal or abnormal $CFR_{pb.}$ [10] Ahn and colleagues studied the prognostic implications of CFR_{pb} in 5029 lesions, and documented that CFR_{pb} yields no incremental prognostic value over FFR. Hence, the authors conclude that CFR fails to independently predict the risk of cardiac events. [11] However, these conclusions focusing on prognostic value of CFR_{pb} and extrapolating these results to overall CFR_{flow} have followed before a proper validation of CFR_{pb} with CFR_{flow} was performed. We documented poor diagnostic agreement between CFR_{pres} or CFR_{pb} and CFR_{flow}. Following the poor diagnostic agreement, we documented a poor association between CFR_{pres} or CFR_{pb} and long-term MACE, whereas CFR_{flow} provided substantial prognostic information in the same patient cohort.

Clinical implications

Simultaneous FFR and CFR measurements have been shown to provide incremental prognostic value over sole FFR measurements, and may augment identification of stenoses most-likely to benefit from PCI. [22][23][24][25] The present study, representing the largest cohort of patients with intermediate CAD to study the relationship between CFR_{pres}, CFR_{pb} and $CFR_{flow,}$ unequivocally documents a poor diagnostic agreement between CFR_{flow} with CFR_{pb}, which translates in the absence of prognostic value of $CFR_{pb,}$ whereas CFR_{flow} provides substantial prognostic value in the same patient cohort.

Limitations

First, the relatively small-sample size limits the statistical power of the MACE-analyses. Secondly, the assessment of adverse-events was partly performed by telephone contact. Such an approach is sensitive towards patient recall-bias, which may result in under-reporting of adverse events. Nonetheless, the long-term MACE-rates reported in the present study are comparable with those reported previously. Thirdly, the present study compromises pooled-data from Doppler flow and thermodilution-derived CFR, and it should be noted that there is only modest agreement between CFR derived from both techniques. [26] This is also reflected by a different, yet overall poor, agreement of CFR_{pres}/CFR_{pb} with the two techniques, of which $CFR_{Doppler}$ shows superior classification agreement. Nonetheless, based on the theoretical limitations as outlined in this manuscript, neither CFR_{pres} nor CFR_{pb} should be used as a reference standard to compare $CFR_{Doppler}$ with CFR_{thermo}. Fourthly, in the present study we excluded lesions with P_d/P_a of 1.00. However, CFR_{pb} may inherently

be less accurate in cases of small resting pressure gradients where effects of pressure drift are most pronounced. Finally, potential unrecognized biological variation when matching pressure and flow data may induce disagreements between CFR_{flow} and CFR_{pres}/CFR_{pb}, which applies to the Doppler-cohort, where pressure and flow velocity were obtained by sequential measurements, and thermodilution-cohort, where extended measurement periods are required throughout a variable hyperemic plateau phase. Yet, the comparable poor agreement in both cohorts supports the understanding that such variability does not drive the outcomes of the present study.

CONCLUSION

Pressure-derived estimations of CFR agree poorly with flow-derived measurements of CFR, which may explain the inferior association with clinical outcomes as compared to flow-derived CFR. The inaccuracy of pressure-derived estimations of CFR means that there is no place for these indices in contemporary diagnostic strategies or scientific efforts towards multimodality assessment of the coronary circulation.

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CHAPTER 6

Physiological Basis and Long-Term Clinical Outcome of Discordance Between Fractional Flow Reserve and Coronary Flow Velocity Reserve in Coronary Stenoses of Intermediate Severity

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ABSTRACT

Background: Discordance between fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) may reflect important coronary pathophysiology but usually remains unnoticed in clinical practice. We evaluated the physiological basis and clinical outcome associated with FFR/CFVR discordance.

Methods and Results: We studied 157 intermediate coronary stenoses in 157 patients, evaluated by FFR and CFVR between April 1997 and September 2006 in which revascularization was deferred. Long-term follow-up was performed to document the occurrence of major adverse cardiac events: cardiac death, myocardial infarction, or target vessel revascularization. Discordance between FFR and CFVR occurred in 31% and 37% of stenoses at the 0.75, and 0.80 FFR cut-off value, respectively, and was characterized by microvascular resistances during basal and hyperemic conditions. Follow-up duration amounted to 11.7 years (Q1–Q3, 9.9–13.3 years). Compared with concordant normal results of FFR and CFVR, a normal FFR with an abnormal CFVR was associated with significantly increased major adverse cardiac events rate throughout 10 years of follow-up, regardless of the FFR cut-off applied. In contrast, an abnormal FFR with a normal CFVR was associated with equivalent clinical outcome compared with concordant normal results: ≤3 years when FFR <0.75 was depicted abnormal and throughout 10 years of follow-up when FFR ≤0.80 was depicted abnormal.

Conclusions: Discordance of CFVR with FFR originates from the involvement of the coronary microvasculature. Importantly, the risk for major adverse cardiac events associated with FFR/CFVR discordance is mainly attributable to stenoses where CFVR is abnormal. This emphasizes the requirement of intracoronary flow assessment in addition to coronary pressure for optimal risk stratification in stable coronary artery disease.

What is known

- Fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) have an equivalent diagnostic accuracy for inducible myocardial ischemia.
- FFR and CFVR provide discordant results in 30% to 40% of cases, which was proposed to originate from a divergent distribution of epicardial and microvascular involvement in coronary artery disease, thus reflecting important coronary pathophysiology.

What this study adds

- Discordance of CFVR with FFR is characterized by the magnitude of coronary microvascular resistance during basal and hyperemic conditions, implicating a pivotal role of the coronary microvasculature in the physiologically guided identification of coronary artery disease severity.
- Discordance of FFR and CFVR is associated with adverse outcome compared with cases where FFR and CFVR are concordantly normal.
- The adverse outcome of discordance between FFR and CFVR compared with cases in which FFR and CFVR are normal is particularly attributable to those cases where FFR is normal but CFVR is abnormal, whereas discordance with an abnormal FFR and a normal CFVR is predominantly associated with equivalent clinical outcome compared with concordantly normal FFR and CFVR.

INTRODUCTION

Because the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study demonstrated that fractional flow reserve (FFR) [1]–guided coronary revascularization results in better clinical outcomes compared with angiographic guidance, coronary pressure–based evaluation of the functional severity of coronary stenoses has emerged as a routine diagnostic strategy in clinical practice [2][3] Nonetheless, the impact of a coronary stenosis on myocardial perfusion may alternatively be quantified by the coronary blood flow–derived coronary flow velocity reserve (CFVR). [4] Despite the fact that the diagnostic accuracy of FFR and CFVR is known to be equivalent, [5] FFR and CFVR results are discordant in 30% to 40% of coronary stenoses [6][7]: a phenomenon proposed to originate from divergent distribution of epicardial and microvascular involvement in coronary artery disease (Figure 1).[8][9]

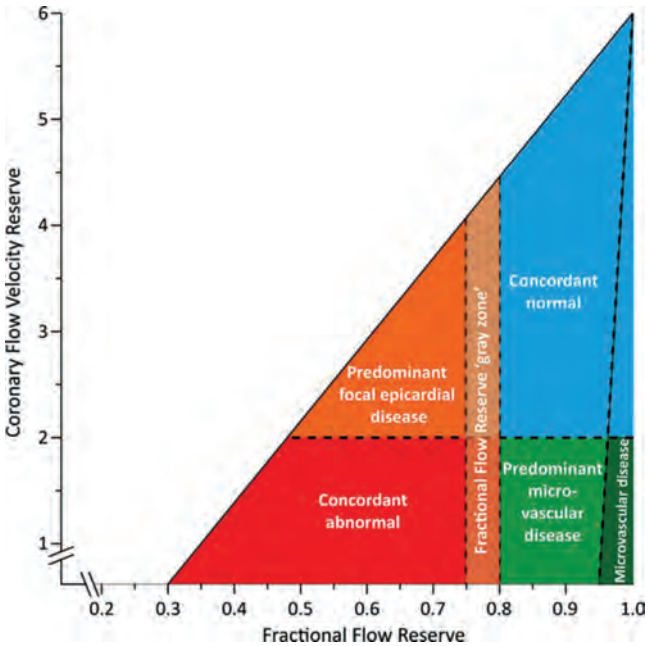

Figure 1: Conceptual plot of the fractional flow reserve (FFR)–coronary flow velocity reserve (CFVR) relationship. Four main quadrants can be identified by applying the clinically applicable cut-off values for FFR and CFVR, indicated by the dotted lines. Patients in the upper right blue area are characterized by concordantly normal FFR and CFVR, and patients in the red lower left area are characterized by concordantly abnormal FFR and CFVR. Patients in the upper left orange area and lower right light green area are characterized by discordant results between FFR and CFVR, where the combination of an abnormal FFR and a normal CFVR indicates predominant focal epicardial, but nonflow-limiting, coronary artery disease, and the combination of a normal FFR and an abnormal CFVR indicates predominant microvascular involvement in coronary artery disease. The small dark green region in the lower right is characterized by an FFR near 1 and an abnormal CFVR, indicating sole involvement of the coronary microvasculature. The FFR gray zone indicates the equivocal 0.75 to 0.80 FFR range.

Daily practice is likely governed by a combination of epicardial and microvascular involvement, where the extent of microvascular involvement remains elusive to the interventionalist when only coronary pressure is assessed. This diagnostic gap is important because microvascular disease is increasingly recognized as an essential component in the spectrum of ischemic heart disease, [10] particularly its prognosis.[11][12][13] Moreover, the presence of microvascular disease may unaccountably obscure the information on functional epicardial stenosis severity derived from coronary pressure measurements. [14] Although the combined assessment of coronary pressure and flow velocity may enable detailed evaluation of the hemodynamic consequences of abnormalities throughout the coronary vasculature, there is a paucity of data on the physiological basis, as well as the clinical pertinence of discordance between the coronary pressure–derived FFR and the coronary flow–derived CFVR. The aim of the present study was to document the intracoronary hemodynamic characteristics that delineate discordance between FFR and CFVR and to evaluate long-term clinical outcome after deferral of revascularization in coronary stenoses with discordant FFR and CFVR results compared with coronary stenoses in which FFR and CFVR results are concordantly normal.

METHODS

Data source

Between April 1997 and September 2006, we evaluated patients with stable coronary artery disease referred for intracoronary evaluation of ≥1 intermediate coronary artery stenosis (40%–70% diameter stenosis at visual assessment). These patients were enrolled in a series of study protocols, [6][7][15][16] and patient and procedural characteristics were entered into a dedicated database. The study protocols excluded patients with ostial stenoses, serial stenoses, severe renal function impairment (glomerular filtration rate calculated according to the modification of diet in renal disease formula <30mL/min per 1.73 m2), significant left main coronary artery stenosis, atrial fibrillation, recent myocardial infarction (<6 weeks before screening), prior coronary artery bypass graft surgery, or visible collateral development to the perfusion territory of interest. The institutional ethics committee approved the study procedures, and all patients gave written informed consent.

Study Procedures and Subsequent Treatment

Coronary angiography was performed according to standard clinical practice, during which angiographic images were obtained in a manner suitable for quantitative coronary angiography analysis. Quantitative coronary angiography analysis was performed offline to determine percentage diameter stenosis with the use of a validated automated contour detection algorithm (QCA-CMS version 3.32, MEDIS, Leiden, The Netherlands). At the

start of the procedure, intracoronary pressure was measured with a 0.014" pressure sensor equipped guidewire (Volcano Corp, San Diego, CA). Coronary blood flow velocity was subsequently measured with a 0.014" Doppler crystal equipped guidewire (Volcano Corp, San Diego, CA). Hyperemia was induced by an intracoronary bolus of adenosine (20–40 μg).

Revascularization of the intermediate coronary stenosis was performed at the discretion of the operator. Decisions on further treatment and medication during follow-up were entirely left to the discretion of the treating cardiologist

Long-Term Follow-up

Three-, 6-, 12-month, and long-term follow-up was performed by a clinical visit or by telephone contact to document the occurrence of major adverse cardiac events (MACEs). MACE was defined as the composite of cardiac death, acute myocardial infarction not clearly attributable to a nontarget vessel, and clinically driven (urgent) revascularization of the target vessel by means of coronary artery bypass graft surgery or percutaneous coronary intervention (PCI). All patient-reported adverse events were verified by evaluating hospital records or contacting the treating cardiologist or general practitioner.

Data Analysis

FFR was calculated as the ratio of mean distal coronary pressure to mean aortic pressure during maximal hyperemia and was evaluated at both the ischemic cut-off value of 0.75, where FFR <0.75 was considered abnormal, [17][18] and the clinically adopted cut-off value of 0.80, where FFR ≤0.80 was considered abnormal. [3][17] CFVR was calculated as the ratio of hyperemic to basal average peak blood flow velocity distal to the target stenosis, and CFVR <2.0 was considered abnormal. [17] We additionally determined the hyperemic stenosis resistance index, [6] defined as the ratio between the pressure drop across the stenosis and distal average peak blood flow velocity, as well as the microvascular resistance (MR) index, [8] defined as the ratio of mean distal coronary pressure to distal average peak blood flow velocity, which was determined during basal conditions (basal MR [BMR]) and hyperemia (hyperemic MR [HMR]). The MR reserve was defined as the absolute difference between BMR and HMR.

Statistical Analysis

In the presence of multiple coronary stenoses of intermediate severity, one of the intermediate stenoses was randomly marked the index-stenosis and was used for subsequent analyses. Event rates at 1, 3, 5, and 10 years of follow-up were estimated using the Kaplan–

Meier method. Relative risks (RRs) were calculated as the ratio of Kaplan–Meier–estimated event rates at each time point. The 95% confidence interval for the RR was calculated by calculating the SE of the logarithm of the RR with a Taylor approximation, that is, as $(SE(RR))^2/(RR)^2$, and its 95% confidence interval. The latter was then exponentiated to obtain the 95% confidence limits of the RR. The statistical significance of differences in event rates between groups was assessed with the use of the log-rank test. The distribution of FFR and CFVR values was assessed using the Shapiro–Wilk statistic to assess normality of the distribution and the Hartigan dip test to assess unimodality of the distribution. Between groups, continuous variables were compared with Student t test or Mann–Whitney U test, according to their normal or skewed distribution, and categorical variables were compared with χ^2 or Fisher exact test, as appropriate. Trend analyses across concordance and discordance groups were computed, where overall differences were compared with 1-way ANOVA, Kruskal–Wallis, χ^2 or Fisher exact test, followed by post hoc t test, Mann–Whitney U or Fisher exact test, with Bonferroni-adjusted significance level. Variables are presented as mean (±SD), median (25th–75th percentile), or frequency (percentage), where appropriate. A *P* value below the 2-sided α-level of 0.05 was considered statistically significant. The STATA 13.1 statistical software package (StataCorp, College Station, TX) was used for all calculations.

RESULTS

Patient population

In a total of 214 patients, both coronary pressure and flow velocity were determined distal to 279 coronary stenoses. Follow-up was obtained in 209 of 214 patients (97.7%), with 273 of 279 stenoses (97.8%). In the other 5 patients (2.3%) no procedural and postprocedural data were available. PCI was deferred in 157 of 209 patients (75.1%), with 186 coronary stenoses (68.1%), 29 of which were considered nonindex stenoses and were discarded for the current analyses. Therefore, the final study population consisted of 157 patients, with 157 coronary stenoses in which revascularization was deferred. The clinical characteristics of the final study population are shown in Table 1. Table I in the Data Supplement depicts the clinical, angiographic, and physiological characteristics of all patients in whom follow-up was obtained stratified by revascularization (PCI group) or deferral of revascularization (Defer group), as well as the angiographic and physiological characteristics of the index stenoses.

Table 1. Baseline Characteristics of the Final Study Population

No. of Patients	157
Demographics	
Age, y	60±13
Male	112 (71)
Coronary risk factors	
Hypertension	61 (39)
Hyperlipidemia	91 (58)
Positive family history	77 (49)
Cigarette smoking	49 (31)
Diabetes mellitus	25 (16)
Prior myocardial infarction	58 (37)
Prior coronary intervention	35 (22)
Medication at hospital admission	
β-Blocker	123 (78)
Nitrates	113 (72)
Calcium antagonists	103 (66)
ACE-inhibitors	29 (19)
Lipid-lowering drugs	90 (57)
Aspirin	152 (97)

ACE indicates angiotensin-converting enzyme.

The mean age of the final study population was 60±13 years, and 71% of patients were men. The median follow-up duration amounted to 11.7 years (9.9–13.3 years). Figure 2A through 2C show the distribution of FFR and CFVR values across the study population. Both FFR and CFVR showed a normal (Shapiro–Wilk statistic: 0.97 and 0.94, respectively), and unimodal distribution (dip 0.026, P=0.75 and dip 0.022, P=0.91, respectively).

Frequency and Clinical Characteristics of FFR/CFVR Discordance

Using a cut-off value of <0.75 to indicate an abnormal FFR, [18] a stenosis yielding discordant results between FFR and CFVR was present in 30.6% of patients (48 of 157), with FFR ≥0.75 and CFVR <2.0 in 14.0% (22 of 157) and FFR <0.75 and CFVR ≥2.0 in 16.6% of patients (26 of 157). Using the clinically adopted cut-off value of ≤0.80 to indicate an abnormal FFR, [3][19][20][21] a stenosis yielding discordant results between FFR and CFVR was present in 36.9% of patients (58 of 157), with FFR >0.80 and CFVR <2.0 in 6.4% of patients (10 of 157) and FFR ≤0.80 and CFVR ≥2.0 in 30.6% of patients (48 of 157). Table II in the Data Supplement depicts the demographic and clinical characteristics of the study population according to FFR and CFVR concordance and discordance at the 0.75 FFR

cut-off value, as well as at the 0.80 FFR cut-off value. No pertinent differences in clinical characteristics were present between groups, regardless of the cut-off value used to depict abnormal FFR.

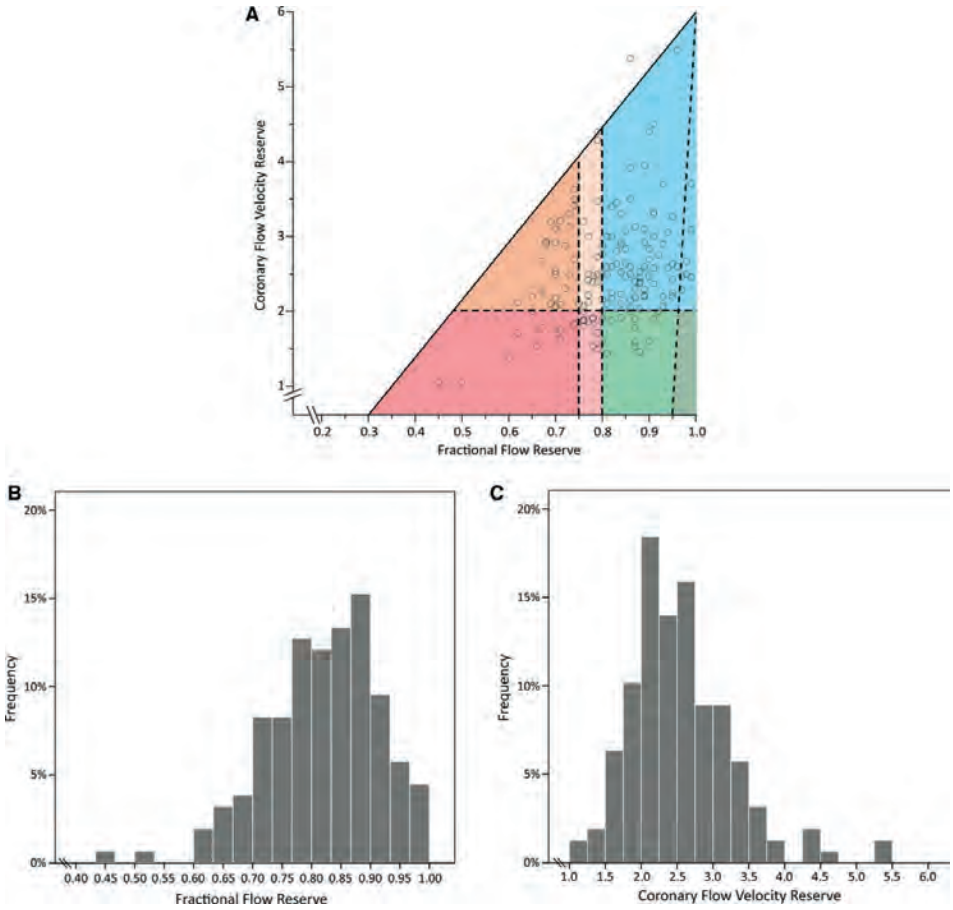

Figure 2: Distribution of fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) values across the study population. A, Scatterplot of FFR and CFVR values, (B) distribution of FFR, and (C) distribution of CFVR.

FFR/CFVR Discordance in Relation to the Magnitude of Stenosis and Microvascular Resistance

Table 2 depicts the angiographic and physiological characteristics of the study population according to concordance and discordance at the 0.75 FFR cut-off value, as well as at the 0.80 FFR cut-off value. Discordance between FFR and CFVR among stenoses with equivalent epicardial disease, as identified by FFR, was characterized by the magnitude of MR

Table 2. Procedural Characteristics According to Concordant and Discordant Groups by the 0.75 and 0.80 FFR Cut-Off Value

	FFR 0.75 Cut-Off					FFR 0.75 Cut-Off				
	Concordant Normal	Discordant		Concordant Abnormal		Concordant Normal	Discordant		Concordant Abnormal	
	FFR ≥0.75 CFVR ≥2.0	FFR ≥0.75 CFVR <2.0	FFR <0.75 CFVR ≥2.0	FFR <0.75 CFVR <2.0	Overall P value	FFR >0.80 CFVR ≥2.0	FFR >0.80 CFVR <2.0	FFR ≤0.80 CFVR ≥2.0	FFR ≤0.80 CFVR <2.0	Overall P value
	(n=100]	(n=22)	(n=26)	(n=9)		(n=78)	(n=10)	(n=48)	(n=21)	
LAD	50 (50)	8 (36)	18 (69)	6 (67)	0.1	35 (45)	4 (40)	33 (69)	10 (48)	0.05
LCX	22 (22)	10 (45)*,†	3 (12)b	0 (0)§	0.01	20 (26)	2 (20)	5 (10)	8 (38)	0.06
RCA	28 (28)	4 (18)	5 (19)	3 (33)	0.62	23 (29)	4 (40)	10 (21)	3 (14)	0.3
Diameter stenosis, %	53 (45–57)	52 (47–56)	54 (52–57)	61 (55–66)	0.046	52 (45–57)	53 (48–53)	54 (50–57)	55 (49–63)	0.39
Reference diameter, mm	3.0 ± 0.7	2.9 ± 0.4	2.8 ± 0.6	2.6 ± 0.7	0.31					
Minimal lumen diameter, mm	1.4 (1.1–1.7)†	1.3 (1.2–1.5)†	1.2 (1.1–1.3)	1.0 (0.9–1.0)‡,§	0.003	1.5 (1.1–1.7)†	1.4 (1.3–1.4)	1.3 (1.1–1.50	1.1 (1.0–1.3)	0.04
FFR	0.86 (0.81–0.91)*,†,§	0.80 (0.78–0.87)*,†,‡	0.70 (0.68–0.73)‡,§	0.66 (0.60–0.71)‡,§	<0.001	0.89 (0.85–0.93)*,†	0.87 (0.84–0.88)*,†	0.74 (0.70–0.78)‡,§	0.76 (0.67–0.78)‡,§	<0.001
CFVR	2.6 (2.3–3.0)†,§	1.8 (1.6–1.9)*,‡	2.7 (2.2–3.1)†,§	1.6 (1.4–1.8)*,‡	<0.001	2.6 (2.3–3.1)†,§	1.7 (1.5–1.9)*,‡	2.5 (2.2–3.1)†,§	1.8 (1.5–1.9)*,‡	<0.001
HSR, mmHg/cm per second	0.31 (0.19–0.48)*,†,§	0.52 (0.36–0.70)*,‡	0.79 (0.67–0.89)‡,§	0.78 (0.61–0.94)‡	<0.001	0.26 (0.16–0.39)*,†	0.34 (0.25–0.49)*,†	0.70 (0.50–0.81)‡,§	0.67 (0.55–0.80)‡,§	<0.001
BMR, mmHg/cm per second	6.29 (5.00–8.00)†,§	4.71 (3.81–6.07)‡	6.52 (4.25–7.45)†	3.60 (2.80–4.18) *,‡	<0.001	6.50 (5.06–7.92)†,§	4.91 (4.15–5.29)‡	6.29 (4.20–7.73)†	3.90 (3.41–4.82)*,‡	<0.001
HMR, mmHg/cm per second	2.08 (1.67–2.63)*	2.29 (1.83–2.81)*,†	1.73 (1.43–1.99)‡,§	1.52 (1.31–1.88)§	0.001	2.08 (1.78–2.63)*	2.51 (2.05–2.96)	1.83 (1.32–2.27)	1.88 (1.42–2.32)	0.01
MR reserve, mmHg/cm per second	4.17 (3.06–5.39)†,§	2.26 (1.91–2.99)*,‡	4.61 (3.23–5.38)†,§	2.06 (1.40–2.21)*,‡	<0.001	4.27 (3.23–5.37)†,§	2.26 (1.98–2.74)*,‡	4.56 (2.91–5.57)†,§	2.06 (1.59–2.68)*,‡	<0.001
h-Pa, mmHg	93 (86–102)	93 (85–100)	91 (82–99)	97 (90–100)	0.77	93 (86–103)	90 (85–101)	91 (86–100)	95 (90–100)	0.99
b-Pd, mmHg	92 (85–102)	91 (79–99)	86 (80–96)	90 (71–98)	0.12	94 (87–102)	89 (85–109)	87 (82–97)	90 (78–98)	0.06
h-Pd, mmHg	81 (74–89)*,†,§	74 (68–81)*,†,‡	64 (60–70)‡,§	61 (50–71)‡,§	<0.001	82 (76–91)*,†	79 (75–88)*,†	68 (63–76)‡,§	71 (61–73)‡,§	<0.001

h-ΔP, mmHg	12 (9–18)*,†,§	17 (12–22)*,†,‡	27 (24–31)‡,§	31 (28–36)‡,§	<0.001	11 (7–14)*,†	12 (10–15)*,†	24 (21–30)‡,§	23 (21–30)‡,§	<0.001
b-APV, cm/s	15 (11–19)†,§	19 (14–26)*,‡	14 (11–18)†,§	25 (21–31)*,‡	<0.001	15 (12–18)†,§	20 (16–27)‡	14 (11–20)†	21 (17–28)*,‡	<0.001
h-APV, cm/s	38 (31–49)	34 (26–43)	38 (31–46)	39 (33–53)	0.41	38 (31–48)	36 (25–45)	36 (30–51)	36 (30–44)	0.69

APV indicates average peak flow velocity; BMR, basal microvascular resistance; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HSR, hyperemic stenosis resistance index; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; Pa, aortic pressure; Pd, distal coronary pressure; ΔP, pressure drop across the stenosis; and RCA, right coronary artery.
*P<0.05 versus discordant CFVR normal FFR abnormal; †P<0.05 versus concordant abnormal; ‡P<0.05 compared with concordant normal; and §P<0.05 versus discordant CFVR abnormal and FFR normal.

during basal conditions (BMR). Both among stenoses with FFR ≥0.75, and among stenoses with FFR <0.75, BMR was significantly lower when CFVR was abnormal compared with when CFVR was normal (P<0.001 for both; Table 2). Notably, a low BMR was associated with a high basal average peak blood flow velocity (Table 2). Similar results were observed at the 0.80 FFR cut-off value (Table 2).

Discordance between FFR and CFVR among stenoses with similar coronary flow reserve was characterized by the magnitude of MR during hyperemic conditions (HMR). Both among stenoses with CFVR ≥2.0, and among stenoses with CFVR <2.0, HMR was significantly lower when FFR <0.75 (P=0.015 and P=0.042, respectively; Table 2). Similar results were observed at the 0.80 FFR cut-off value (Table 2).

The 2 groups in which FFR and CFVR were discordant were characterized by divergence of hyperemic stenosis resistance index, BMR, HMR, and MR reserve (Table 2).

Clinical Outcome After Deferral of Revascularization in Lesions With FFR/CFVR Discordance

Table III in the Data Supplement shows the incidence of MACE and its components among patients in the different concordance and discordance groups at 1, 3, 5, and 10 years of follow-up. In general, MACE was governed by coronary revascularizations.

Figures 3A, 3B, 4A, and 4B show the Kaplan–Meier curves for MACE among patients in the concordant normal and discordant groups, Kaplan–Meier estimates and statistical comparison of which are presented in Tables 3 through 5. Overall, discordance between FFR and CFVR was associated with a significantly increased MACE rate throughout follow-up compared with concordant normal FFR and CFVR results, regardless of whether the 0.75 (Figure 3A and Table 3) or 0.80 (Figure 3B and Table 3) cut-off was used to depict an abnormal FFR.

Importantly, the combination of a normal FFR and an abnormal CFVR, indicating predominant microvascular disease (Figure 1), was associated with a high MACE rate early after deferral of revascularization. This high early MACE rate remained significantly higher throughout 10-year follow-up compared with concordantly normal FFR and CFVR results, regardless of whether FFR <0.75 or FFR ≤0.80 was depicted as abnormal (Figure 4A and 4B and Tables 4 and 5).

In contrast, an abnormal FFR with a normal CFVR, indicating predominant focal but nonflow-limiting epicardial disease (Figure 1), was associated with equivalent clinical outcome compared with concordant normal FFR and CFVR results for up to 3 years after deferral of revascularization when FFR <0.75 was depicted abnormal (Figure 4A and Table 4), and up to 10 years after deferral of revascularization when FFR ≤0.80 was depicted abnormal (Figure 4B and Table 5). Moreover, the MACE rate associated with a normal FFR and abnormal CFVR was significantly higher than that associated with an abnormal FFR and normal CFVR: up to 3 years of follow-up when FFR <0.75 was depicted abnormal (Figure 4A and Table 4), and up to 10 years of follow-up when FFR ≤0.80 was depicted abnormal (Figure 4B and Table 5).

Table 3. Cumulative Major Adverse Cardiac Event Rate at 1, 3, 5, and 10 Years of Follow-Up Stratified by Accordance or Discordance Between CFVR and FFR at the 0.75 and 0.80 FFR Cut-Off Value

	Concordant Normal, %	Discordant, %	Relative Risk* (95% Confidence Interval)	P Value†
FFR 0.75 cut-off‡				
1-year follow-up MACE	2	20	10.0 (2.3–44.5)	<0.001
3-year follow-up MACE	4	25	4.2 (1.7–10.5)	0.001
5-year follow-up MACE	10	40	3.9 (2.0–7.7)	<0.001
10-year follow-up MACE	28	55	1.9 (1.3–2.9)	<0.001
FFR 0.80 cut-off‡				
1-year follow-up MACE	1	12	9.3 (1.2–74.5)	0.002
3-year follow-up MACE	5	19	3.7 (1.2–10.8)	0.009
5-year follow-up MACE	9	33	3.6 (1.6–8.0)	<0.001
10-year follow-up MACE	2	47	1.7 (1.1–2.6)	0.010

CFVR indicates coronary flow velocity reserve; FFR, fractional flow reserve; and MACE, major adverse cardiac event. *Relative risks and their 95% confidence intervals were calculated with the use of the Kaplan–Meier–estimated MACE rates and their respective SEs. †P values are log-rank P values. ‡Event rates were estimated with the Kaplan–Meier method.

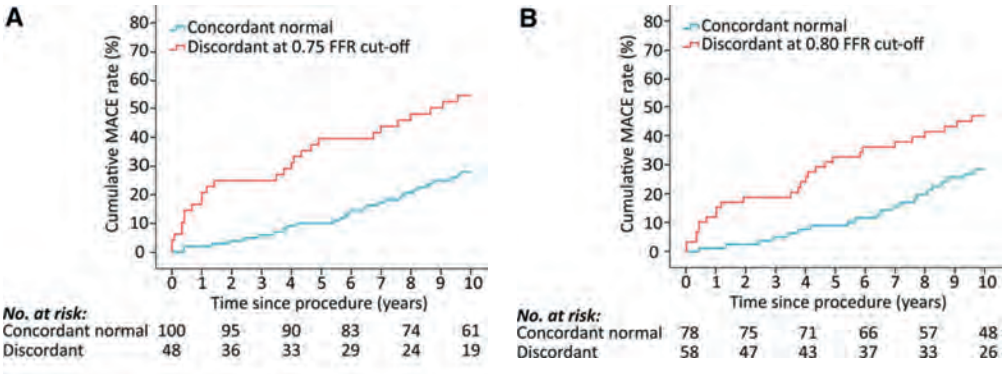

Figure 3: Kaplan–Meier curves according to concordance with normal fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR), and discordance between FFR and CFVR by an FFR cut-off value of (A) 0.75 and (B) 0.80. MACE indicates major adverse cardiac event.

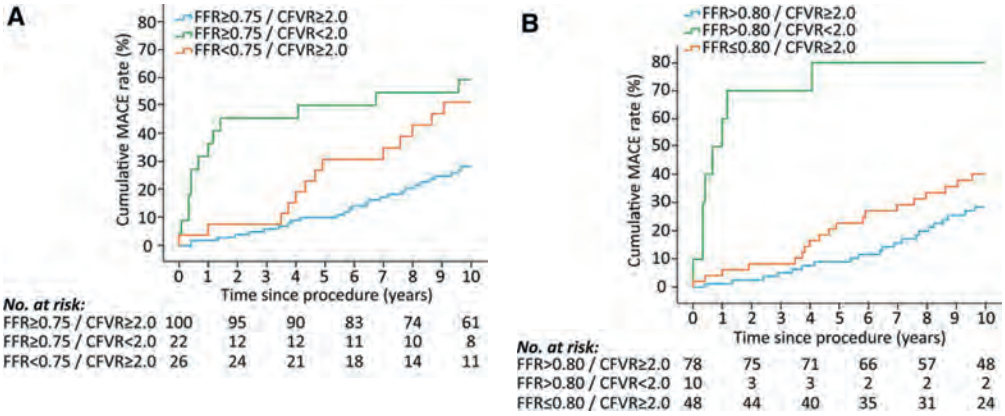

Figure 4: Kaplan–Meier curves according to concordance with normal fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR), and the different discordance groups according to an FFR cut-off value of (A) 0.75 and (B) 0.80. MACE indicates major adverse cardiac event.

Table 4. Cumulative Major Adverse Cardiac Event Rate at 1, 3, 5, and 10 Years of Follow-Up Stratified by the Specific Accordance and Discordance Groups According to the 0.75 FFR Cut-Off Value

FFR 0.75 Cut-Off*	FFR ≥0.75 CFVR ≥2.0	FFR ≥0.75 CFVR <2.0	FFR <0.75 CFVR ≥2.0	Concordant Normal vs FFR ≥0.75 CFVR <2.0		Concordant Normal vs FFR <0.75 CFVR ≥2.0		FFR ≥0.75 CFVR <2.0 vs FFR <0.75 CFVR ≥2.0	
				Relative Risk†	P Value‡	Relative Risk†	P Value‡	Relative Risk†	P Value‡
1-year follow-up MACE	2%	36%	8%	18.2 (4.1–79.9)	<0.001	3.9 (0.6–25.9)	0.139	4.7 (1.1–19.9)	0.015
3-year follow-up MACE	4%	46%	8%	11.4 (3.2–40.2)	<0.001	1.9 (0.3–11.3)	0.734	5.9 (1.5–24.0)	0.003
5-year follow-up MACE	10%	50%	31%	5.0 (2.4–10.2)	<0.001	3.1 (1.3–6.9)	0.009	1.6 (0.8–3.3)	0.089
10-year follow-up MACE	28%	59%	51%	2.1 (1.3–3.4)	<0.001	1.8 (1.1–3.0)	0.017	1.2 (0.7–1.9)	0.27

CFVR indicates coronary flow velocity reserve; FFR, fractional flow reserve; and MACE, major adverse cardiac event. *Event rates were estimated with the Kaplan–Meier method. †Relative risks and their 95% confidence intervals were calculated with the use of the Kaplan–Meier estimated MACE rates and their respective SEs. ‡P values are log-rank P values.

Table 5. Cumulative Major Adverse Cardiac Event Rate at 1, 3, 5, and 10 Years of Follow-Up Stratified by the Specific Accordance and Discordance Groups According to the 0.80 FFR Cut-Off Value

FFR 0.80 Cut-Off*	FFR ≥0.80 CFVR ≥2.0	FFR ≥0.80 CFVR <2.0	FFR <0.80 CFVR ≥2.0	Concordant Normal vs FFR ≥0.80 CFVR <2.0		Concordant Normal vs FFR <0.80 CFVR ≥2.0		FFR ≥0.80 CFVR <2.0 vs FFR <0.80 CFVR ≥2.0	
				Relative Risk†	P Value‡	Relative Risk†	P Value‡	Relative Risk†	P Value‡
1-year follow-up MACE	1%	60%	6%	46.2 (6.1–349.4)	<0.001	4.9 (0.5–45.6)	0.124	9.5 (2.9–31.7)	<0.001
3-year follow-up MACE	5%	70%	8%	13.5 (4.8–37.6)	<0.001	1.6 (0.4–6.1)	0.465	8.4 (3.0–23.6)	<0.001
5-year follow-up MACE	9%	80%	23%	8.8 (4.1–19.1)	<0.001	2.5 (1.0–6.1)	0.035	3.5 (1.9–6.4)	<0.001
10-year follow-up MACE	28%	80%	40%	2.8 (1.8–4.6)	<0.001	1.4 (0.9–2.4)	0.13	2.0 (1.3–3.2)	<0.001

CFVR indicates coronary flow velocity reserve; FFR, fractional flow reserve; and MACE, major adverse cardiac event. *Event rates were estimated with the Kaplan–Meier method. †Relative risks and their 95% confidence intervals were calculated with the use of the Kaplan–Meier estimated MACE rates and their respective SEs. ‡P values are log-rank P values.

DISCUSSION

The main finding in this study is that discordance with a normal FFR and abnormal CFVR is associated with adverse long-term clinical outcome compared with stenoses in which FFR and CFVR are concordantly normal, whereas discordance with an abnormal FFR and a normal CFVR is predominantly associated with equivalent clinical outcome compared with concordantly normal FFR and CFVR. Because discordance is a frequent phenomenon, occurring in 31% to 37% of intermediate coronary stenoses, its substantial clinical impact that contrasts with the information derived from FFR implicates a necessity of coronary flow assessment in addition to coronary pressure for optimal physiological evaluation of stable coronary artery disease.

According to our observations, coronary flow plays a dominant role in the functional consequences of stable coronary artery disease, which is not identified by solitary measurement of coronary pressure–derived FFR. Nonetheless, after 3 years of follow-up, an increase in MACE was observed in patients with a normal CFVR and an abnormal FFR, particularly at the 0.75 cut-off; this is likely attributable to disease progression. Because FFR <0.75 distal to these stenoses indicates that epicardial conductance is substantially impaired relative to vessels in which both FFR and CFVR are normal, it is likely that these initially nonflow-limiting stenoses more frequently lead to a flow-limiting stenosis at long-term follow-up as part of progression of obstructive coronary artery disease and are therefore associated with a long-term increase in MACE.

This is supported by the finding that the observed increase in MACE was substantially more pronounced when FFR <0.75, than when FFR ≤0.80, suggesting that the extent of epicardial disease is indeed a contributing factor to the occurrence of MACE at long-term follow-up. In addition, coronary flow reserve decreases with advancing age, [22] and a progressive decrease in CFVR associated with aging during a 10-year follow-up period may alternatively explain the long-term gain in MACE in these patients. Nonetheless, these findings strongly indicate that a favorable clinical outcome after deferral of revascularization in stenoses of intermediate severity can only be assumed in the presence of a normal CFVR, even when FFR is normal. Hence, our current observations emphasize the need for combined assessment of coronary flow and pressure in clinical practice.

Discordance Between FFR and CFVR: Is Only One of Them Correct?

It is often implied that discordance between FFR and CFVR stems from inaccuracy in the determination of one of these parameters, whereby the inaccuracy is typically attributed to limitations of CFVR. However, FFR and hyperemic flow velocity, as an important factor in CFVR, are intrinsically related by a curvilinear pressure drop—flow velocity relationship

resulting from the combined effect of Poiseuille's and Bernouilli's Law on stenosis hemodynamics. [4][14] As a result, the pressure drop across a stenosis increases with increasing flow through the stenosis. Consequently, for a given stenosis, FFR and CFVR per definition move in opposite directions with changing hyperemic flow through the stenosis. [14] Hence, discordance between FFR and CFVR can be explained from basic physiological principles, and neither FFR nor CFVR can be considered incorrect in case of discordant results.

Coronary Microvasculature Characterizes Discordance Between FFR and CFVR

Meuwissen et al first described the pivotal role of the functional status of the coronary microvasculature during hyperemic conditions in the occurrence of both extremes of the discordance spectrum.[8] Our observations expand on the role of the coronary microvasculature as a pivotal component not only in the extremes of the discordance spectrum but as the main determinant of discordance of CFVR with FFR and indicate that its functional status during basal conditions provides substantial additional information.

The 4 major quadrants in which the relationship between FFR and CFVR can be divided (Figure 1), as proposed by Johnson et al, [9] are individually characterized by the status of the coronary microvasculature, where the magnitude of BMR and HMR in vessels with concordant normal FFR and CFVR results (Figure 1, blue area) can be considered normal in the absence of a stenosis inducing a pressure drop, or microvascular disease reducing myocardial blood flow (Table 2). In comparison, in vessels with a normal FFR and abnormal CFVR (Figure 1, green area), BMR is low, whereas HMR is relatively high (Table 2), despite epicardial disease of equivalent severity. This probably results from predominant microvascular disease, as the low BMR indicates compensatory microvascular vasodilation during basal conditions, and the relatively high HMR may indicate impaired hyperemic vasodilator response of the coronary microvasculature. Apparently, more extensive microvascular disease not only limits the vasodilatory capacity of the coronary microcirculation but also necessitates compensatory vasodilation of the coronary resistance vessels, and thus a decrease in BMR, to accommodate equivalent myocardial demand during basal conditions. [12] [14][23]

In vessels with an abnormal FFR and a normal CFVR (Figure 1, orange area), BMR is normal, and HMR is low compared with vessels with concordant normal FFR and CFVR (Table 3). This probably results from predominant focal, but nonflow-limiting, epicardial disease in the absence of microvascular abnormalities, because the normal BMR indicates that myocardial perfusion is preserved in basal conditions, which allows BMR to remain unaltered, [24] and HMR indicates that the vasodilatory response of the microvasculature is intact. In these stenoses with a substantial pressure drop, the low HMR may be attributed to chronic deprivation of distal perfusion pressure, leading to structural adaptation of the coronary vasculature and a reduced vascular tone at maximal hyperemia. [25][26]

Vessels with concordant abnormal FFR and CFVR (Figure 1, red area) are characterized by a low BMR and a relatively low HMR (Table 3), most likely indicating extensive epicardial disease yielding similar structural adaptation to a loss of perfusion pressure, but additionally limiting blood flow to such extent necessitating compensatory microvascular vasodilation already during basal conditions. [24] However, a combination of epicardial and microvascular disease cannot be excluded in this setting, although this is unlikely in the presence of a low HMR, which indicates a normal physiological vasodilatory response of the microvasculature during hyperemia.

Disturbed Coronary Autoregulation May Drive Discordance of CFVR With FFR

We observed that discordance of CFVR with FFR among stenosis with equivalent epicardial disease is particularly characterized by abnormalities in BMR (Table 2). Notably, in patients in whom CFVR was abnormal, a decreased resistance of the microvasculature during basal conditions coexisted with an increased basal coronary flow velocity. Because normal coronary autoregulatory function would provide compensatory vasodilation only to the point necessary to maintain stable coronary flow, [4] an increase in basal coronary flow in this setting suggests that coronary autoregulation is disturbed. [13][23][26] Such disturbed autoregulation is consistent with an important role of microvascular (dys)function in the discordance between FFR and CFVR and may be attributed to structural vascular adaptation in the setting of microvascular disease or in the setting of chronic deprivation of perfusion pressure in the presence of substantial epicardial disease.[13][23][26]

Focal or Diffuse Epicardial Coronary Artery Disease in FFR/CFVR Discordance

Because it cannot be inferred from an FFR value at a single location whether a pressure drop occurs from focal or diffuse disease of the epicardial conduit artery, which would require a distal-to-proximal pressure pullback, the epicardial component of coronary artery disease summarized by FFR includes the hemodynamic effect of both focal and diffuse epicardial atherosclerosis. Nonetheless, diffuse disease is in general less likely to induce an abnormal FFR because of a lack of convective acceleration of blood flow, limiting the resulting pressure drop over the diseased epicardial artery. [27] Therefore, as suggested by Johnson et al, [9] diffuse coronary artery disease may particularly provide a coexisting or alternative explanation for a reduction in CFVR, which may also be associated with adverse clinical outcome. [28] Nonetheless, we have attributed the reduction in CFVR to a predominance of microvascular abnormalities. Complementary to the study by Johnson et al, our study allowed detailed evaluation of the relative distribution of epicardial and MRs. Our interpretation was therefore governed by the observation that abnormality of CFVR in our study population was generally associated with alterations in the resistance induced by the microvascular compartment instead of the epicardial compartment (Table 2). Nonetheless, in individual cases both diffuse epicardial and microvascular disease may provide coexisting explanations for a reduction in CFVR.

Comparison With Previous Studies

Information on the prognostic value of discordance between invasively assessed FFR and CFVR for long-term clinical outcome is limited. Our report is the first to identify a dominant role of invasively measured CFVR over FFR at its contemporary 0.80 cut-off value in the long-term prognosis of stable coronary artery disease patients. Moreover, this study is the first to identify a pivotal role of microvascular function in basal conditions in the discordance of CFVR and FFR and its important implications for clinical outcome of coronary stenoses of intermediate severity. Thereby, our results extend the observations of Meuwissen et al, [7] whom showed that 1-year MACE rate after deferral of coronary revascularization of stenoses with FFR ≥0.75 was substantially higher when CFVR was abnormal than when CFVR was normal. Moreover, these results are consistent with studies using noninvasive imaging modalities to assess coronary flow reserve. In patients with normal hyperemic myocardial perfusion (as a surrogate for a normal FFR), [14] Herzog et al [29] reported an abnormal CFR to be associated with a significantly increased MACE rate compared with when CFR was normal (6.3% versus 1.4% per year; P<0.05). Similarly, Murthy et al [30] identified an impaired CFR to be associated with a 3.2- and 4.9-fold increase in cardiac mortality rates among diabetic and nondiabetic patients, respectively, when hyperemic myocardial perfusion was normal.

Several studies support our current observations on the pertinence of microvascular function in basal conditions. We have reported recently that abnormalities in microvascular function under basal autoregulation conditions, in the absence of hyperemic blood flow impairment, impart a particularly important risk for long-term adverse events, both in patients with stable coronary artery disease [13] and in patients after primary PCI for ST-segment–elevation myocardial infarction. [12] Moreover, the previously mentioned noninvasive imaging studies support this hypothesis, because both studies indicate that an abnormal coronary flow reserve in the presence of normal hyperemic perfusion, indicating alterations in basal flow, is an important marker for adverse outcome. [29][30] Apparently, substantial risk for long-term MACE is attributable to abnormalities in basal coronary flow regulation, implicating that indeed microvascular dysfunction is an elementary component in the diagnosis and prognosis of patients with coronary artery disease. [31][32]

Finally, a recent study by Jespersen et al [28] reported that patients with stable chest pain syndromes and coronary arteries without focal epicardial obstructive disease, considered indicative of diffuse epicardial narrowing, are at an 1.85-fold increased risk for MACE at long-term follow-up. Because diffuse epicardial narrowing may provide a coexisting explanation for a reduction in CFVR, or angina in the absence of focal epicardial disease may alternatively indicate microvascular disease, our observations are also consistent with those of Jespersen et al. Generally, the observations in these studies implicate that a normal

epicardial coronary artery, documented either angiographically, noninvasively, or by FFR, does not imply a normal coronary vasculature. The presence of microvascular disease is an important element in coronary artery disease, which imposes an important risk for adverse outcome, and its identification may allow more accurate risk stratification in the setting of stable coronary artery disease.

Future Perspectives

The results of the present study emphasize the implications of discordance between coronary pressure and flow-derived parameters for clinical outcome in patients with stable coronary artery disease and indicate the importance of its recognition in clinical practice. Recent data have indicated that discordance with CFVR may be less frequent with the use of a basal pressure-derived index, the instantaneous wave-free ratio, compared with FFR. [33] This was particularly relatable to the relative insensitivity of instantaneous wave-free ratio toward nonflow-limiting coronary stenoses, where the large pressure gradient during hyperemia, responsible for a positive FFR, results from a large increase in coronary flow during hyperemia: particularly those stenoses where we documented that clinical outcome is favorable. Hence, in contrast to current assumptions, it may be speculated that basal conditions could provide an advantage over hyperemia in some cases, prompting further evaluation of this phenomenon in future studies.

Limitations

The results from the present study should be interpreted in consideration of some limitations. First, the relatively small sample size limits the statistical power and the strength of the conclusions. However, the present study comprises the largest cohort of stenoses with discordant FFR and CFVR results reported to date and the first to report long-term clinical follow-up of discordance at the 0.80 FFR cut-off value. Moreover, the differences between normal and abnormal CFVR results are large, indicating an important role of coronary flow for long-term MACE. Nonetheless, our results warrant evaluation in a larger discordance cohort, in particular, to identify the pertinence of revascularization in patients with discordant FFR and CFVR results.

Second, consistent with the era in which the data were obtained, the composition of the study population was based on the operator's decision not to intervene. As a result, coronary

stenoses in which revascularization was deferred were angiographically less severe, compared with stenoses in which PCI was performed. Secondary to the well-known discrepancy between the angiographic and physiological severity of a coronary stenosis, the stenoses in which revascularization was deferred included stenoses that are considered physiologically significant and would have been treated in contemporary clinical practice. However, as a corollary, the study population of deferred coronary stenoses represented a clinical population routinely referred for FFR assessment before intervention in contemporary clinical practice (Figure 2B and 2C). [34] This allowed to study the natural (untreated) clinical course of FFR and CFVR discordance in a representative patient population, which can be considered a strength for the extrapolation of our results and conclusions to contemporary clinical practice.

Finally, this study is limited by the assessment of adverse events at long-term follow-up partly performed by means of a telephone survey. Such an approach is sensitive toward a possible patient recall bias, which may have resulted in under-reporting of adverse events. Nonetheless, the long-term MACE rates reported in the present study are generally comparable with those reported by Li et al. [35]

CONCLUSIONS

Discordance between FFR and CFVR with a normal FFR but reduced CFVR, indicating predominant microvascular disease, is associated with a particularly unfavorable prognosis, whereas a preserved CFVR in the presence of an abnormal FFR, indicating nonflow-limiting epicardial coronary artery disease, yields a long-term clinical outcome comparable with concordantly normal FFR and CFVR. Our observations indicate a dominant role of coronary flow in the functional severity of coronary stenoses and implicate a necessity for identification of stenoses with discordance between coronary pressure and flow-derived parameters for optimal distinction between functionally significant and nonsignificant coronary stenoses.

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CHAPTER 7

Coronary Flow Capacity after Percutaneous Coronary Interventions in concordant and discordant lesions

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Submitted

ABSTRACT

Background: Percutaneous coronary intervention does not reduce the occurrence of myocardial infarction or cardiac death in patients with ischemic stable heart disease, which indicates critical revision of our understandings concerning the treatment of ischemic heart disease. Combined fractional flow reserve (FFR) and coronary flow reserve (CFR) measurements may augment diagnosis of myocardial ischemia, yet the effect of PCI on vessels evaluated by pressure and flow measurements remains poorly studied. We evaluated the impact of PCI on coronary flow parameters in patients with coronary artery disease.

Methods: We evaluated 100 lesions with simultaneous pressure and flow measurements before and after PCI. CFR<2.0 and FFR≤0.80 was considered abnormal. Severely/moderately reduced CFC was considered ischemic and normal or mildly reduced CFC was considered non-ischemic.

Results: PCI decreased the rate of severely or moderately reduced CFC from 88% (44 out of 50) to 14% (7 out of 50) (p<0.001) for lesions with a FFR≤0.80 and CFR<2.0. PCI reduced the rate of severely/moderately reduced CFC from 19% (4 out of 21) to 5% (1 out of 21) (p=0.153) in non-flow limiting lesions with a FFR≤0.80 and CFR≥2.0. PCI the rate of severely/moderately reduced CFC from 59% (10 out of 17) to 24% (4 out of 17) (p=0.037) for lesions with a FFR>0.80 and CFR<2.0. PCI did not alter the rate of severely or moderately reduced CFC (8%, 1 out of 12) (p=1.00) in lesions with a FFR>0.80 and CFR≥2.0.

Conclusions: In patients with FFR>0.80 and CFR<2.0, myocardial ischemia is frequently present (59%) according to the CFC concept and PCI improves flow parameters to non-ischemic levels, whereas in patients with FFR≤0.80 and CFR≥2.0, myocardial ischemia is infrequent (19%) and PCI does not improve the ischemic status.

INTRODUCTION

Myocardial ischemia is considered a critical prognostic determinant in patients with stable ischemic heart disease (IHD). Intuitively, myocardial ischemia is best managed by revascularization therapy, either surgically or by percutaneous coronary intervention (PCI). [1][2] To date, however, there is no scientific evidence that revascularization therapy significantly reduces cardiovascular event compared to an optimal medical treatment strategy. [3][4][5] It was even shown that PCI did not improve exercise-time compared to a sham placebo-PCI in patients with stable heart disease treated medically. [6] This suggests further refinement of our understandings regarding treatment strategies in patients with stable ischemic heart disease is urgently needed. Combined fractional flow reserve (FFR) and coronary flow reserve (CFR) measurements have been well-documented to allow comprehensive separation of epicardial and microvascular involvement in IHD, which not only augments the diagnosis of myocardial ischemia but also identifies its pathophysiologic origin. The obtained characterization of IHD by means of combined FFR and CFR assessment also documented that coronary flow parameters confer dominant prognostic value, regardless of the trans-stenotic pressure gradient. [7][8][9] Hence, multimodal assessment by FFR and CFR may augment the identification of coronary lesions likely to benefit from revascularization therapy. However, the physiological impact of PCI of lesions evaluated by combined FFR and CFR measurements remain to be elucidated. The present study sought to evaluate the impact of PCI on coronary flow parameters and coronary flow capacity (CFC) in patients with coronary artery disease.

METHODS

Data source

This study retrospectively analyzed patients with ≥1 intermediate coronary stenosis (40%–70% diameter stenosis at visual assessment) who were scheduled for intracoronary evaluation with combined pressure and flow measurements at the Academic Medical Center, Amsterdam, The Netherlands, Imperial College London, United Kingdom, Hospital Clinico San Carlos, Madrid, Spain, and VU University Medical Center, Amsterdam, The Netherlands. Patients were considered eligible for the present study if combined pressure and flow measurements were repeated post-PCI. Composite exclusion criteria were left main disease, severe valvular heart disease, weight >200 kg, previous coronary artery bypass surgery, vessels with angiographically identifiable myocardial bridging or collateral arteries and recent myocardial infarction (<6 weeks) in the target vessel perfusion area. Patients that were enrolled in a consecutive study protocol agreed with the declaration of Helsinki and

these patients delivered written informed consent after ample time of consideration prior to physiological assessment.

Coronary pressure and flow measurements

Local practice standards and guidelines were followed towards the onset of the procedure. Coronary angiography was performed in a manner suitable for quantitative coronary angiography analysis (QCA). Combined intracoronary pressure and Doppler-flow velocity measurements were performed using 0.014" sensor-equipped guide wires (Philips-Volcano Corp, San Diego, CA). All patients received 200 to 300 microgram (mcg) nitroglycerine at the start of the procedure, which was repeated every 30 minutes if indicated. Measurements were made distal to the stenosis at least three vessel diameters from the stenosis during resting and hyperemic conditions. Hyperemia was induced by intracoronary bolus injection of (20-150mcg) adenosine directly into the coronary artery or by continuous intravenous infusion (140mg/kg/min). Revascularization was performed at the operator's discretion, and combined pressure and flow measurements were repeated immediately post PCI. The dual sensor-equipped guide wire was retracted into the guiding catheter after each measurement to assess pressure drift. In the occurrence of considerable pressure drift (>2mmHg), measurements were repeated or corrected upon analysis.

Data analysis

Combined pressure and Doppler flow velocity measurements as well as ECG tracings were recorded on their dedicated console (Philips-Volcano, San Diego, CA, USA). Data were retracted from the digital archive and analyzed off-line by experienced analysts blinded to the coronary angiograms or patient characteristics, using a custom software package designed with MATLAB (Mathworks, Inc, Natick, MA, USA). Definitions of the respective physiologic parameters of stenosis severity are summarized in table 1. A CFR<2.0 and FFR≤0.80 were considered abnormal. Offline QCA analysis was performed to determine percentage diameter stenosis and reference artery diameter with the use of a validated automated contour detection algorithms (CAAS II, Pie Medical, Maastricht, The Netherlands or McKesson, San Francisco, USA).

Table 1: Physiological parameters of stenosis severity

Functional parameter of stenosis severity	Equation
P_d/P_a	P_d/P_a (during baseline)
FFR	P_d/P_a (during hyperemia)
iFR	P_d/P_a (during baseline wave-free period)
CFR	hyperemic APV/ baseline APV

P_d = distal pressure; P_a = aortic pressure; FFR = fractional flow reserve; iFR = instantaneous wave-free period; CFR = coronary flow reserve

The concept of coronary flow capacity

CFC is a concept that combines CFR and hyperemic coronary flow velocity measurements into a clinically relevant framework that distinguishes a mildly, moderately and severely reduced CFC from a normal CFC. Using the well-documented thresholds of CFR derived from intracoronary measurements, in alliance with hyperemic average peak flow velocity (APV) values matched according to the corresponding percentiles of CFR, the concept classifies normal CFC as a CFR ≥2.8, as encountered in patients with risk factors for IHD without epicardial narrowing, with its corresponding hyperemic APV of ≥49.0 cm/s. Mildly reduced CFC was defined as a CFR <2.8 but >2.1, which reflects the upper limit of reported CFR cut-off values for inducible ischemia, and the corresponding hyperemic APV of <49.0 and >33.0 cm/s, respectively. Moderately reduced CFC was defined as CFR ≤2.1 and >1.7, analogous to the reported range of CFR cut-off values for inducible myocardial ischemia, and the corresponding hyperemic APV of ≤33.0 and >26.0 cm/s, respectively. Finally, severely reduced CFC was defined as a CFR ≤1.7, which is the lower limit of CFR cut-off values reported for inducible myocardial ischemia and analogous to the ischemic CFR threshold in noninvasive imaging and the corresponding hyperemic APV of ≤26.0 cm/s. [10]

Statistical analysis

Data are expressed as mean±standard deviation (SD). Effects of PCI on angiographic and contemporary physiologic parameters were compared using paired Student's t-test. Overall differences between the quadrant of FFR and CFR (dis)agreement were compared with one-way ANOVA with Bonferroni correction. Categorical variables are presented as counts(percentages), and were compared with the two proportion Z-test, Chi square or Fisher´s exact test. A two-sided P value less than 0.05 were considered statistically significant. The STATA 14.1 statistical software package (StataCorp, College Station, TX) was used for all calculations.

RESULTS

Patient characteristics

We comprehensively evaluated the functional significance of 100 coronary lesions (100 patients) before and after PCI by combined pressure and flow measurement. The mean age of the study population was 61±0 years and 73% of patients (73 out of 100 patients) were male. Remainder baseline criteria are summarized in table 2. The study population consisted of angiographically intermediate coronary stenoses with a mean diameter stenosis of 61±14%, mean FFR of 0.68±0.17, mean iFR of 0.74±0.23, and mean CFR of 1.8±0.8.

Table 2. Baseline characteristics of the study population

	N=100
Demographic characteristics	
Age, yrs	61 ± 9
Male gender	73 (73.0)
Risk factors for coronary artery disease	
Hypertension	53 (53.0)
Hyperlipidemia	72 (72.0)
Positive family history	39 (39.0)
Cigarette smoking	44 (44.0)
Diabetes mellitus	26 (26.0)
Prior myocardial infarction	16 (16.0)
Medication at hospital admission	
Beta-blocker	46 (46.0)
Calcium antagonists	19 (19.0)
ACE-inhibitors	14 (14.0)
Statins	44 (44.0)
Aspirin	48 (48.0)

Values are mean ± SD, N (%)
yrs = years; ACE = angiotensin converter enzyme

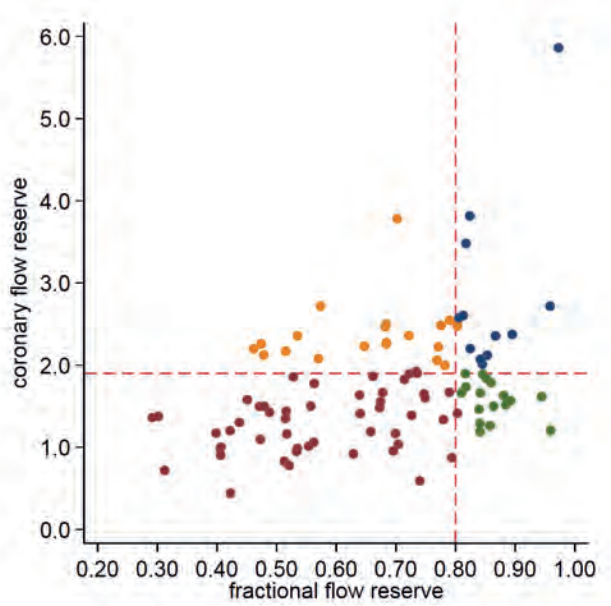

Figure 1: Distribution of fractional flow reserve and coronary flow reserve before percutaneous coronary intervention.

Impact of PCI on coronary flow and resistance parameters

In 100 patients evaluated by combined pressure and flow measurement before and after percutaneous revascularization, PCI significantly improved CFR (1.8±0.8 to 2.5±0.9, p<0.001; table 3), hyperemic APV (29.5±18.3 to 50.2±23.0, p<0.001) and baseline APV (17.3±8.6 to 21.2±8.7, p<0.001) (table 3). Restoration of vessel patency by PCI decreases the rate of severely and moderately reduced CFC from 59% to 12% (p<0.001; figure 2 and 3).

Table 3: Angiographic and physiologic characteristics of the overall study population

Angiographic characteristics		n=100	
Vessel of interest			
Left anterior descending		52 (52.0)	
Ramus circumflex		20 (20.0)	
Right coronary artery		28 (28.0)	
	Pre PCI	Post PCI	p-value
Diameter stenosis (%)	61.1 ± 13.7	17.1 ± 11.0	<0.001
Minimum lumen diameter (MLD	0.97 ± 0.36	2.38 ± 0.66	<0.001
Reference diameter	2.62 ± 0.72	2.98 ± 0.73	<0.001
Physiologic parameters			
FFR	0.68 ± 0.18	0.90 ± 0.07	<0.001
hPd	61.3 ± 17.9	82.1 ± 17.2	<0.001
hPa	90.9 ± 15.7	91.3 ± 17.0	0.741
P_d/P_a	0.82 ± 0.16	0.96 ± 0.04	<0.001
bPd	80.6 ± 20.6	96.8 ± 15.5	<0.001
bPa	98.7 ± 15.7	100.8 ± 15.7	0.088
iFR	0.74 ± 0.23	0.94 ± 0.07	<0.001
iFR-Pd	64.7 ± 22.7	85.1 ± 14.8	<0.001
iFR-Pa	87.5 ± 14.1	90.2 ± 14.0	0.011
CFR	1.8 ± 0.8	2.5 ± 0.9	<0.001
Baseline APV	17.3 ± 8.6	21.2 ± 8.7	<0.001
Hyperemic APV	29.5 ± 18.3	50.2 ± 23.0	<0.001

PCI: percutaneous coronary intervention; FFR: fractional flow reserve; Pd/Pa: coronary distal-to-aortic pressure ratio; iFR: instantaneous wave-free ratio; CFR: coronary flow reserve; APV: averaged peak flow velocity;

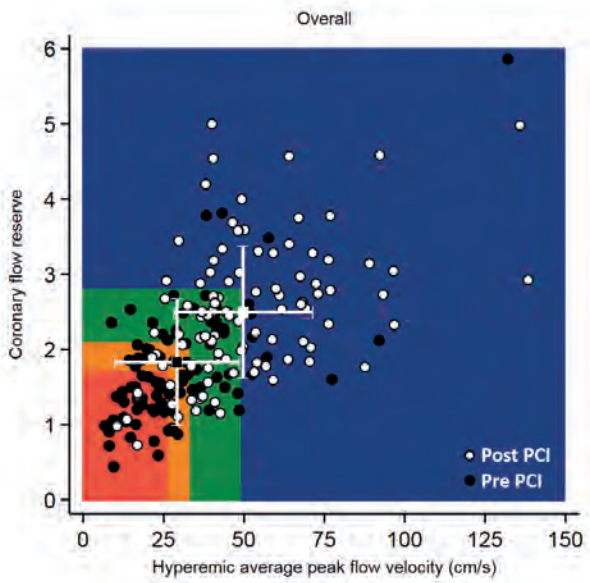

Figure 2: Impact of percutaneous coronary intervention on hyperemic average peak flow velocity (APV), coronary flow reserve (CFR) and coronary flow capacity in the overall population. Colored areas indicating the coronary flow capacity classifications; Normal (blue), mildly reduced (green), moderately reduced (orange), severely reduced (red).

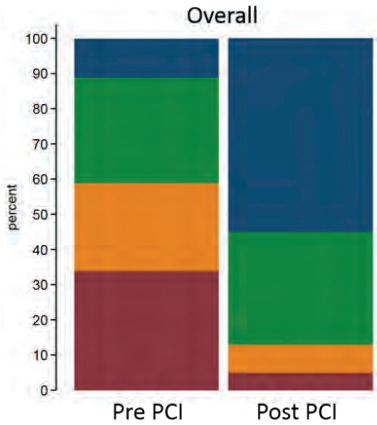

Figure 3: Distribution of coronary flow capacity classification before and after percutaneous coronary intervention. Coronary flow capacity classifications; Normal (blue), mildly reduced (green), moderately reduced (orange), severely reduced (red).

Impact of PCI on coronary flow parameters, stratified according FFR/CFR (dis)agreement

The impact of PCI on flow-derived coronary parameters stratified according FFR/CFR (dis) agreement is displayed in figure 4 and summarized in table 4. For lesions with a FFR≤0.80 and CFR<2.0, PCI improved CFR (1.3±0.4 to 2.3±0.9, p<0.001), hyperemic APV (22.2±13.5 to 50.9±21.8, p<0.001) and baseline APV (17.3±8.6 to 21.2±8.7, p<0.001) (table 4, figure 4a). For lesions with a FFR>0.80 and CFR<2.0, PCI improved CFR (1.6±0.2 to 2.1±0.4, p<0.001) and hyperemic APV (31.7±10.5 to 40.5±13.0, p=0.008), but did not change baseline APV (20.5±7.1 to 20.1±6.0, p=0.823) (table 4, figure 4b). For lesions with a FFR≤0.80 and CFR≥2.0, PCI improved CFR (2.4±0.4 to 3.2±0.9, p=0.001), hyperemic APV (32.6±12.1 to 54.7±24.4, p<0.001) and baseline APV (13.8±5.2 to 17.4±6.4, p=0.010) (table 4, figure 4c). For vessels with FFR>0.80 and CFR≥2.0, PCI did not change CFR nor hyperemic APV nor baseline APV (CFR: 2.8±1.1 to 2.5±0.7, p=0.336; hyperemic APV: 51.3±31.3 to 52.7±33.4, p=0.450; baseline APV: 18.0±8.9 to 20.9±10.9, p=0.318) (table 4, figure 4d).

Impact of PCI on coronary flow capacity stratified according FFR/CFR (dis)agreement

The impact of PCI on CFC classification is displayed in figure 5. For lesions with a FFR≤0.80 and CFR<2.0, PCI decreased the rate of severely or moderately reduced CFC from 88% (44 out of 50) to 14% (7 out of 50) (p<0.001).For lesions with a FFR>0.80 and CFR<2.0, PCI reduced the rate of severely or moderately reduced CFC from 59% (10 out of 17) to 24% (4 out of 17)(p=0.037), for lesions with a FFR≤0.80 and CFR≥2.0, PCI reduced the rate of severely or moderately reduced CFC from 19% (4 out of 21) to 5% (1 out of 21) (p=0.153). For lesions with a FFR>0.80 and CFR≥2.0, PCI did not alter the rate of severely or moderately reduced CFC (8%, 1 out of 12) (p=1.00).

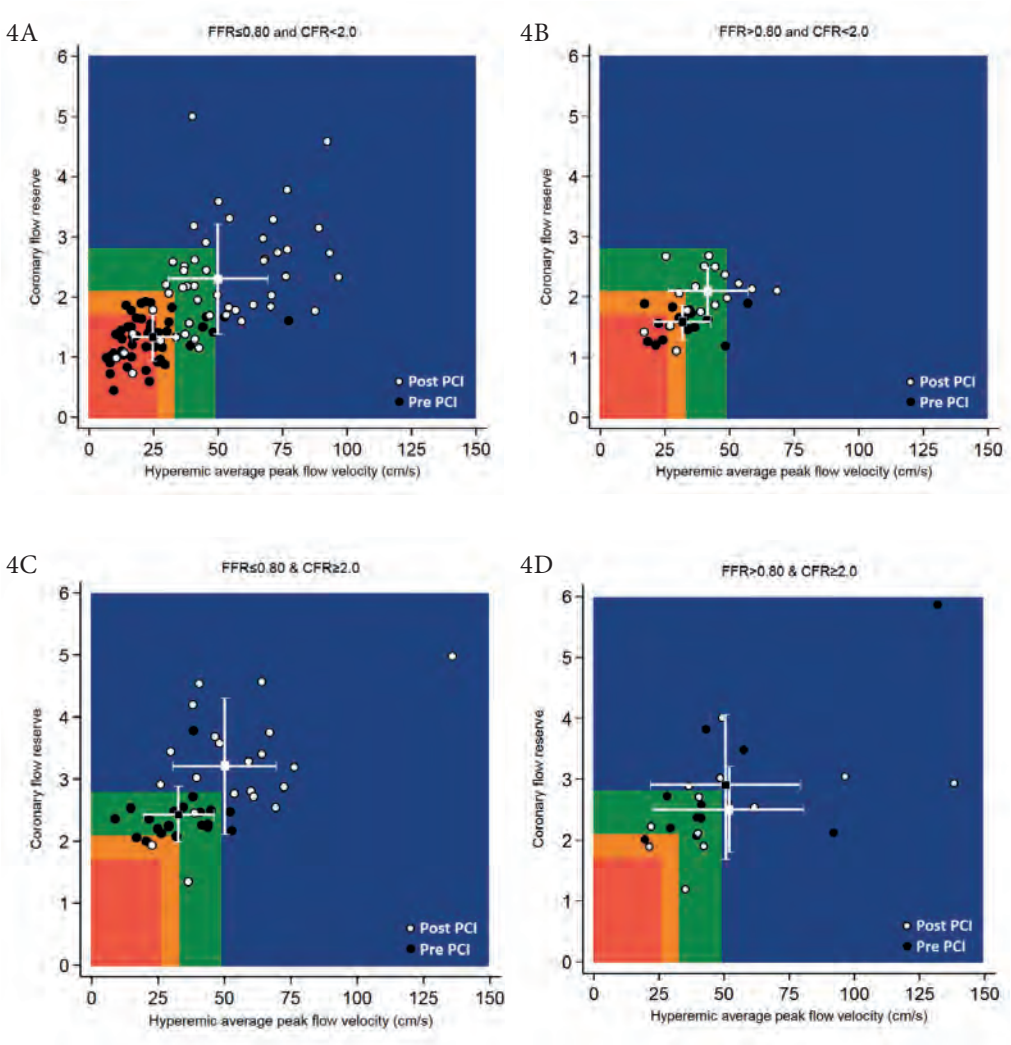

Figure 4: Impact of percutaneous coronary intervention on hyperemic average peak flow velocity (APV), coronary flow reserve (CFR) and coronary flow capacity according to A) concordant abnormal fractional flow reserve (FFR) and CFR before PCI; B) discordant abnormal FFR and normal CFR; C) discordant normal FFR and abnormal CFR, and D) concordant normal FFR and CFR. Colored areas indicating the coronary flow capacity classifications; Normal (blue), mildly reduced (green), moderately reduced (orange), severely reduced (red).

Table 4: Physiologic values stratified by FFR-CFR (dis)agreement

	FFR≤0.80 & CFR<2.0 N = 50			FFR>0.80 & CFR<2.0 N = 17			FFR≤0.80 & CFR≥2.0 N = 21			FFR>0.80 & CFR≥2.0 N = 12		
	pre-PCI	post-PCI	p-value	pre-PCI	post-PCI	p-value	pre-PCI	post-PCI	p-value	pre-PCI	post-PCI	p-value
Angiographic parameters												
Interrogated vessel												
LAD	29 (58.0%)			6 (35.3%)			11 (52.4%)			6 (50.0%)		0.450
LCx	12 (24.0%)			3 (17.6%)			4 (19.0%)			1 (8.3%)		0.661
RCA	9 (18.0%)			8 (47.1%)			6 (28.6%)			5 (41.7%)		0.084
Segment												
proximal	23 (46.0%)			7 (41.2%)			9 (42.9%)			6 (50.0%)		0.952
Middle	25 (50.0%)			10 (58.8%)			12 (57.1%)			5 (41.7%)		0.975
Distal	2 (4.0%)			0 (0%)			0 (0%)			1 (8.3%)		0.703
Diameter stenosis ǂ (%)	65.8 ± 13.9	16.4 ± 10.7	<0.001	58.4 ± 13.6	18.1 ± 14.1	<0.001	58.0 ± 12.0	18.7 ± 11.3	<0.001	52.3 ± 8.8	16.0 ± 8.2	<0.001
MLD ǂ (mm)	0.81 ± 0.31	2.30 ± 0.64	<0.001	1.00 ± 0.32	2.32 ± 0.87	0.001	1.05 ± 0.45	2.57 ± 0.61	<0.001	1.23 ± 0.25	2.59 ± 0.66	0.002
Reference diameter (mm)	2.54 ± 0.75	2.95 ± 0.79	0.003	2.53 ± 0.43	2.90 ± 0.79	0.146	3.08 ± 1.02	3.20 ± 0.58	0.660	2.53 ± 0.42	3.04 ± 0.59	0.063
Physiologic parameters												
iFR ǂ	0.60 ± 0.24	0.94 ± 0.08	<0.001	0.91 ± 0.05	0.95 ± 0.05	0.013	0.82 ± 0.12	0.95 ± 0.07	<0.001	0.94 ± 0.03	0.95 ± 0.04	0.302
iFR-Pd ǂ	53.3 ± 23.3	86.0 ± 16.7	<0.001	31.7 ± 10.4	40.5 ± 13.0	0.008	32.6 ± 12.1	54.7 ± 24.4	<0.001	51.3 ± 31.3	52.7 ± 33.4	0.450
iFR-Pa	88.4 ± 14.4	91.6 ± 14.8	0.086	82.2 ± 15.4	88.5 ± 15.0	0.015	88.2 ± 13.8	88.4 ± 13.9	0.917	88.6 ± 11.3	89.6 ± 9.6	0.616
P_d/P_a ǂ	0.73 ± 0.18	0.96 ± 0.05	<0.001	0.94 ± 0.03	0.97 ± 0.04	0.014	0.86 ± 0.10	0.96 ± 0.04	<0.001	0.96 ± 0.03	0.96 ± 0.04	0.400
bPd ǂ	72.5 ± 21.4	97.9 ± 16.2	<0.001	90.4 ± 16.1	99.0 ± 16.2	0.025	84.4 ± 17.6	93.2 ± 14.9	<0.001	93.5 ± 13.4	94.9 ± 13.1	0.586
bPa	99.9 ± 15.7	102.3 ± 15.9	0.196	96.2 ± 17.5	102.6 ± 16.8	0.066	98.1 ± 16.2	97.0 ± 16.3	0.650	97.7 ± 13.0	98.6 ± 11.9	0.733
FFR ǂ	0.58 ± 0.14	0.89 ± 0.07	<0.001	0.86 ± 0.04	0.92 ± 0.05	0.003	0.66 ± 0.12	0.90 ± 0.06	<0.001	0.86 ± 0.06	0.90 ± 0.06	0.090
hPd ǂ	52.5 ± 14.7	82.1 ± 18.2	<0.001	74.6 ± 15.9	82.5 ± 19.3	0.023	62.2 ± 14.8	82.9 ± 14.7	<0.001	77.7 ± 15.8	80.2 ± 16.1	0.475
hPa	91.0 ± 14.7	91.8 ± 17.0	0.614	86.4 ± 16.9	89.7 ± 20.5	0.260	94.5 ± 16.8	92.1 ± 15.5	0.304	90.2 ± 16.3	89.3 ± 15.5	0.777
CFR ǂ	1.3 ± 0.4	2.3 ± 0.9	<0.001	1.6 ± 0.2	2.1 ± 0.4	<0.001	2.4 ± 0.4	3.2 ± 0.9	0.004	2.8 ± 1.1	2.5 ± 0.7	0.336
bAPV	17.4 9.7	23.3 ± 9.3	0.002	20.5 ± 7.1	20.1 ± 6.0	0.823	13.8 ± 5.2	17.4 ± 6.4	0.010	18.0 ± 8.9	20.9 ± 10.9	0.318
hAPV ǂ	22.2 ± 13.5	50.9 ± 21.8	<0.001	31.7 ± 10.5	40.5 ± 13.0	0.008	32.6 ± 12.1	54.7 ± 24.4	<0.001	51.3 ± 31.3	52.7 ± 33.4	0.450
CFC												
Normal CFC	2 (4.0%)	27 (54.0%)	<0.001	1 (5.9%)	4 (19.0%)	0.146	3 (14.2)	18 (85.7%)	<0.001	5 (41.7%)	6 (50.0%)	0.682
Mildly recuded CFC	4 (8.0%)	16 (32.0%)	0.003	6 (35.3%)	9 (52.9%)	0.300	14 (66.7%)	2 (9.5%)	<0.001	6 (50.0%)	5 (41.7%)	0.682
Moderately reduced CFC	14 (28.0%)	3 (6.0%)	0.003	6 (35.3%)	3 (17.6%)	0.244	4 (19.0%)	1 (4.8%)	0.153	1 (8.3%)	1 (8.3%)	-
Severly reduced CFC	30 (60.0%)	4 (8.0%)	<0.001	4 (19.0%)	1 (5.9%)	0.146	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-

ǂ Pre-PCI value significantly different between quadrants
$ Post-PCI value significantly different between quadrants
FFR = fractional flow reserve; CFR = coronary flow reserve; PCI = percutaneous coronary intervention; LAD = left anterior descending; Cx = circumflex; RCA = right coronary artery; MLD = mean lumen diameter; iFR = instantaneous wave-free ratio; Pd/Pa = coronary distal-to-aortic pressure ratio; hPd = hyperemic distal pressure; hPa = hyperemic aortic pressure; bAPV = baseline average peak flow velocity; hAPV = hyperemic average peak flow velocity; BSR = basal stenotic resistance; HSR = hyperemic stenotic resistance; BMR = basal microvascular resistance; HMR = hyperemic microvascular resistance; MRR = microvascular resistance reserve

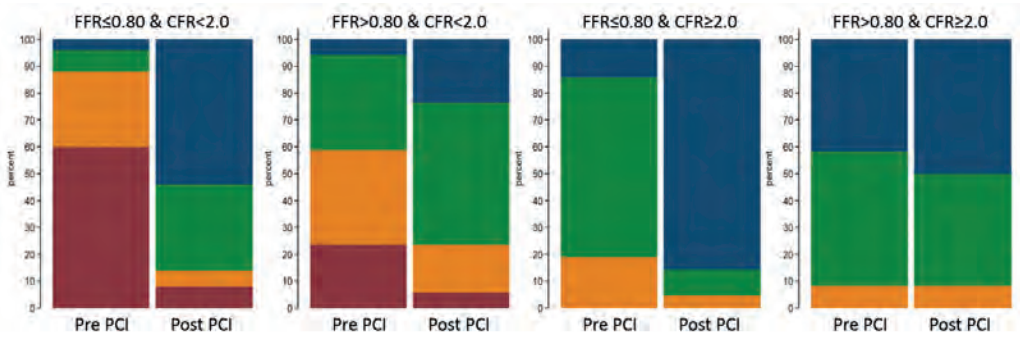

Figure 5: Distribution of coronary flow capacity classification before and after percutaneous coronary intervention stratified by the four quadrants of FFR and CFR (dis)agreement. Coronary flow capacity classifications; Normal (blue), mildly reduced (green), moderately reduced (orange), severely reduced (red).

DISCUSSION

The present study evaluated the impact of PCI on coronary flow parameters in patients with coronary artery disease. Our results show that PCI increases coronary flow parameters in a variable fashion according to the initial CFR and FFR values, with the largest increases in both CFR and FFR abnormal values and the smallest increases in both normal CFR and FFR values. Notably in vessels with FFR>0.80 and CFR<2.0, myocardial ischemia according to the CFC grading is frequently present, and PCI improves flow parameters to non-ischemic levels in a high proportion of these patients. Contrarily, in patients with FFR≤0.80 and CFR≥2.0, myocardial ischemia according to the CFC grading is infrequent, and PCI does not further improve the ischemic status.

Physiological principles of FFR/CFR disagreement

The basic principles of coronary physiology state that a pressure drop over a lesion is dictated by the magnitude of flow through the lesion. Hence, the higher coronary flow becomes, the higher the pressure drop over the lesion and the lower the FFR-value. This illustrates that, for a given lesion, variations in maximal coronary flow drive CFR and FFR in opposite directions, giving rise to FFR-CFR discordance. The combination of an abnormal FFR and normal CFR may occur on the basis of a focal epicardial lesion in combination with a preserved compensatory vasodilatory capacity of the coronary microcirculation. Since the microcirculation is functioning normal and unaffected by the epicardial lesions, the high hyperemic coronary flow induces a significant pressure drop and thus abnormal FFR. Such lesions are by definition non-flow-limiting and it is documented that these vessels with FFR<0.80 and CFR≥2.0 have a favorable long-term prognosis when managed medically.

[7][11] Hence, one may argue that PCI offers no incremental clinical benefit compared to OMT. Vice versa, the combination of a normal FFR and abnormal CFR in the setting of intermediate epicardial coronary stenosis may occur on the basis of an epicardial lesion superimposed on a background of diffuse and/or microcirculatory disease that impacts the vasodilatory capacity of the coronary microcirculatory during resting conditions. [12] As a consequence, hyperemic stimuli will only enable a modest increase in coronary flow velocity, potentially resulting in a FFR>0.80 and CFR<2.0. These vessels are associated with adverse long-term prognosis when deferred from revascularization and the optimal treatment strategy remains a topic of debate. [7][9][12]

Impact of PCI on coronary flow parameters stratified by FFR/CFR (dis)agreement

CFC represents a novel concept that enhances the identification of myocardial ischemia by combining CFR with hyperemic flow into a diagnostic platform of incremental levels of ischemia, thereby addressing the sensitivity of CFR towards hemodynamic alterations. [10][13] The concept of CFC is governed by the comprehension that myocardium perfused by vessels with reduced maximal flow and low CFR will show signs of ischemia, whereas ischemia is unlikely in myocardium perfused by vessels with high hyperemic APV or high CFR. CFC grading distinguishes severely and moderately reduced CFC, where signs and symptoms of myocardial ischemia are likely, from mildly reduced and normal CFC, where the presence of myocardial ischemia is unlikely. [10][13][14] Most importantly, CFC grading was documented to improve risk-stratification over the use of CFR alone as the risk of adverse cardiac events increases with increasing impairment of coronary flow capacity. [10][13][14][15] In the present manuscript, we demonstrate that a severely and moderately reduced CFC is frequent for lesions with concordant abnormal FFR and CFR, and PCI undisputedly increases flow parameters to non-ischemic values. Vice versa, for vessels with concordant normal FFR and CFR a severely and moderately reduced CFC is in-frequent and PCI did not alter coronary flow parameters. We documented that, in the setting of angiographically intermediate coronary artery lesions, severely and moderately reduced CFC is frequent for vessels with normal FFR and abnormal CFR, and that PCI may increase flow parameters to non-ischemic levels in a dominant proportion of these patients. On the contrary, severely and moderately reduced CFC was relatively infrequent for vessels with abnormal FFR and normal CFR, and PCI did not affect the overall ischemic status.

Comparison with previous studies

Up to 60% of lesions with FFR≤0.80 left un-revascularized in FAME II did not require PCI up to three-years of follow up , while around 10% of lesions with FFR>0.80 may actually be at risk for adverse events during early follow-up. [3] In addition, the ISCHEMIA trial documented no difference in the occurrence of death and myocardial infarction for OMT versus PCI in patients with stable IHD, warranting a critical revision of contemporary risk

stratification concepts. [16] Adding intracoronary flow assessment by means of CFR to FFR assessment improves this risk stratification in stable IHD. The risk of major adverse events in discordant lesions is mainly characterized by the involvement of the microvasculature. [9] [17] Lesions with a normal FFR and abnormal CFR showed poor prognosis and hyperemic microvascular resistance was found to be elevated. On the contrary, lesions with a abnormal FFR and normal CFR, showed good prognosis and hyperemic microvascular resistance was found to be lower than lesions with a normal FFR and abnormal CFR. The current study adds to the body of evidence that severely and moderately reduced CFC is infrequent in lesions with an abnormal FFR and normal CFR, but is frequently observed in lesions presenting with a normal FFR and abnormal CFR. In a larger sized registry it was documented that CFC can be used to select patient that benefit from PCI. [18] Moreover, it was documented that CFC grading after PCI yields prognostic information compared to CFR. [19][20][21] This can be explained by pertinent coronary physiology as myocardial function thrives on coronary flow and not on perfusion pressure, and reductions in distal coronary perfusion, thus abnormal FFR-values, should therefore not be associated with impaired myocardial function as long as an adequate coronary flow is present, and vice versa. [22] This may explain our findings that for vessels with FFR≤0.80 and CFR≥2.0 severely and moderately reduced CFC is infrequent and, hence PCI does not further improve the ischemic status, whereas for lesions with FFR>0.80 and CFR<2.0 severely and moderately reduced CFC is frequent and PCI increases flow parameters to non-ischemic levels.

Clinical implications

The identification and treatment of stable CAD has been dominated by pressure-based epicardial approaches. Nevertheless, stable CAD comprises a multilevel disease involving both the epicardial and microvascular compartments of the coronary circulation, which can only be evaluated comprehensively by combined pressure and flow measurements. The results of the present manuscript contribute to the growing body of evidence supporting the value of flow assessment analyzed by means of CFC grading. Moreover, the current data suggest that PCI may be advocated for symptomatic intermediate coronary lesions where epicardial lesion severity is obscured by the presence of microvascular disease, hence a presenting with a normal FFR and abnormal CFR. In this group coronary hemodynamics are likely to improve towards non-ischemic values after PCI according to the CFC grading. In contrast, routine PCI for lesions with abnormal FFR and normal CFR seems unnecessary since PCI leads to only limited improvement of coronary hemodynamics.

Limitations

The outcomes of the present study have to be interpreted in consideration of some limitations. First, the manuscript is limited by a relatively small sample size which limits the statistical power. Therefore, the results of the present study need to be interpreted as hypothesis

generating. Second, clinical outcome nor post-PCI angina status were available for this retrospective analysis, which would have strengthened the conclusions. Therefore, the effects of PCI on vessels with FFR/CFR warrant further investigation in a larger prospectively enrolled randomized cohort. Third, the concept of invasive-measured CFC had not been validated against independent ischemic references, hence the claim of that severely-or moderately reduced CFC is likely associated with myocardial ischemia remains to be elucidated. Yet, the concept of CFC was extensively evaluated against positron emission tomography (PET). [13] [21] Moreover, CFC classification, either determined invasively of non-invasively provided more precise stratification of coronary flow impairment than sole CFR measurements and demonstrated meaningful prognostic value. [10][14][15][20][21][23]

CONCLUSION

In patients with FFR>0.80 and CFR<2.0, myocardial ischemia is frequently present (59%) according to the CFC concept and PCI improves flow parameters to non-ischemic levels, whereas in patients with FFR≤0.80 and CFR≥2.0, myocardial ischemia is infrequent (19%) and PCI does not improve the ischemic status.

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PART B

Microvascular function in Acute Coronary Syndromes

CHAPTER 8

Primary PCI: time to change focus from epicardial reperfusion towards protection of the microvasculature

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ABSTRACT

Myocardial tissue perfusion remains compromised in 30-40% of patients with ST-segment elevation myocardial infarction (STEMI) despite restored epicardial patency after primary percutaneous coronary intervention (pPCI). This phenomenon is attributed to microvascular dysfunction secondary to numerous pathophysiological mechanisms, including distal embolisation of plaque and thrombus material. Its association with larger post-infarction myocardial necrosis, impaired left ventricular recovery, and worse clinical outcome illustrates the pertinence of a comprehensive armamentarium for the diagnosis, protection and treatment of microvascular dysfunction in STEMI patients. Current strategies to protect the microvasculature during pPCI are based on the assumption that distal embolisation of thrombotic and atheromatous debris is the main mechanism precipitating impaired myocardial tissue perfusion. However, recent findings suggest that this assumption is only true for the border zone of the ischaemic myocardium, whereas the infarct core consists of intramyocardial haemorrhage secondary to microvascular destruction, rather than obstruction. This observation has pertinent implications for contemporary and future adjuvant treatment strategies in STEMI patients. In this review, we provide an overview of the currently available armamentarium to assess the microvasculature, review contemporary strategies in pPCI to protect the myocardium, and discuss novel insights into microvascular pathophysiology that may help guide our focus from the coronary arteries to the microvasculature.

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) management has evolved dramatically, now encompassing dedicated STEMI networks, potent antithrombotic drugs, rapid achievement of reperfusion, and advanced secondary prevention programmes, which has resulted in a decline in morbidity and mortality in STEMI patients. However, it is well recognised that myocardial tissue perfusion remains compromised in 30-40% of STEMI patients, despite rapid and successful mechanical revascularisation. This phenomenon is associated with larger post-infarction myocardial necrosis, which is a major determinant of morbidity and mortality in STEMI survivors.

Impaired microvascular reperfusion is considered the consequence of numerous pathophysiological mechanisms, including reperfusion injury, distal embolisation of plaque and thrombus material, endothelial dysfunction, leucocyte plugging, and external compression of the microvasculature. Its clinical presentation may range from sudden absence of coronary flow, "no-reflow", to mild flow impairment only appreciated with advanced diagnostic modalities. The clinical pertinence of this phenomenon has triggered tremendous efforts in translational and clinical research in search of a comprehensive armamentarium for the diagnosis, protection and treatment of coronary microvascular dysfunction in the setting of STEMI. In this review, we provide an overview of the currently available armamentarium to assess the microvasculature, review contemporary strategies in pPCI to protect the myocardium, and discuss novel insights into microvascular pathophysiology that may help guide our focus from the coronary arteries to the microvasculature.

CORONARY MICROVASCULATURE: ASSESSING THE "BLACK BOX"

The coronary arterial vasculature comprises the epicardial coronary arteries and the myocardial microvasculature, consisting of extramyocardial prearterioles and intramyocardial arterioles. In normal physiological conditions, the epicardial conductance vessels offer little resistance and predominantly fulfil a capacitance function. The extramyocardial prearterioles, with diameters ranging from 100 to 500 μm, alleviate alterations in perfusion pressure by flow-dependent dilatation and thereby maintain coronary flow within narrow ranges at the origin of the arterioles. The concomitant alterations in the vascular tone of the intramyocardial arterioles, with diameters less than 100 μm, are predominantly regulated by the release of metabolites by the myocardium in response to an increase in oxygen consumption.

At present, no techniques are available that allow in vivo evaluation of the coronary microcirculation in humans, which has consequently long been considered the "black box" of the

coronary circulation. While semi-quantitative assessment of the microvasculature by means of angiography-derived parameters has governed assessment of epicardial and microvascular perfusion after pPCI, more advanced measures of microvascular function have emerged over the last decade – both invasive tools for direct assessment of microvascular function in the catheterisation laboratory, as well as non-invasive tools to assess functional microvascular abnormalities subacutely.

INVASIVE METHODS

Coronary Angiography

Angiography-derived parameters are commonly used to assess reperfusion success after primary PCI, with the Thrombolysis In Myocardial Infarction (TIMI) flow grade as the most widely adopted angiographical surrogate for epicardial flow restoration. However, even optimal TIMI flow may be associated with impaired myocardial tissue perfusion as identified by the myocardial blush grade (MBG) or intracoronary flow velocity measurements, indicating the limited sensitivity of epicardial contrast flow as a surrogate for microvascular function and integrity. [1][2][3] Despite improved sensitivity of MBG for impaired tissue perfusion, direct invasive assessment of coronary flow using sensor-tipped guidewires remains the most sensitive approach to assess impaired coronary flow. [3]

Invasive physiology techniques: Coronary flow

Intracoronary blood flow velocity (CFV) measurements using the Doppler flow technique have been available since the early 1990s, providing Doppler-derived coronary flow velocity reserve (CFVR) as well as morphological characteristics of the flow velocity envelope, diastolic deceleration time (DDT) and early systolic retrograde flow (SRF) (Figure 1). These parameters, assessed in the infarct-related coronary artery, have consistently been shown to correspond to the extent of microvascular dysfunction after reperfusion for STEMI and to be associated with the extent of post-infarction myocardial necrosis and microvascular obstruction (MVO) [4], as well as with recovery of ventricular function and subsequent long-term clinical outcome. [5-7] Moreover, microvascular dysfunction also occurs in perfusion territories remote from the infarcted tissue [6], the extent of which is associated with impaired long-term clinical outcome. [8]

Alternatively, the thermodilution technique was applied to assess coronary flow invasively, in which the temperature sensitivity of a pressure-sensor-equipped guidewire is exploited to measure the mean transit time of a bolus of cold saline injected down a coronary artery (Figure 2). [9] Whereas this technique only allowed assessment of coronary flow reserve, lacking the potential to evaluate the morphological characteristics of the flow velocity envelope, a recent study has suggested that the shape of the thermodilution curve corresponds to distal microvascular functional status. [10]

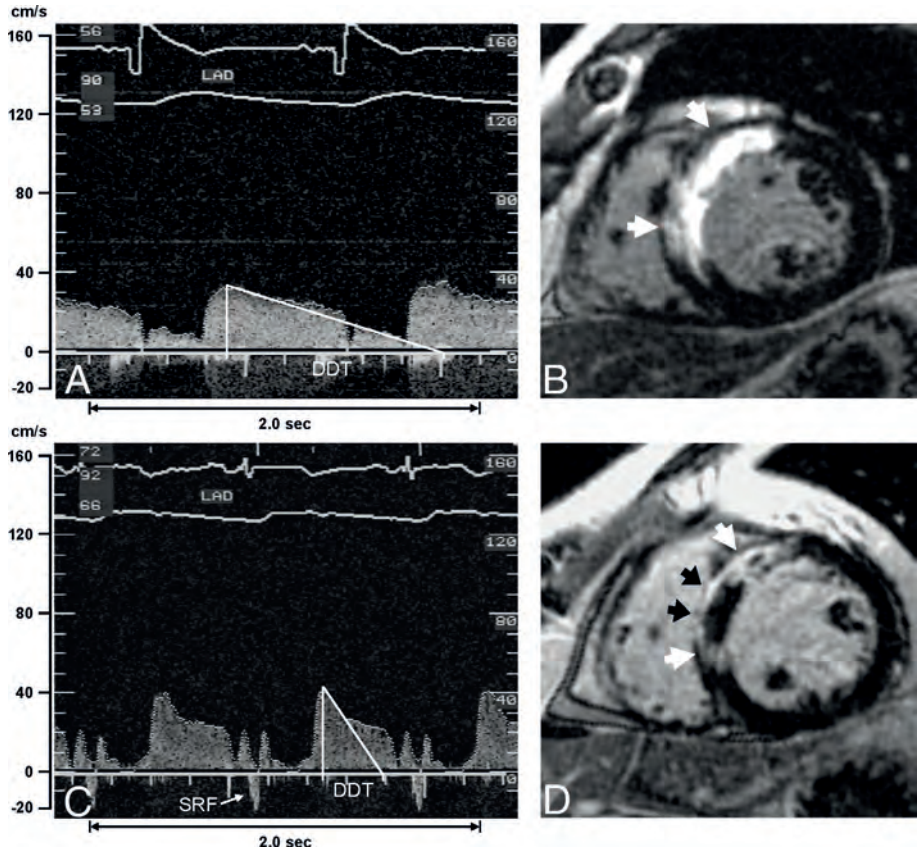

Figure 1. Coronary flow velocity recordings and corresponding late gadolinium-enhanced LGE images of patients without and with microvascular injury (MVI). The coronary flow velocity spectrum (A) of Patient #1 shows antegrade systolic flow without early systolic retrograde flow (SRF) and a normal diastolic deceleration time (DDT). A corresponding LGE image (B) shows transmurally infarcted myocardium (white arrows) in the anteroseptal wall without signs of MVI. The flow velocity pattern (C) of Patient #2 demonstrates SRF and short DDT. The LGE image (D) shows transmurally infarcted myocardium (white arrows) with substantial MVI (black arrows). LAD: left anterior descending coronary artery. (Reproduced with permission). [4]

Invasive physiology techniques: Microvascular resistance parameters

Measuring both distal coronary pressure and a surrogate of coronary flow, either Doppler flow velocity or thermodilution-derived mean transit time, allows the selective evaluation of microvascular resistance to coronary blood flow. [11][12] The minimal microvascular resistance, assessed by the hyperaemic microvascular resistance index (HMR) for Doppler-derived coronary flow (Figure 3) or index of microcirculatory resistance (IMR) for thermodilution-derived coronary flow (Figure 2), is notably associated with ventricular recovery and clinical outcome after STEMI. [6][13] The additional assessment of micro-

vascular resistance during basal, autoregulated conditions allows study of the pathophysiological behaviour of the coronary microcirculation in the setting of STEMI. [6][8] These approaches have shown that, in the acute setting of reperfused STEMI, minimal microvascular resistance is transitorily increased throughout the heart, due to the effects of ischaemia, reperfusion, and neurohumoral activation. After recovery of microvascular vasodilatory function, disturbed microvascular function is typically recognised by the magnitude of microvascular resistance in basal conditions, indicating a persistent stress on the autoregulated mechanism that is associated with impaired clinical outcome. [6][8] In general, the major advantage of microvascular assessment directly in the catheterisation laboratory is to enable immediate instigation of adjunctive therapeutic strategies.

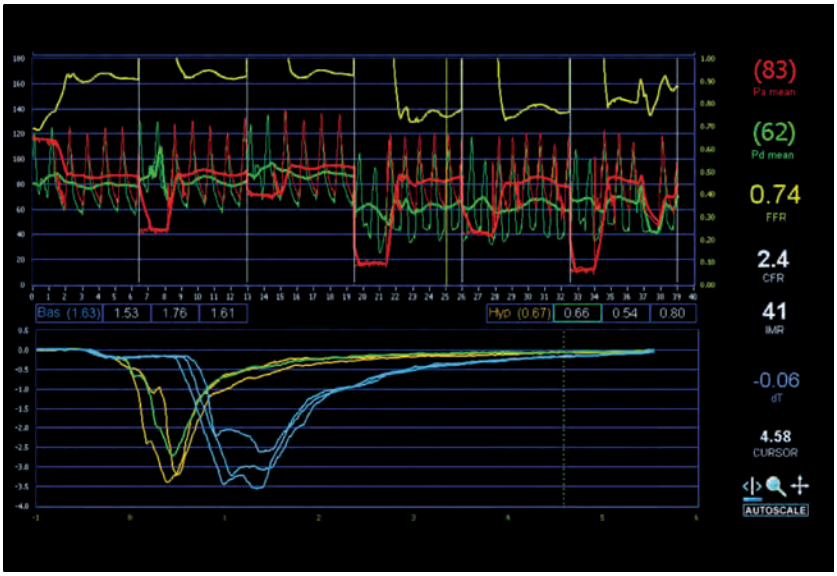

Figure 2. Thermodilution-derived coronary flow using temperature-sensitive pressure-sensor-equipped guidewires (St. Jude Medical, St. Paul, MN, USA) to assess the coronary flow reserve (CFR) and index of microcirculatory resistance (IMR).

NON-INVASIVE METHODS

The non-invasive assessment of microvascular function notably provides important prognostic information, and has allowed critical insights into pathophysiological mechanisms and consequences of impaired microcirculatory perfusion. Non-invasive assessment of the coronary microvasculature may be performed using positron emission tomography (PET), cardio-

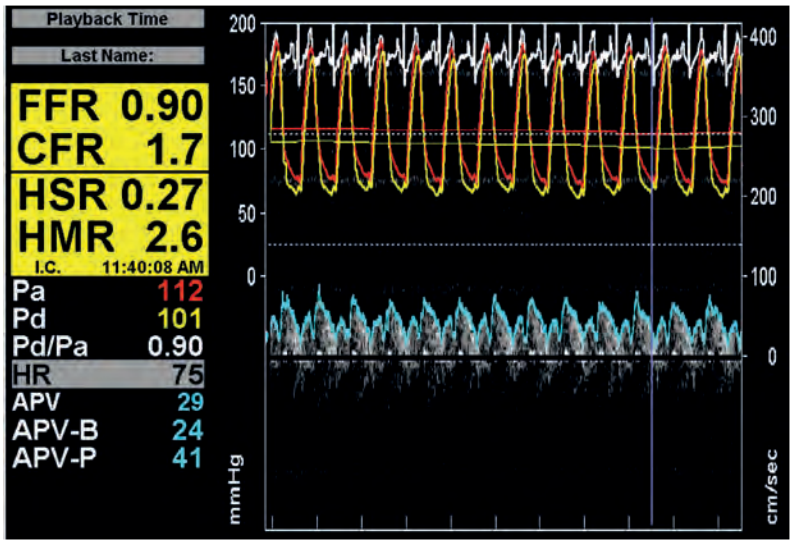

Figure 3. Combined pressure and Doppler flow velocity recordings to assess the coronary flow velocity reserve (CFVR) and the hyperaemic microvascular resistance index (HMR) using the ComboMap® system (Volcano Corp., San Diego, CA, USA).

vascular magnetic resonance (CMR), or even echocardiography. [14] In general, non-invasive techniques allow quantification of myocardial blood flow with the aid of radiolabelled or paramagnetic tracers, measuring the tracer enhancement in the myocardium.

PET provides a non-invasive absolute quantification of regional myocardial tissue perfusion if appropriate tracers and mathematical models are applied. [15] Moreover, sophisticated kinetic modelling and advances in the imaging armamentarium eliminated the necessity of establishing a normal reference region of interest in patients with an increased heterogeneity in myocardial perfusion, as present in the setting of STEMI. [6][16] In addition to absolute perfusion, coronary vascular resistance can be estimated by combining non-invasively derived myocardial blood flow with (mean) arterial blood pressure. Although this method intrinsically does not allow differentiation between flow impairment originating from microvascular dysfunction and (residual) epicardial obstruction, hybrid imaging systems combining PET and CT offer concomitant evaluation of functional and anatomical integrity of the coronary circulation, providing opportunities for advanced hydrodynamic modelling to identify the origin of myocardial flow impairment. [17]

The high anatomical detail of contrast-enhanced CMR has allowed the identification of zones within the infarcted myocardium, with areas of hyperenhancement reflecting infarct

size and a dark hypoenhanced core considered to reflect microvascular obstruction (MVO). These characteristics related to MVO have been consistently associated with impairment of invasive parameters of microvascular function, impaired recovery of ventricular function, and adverse clinical outcome. Hence, the occurrence of MVO on CMR has been used as a surrogate efficacy endpoint for novel therapeutic strategies that target protection of microvascular function in STEMI. [14]

FROM MICROVASCULAR OBSTRUCTION TO MICROVASCULAR INJURY: A PARADIGM SHIFT IN TREATMENT STRATEGIES?

Current strategies to protect the microvasculature during pPCI for STEMI are based on the assumption that distal embolisation of epicardial thrombotic and atheromatous debris is the main mechanism precipitating MVO and no-reflow. This assumption has led to the general inference that the contrast-devoid core of gadolinium-enhanced CMR images represents MVO, and the use of its magnitude as a surrogate of therapeutic efficacy. However, a comprehensive translational study correlating CMR and histological data in a porcine STEMI model with CMR data obtained in STEMI patients undergoing pPCI recently suggested other concomitant pathophysiological mechanisms. The assumption of obstruction as the cause of the lack of contrast uptake was found to be true for the border zone of the infarcted myocardium, but the contrast-devoid core of the infarcted tissue was shown to represent intramyocardial haemorrhage secondary to microvascular destruction, rather than obstruction (Figure 4). [18][19] In detail, the authors identified a border zone of the infarct core with morphologically intact microvasculature that contained microthrombi, and an infarct core with extensive necrosis, loss of vascular integrity and erythrocyte extravasation. These characteristics can be attributed to the ischaemic transmural wavefront, which originates in the subendocardium and progressively moves towards the subepicardial myocardium. [20] At the border of the ischaemic wavefront, injured vessels can still receive and produce coagulation factors, explaining why microthrombi were found, and adding a cause of MVO besides embolisation. [21][22] The loss of cellular integrity in the infarct core is due to complex, interconnected mechanisms following pronounced ischaemia caused by the acute loss of epicardial patency. [23] These hypoxia-induced mechanisms disrupt the endothelial barrier and compromise microvasculature integrity, facilitating extravasation of blood cells upon reperfusion. [24][25] This interpretation of CMR characteristics, previously related to MVO, as a combination of an obstructed border zone and a damaged core led the authors to refer to this condition as microvascular injury (MVI).

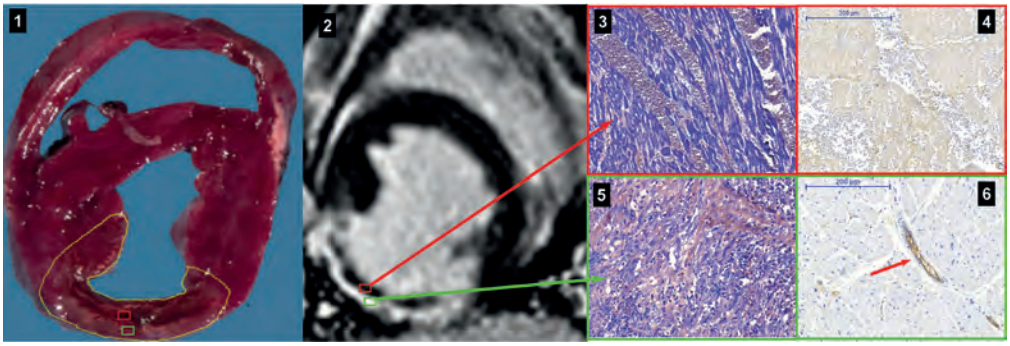

Figure 4. Histology of the porcine model. A) An infarct core (red frame) surrounded by an infarct border zone (green frame). The core corresponds to late gadolinium-enhanced (LGE) images (B) with the area known as "microvascular obstruction". Microscopy reveals extensive haemorrhage on phosphotungstic acid-haematoxylin staining (C, magnification ×200) with a complete loss of the vascular integrity on anti-CD31 staining (D). The border zone corresponds with the enhanced area on LGE (B): this area contains myocyte necrosis, leucocyte influx, and granulation tissue on phosphotungstic acid-haematoxylin (E), with intact vessels on anti-CD31 staining (F, magnification ×200), of which some are plugged by microthrombi (arrow). (Reproduced with permission). [19]

CONTEMPORARY EPICARDIAL REVASCULARISATION STRATEGIES: A FOCUS ON PROTECTION OF THE MICROCIRCULATION

Strategies to protect the microcirculation adopted in contemporary STEMI care are focused on embolic and thrombotic impairment of tissue perfusion to reduce infarct size and improve outcomes, and include the use of thrombus aspiration, novel anticoagulants, adjuvant anticoagulation regimens, and advanced stent designs.

Thrombus aspiration

In order to avoid distal thrombus embolisation, potentially associated with MVO and the no-reflow phenomenon, thrombus aspiration has emerged as a simple, rapid, and relatively inexpensive adjunct to pPCI. [26][30] Thrombus aspiration was shown to improve TIMI flow grade, MBG, as well as clinical outcome. [31][32][33] However, recent large-scale randomised trials have cast doubts on the clinical benefit of routine thrombus aspiration. To date, TAPAS is the only large randomised controlled trial suggesting that routine thrombus aspiration before stenting during pPCI results in improved clinical outcome. [31] INFUSE-AMI was the first to indicate that routine thrombus aspiration was not associated with a reduction in 30-day infarct size, suggesting no protective effect on the microvascular level, even in large anterior wall STEMI patients. [34] Moreover, the 7,244-patient registry-based randomised TASTE trial showed that routine thrombus aspiration before pPCI did not reduce 30-day mortality as compared to pPCI alone. [35] Long-term results

of TASTE are eagerly awaited, and the ongoing TOTAL trial (NCT01149044) will provide additional insights into the benefit of routine thrombus aspiration.

Advanced stent designs

Despite excellent performance of contemporary stent platforms, several new-generation coronary stents with a focus on STEMI treatment are currently being evaluated, in which stent designs are shifting towards prevention of distal embolisation in stenting of thrombus-rich epicardial lesions. An illustrative example is a bare metal stent covered with a micronet mesh (MGuard™; InspireMD, Tel Aviv, Israel) , designed to mitigate distal embolisation and associated no-reflow by trapping embolism-prone material within the mesh. In pPCI for STEMI, its use resulted in superior rates of restored epicardial coronary flow and complete ST-segment resolution compared with conventional stents. [36] A large randomised clinical trial evaluating its effects on infarct size is ongoing (NCT01869738). Self-expanding coronary stents are also being proposed to limit distal embolisation since they do not require aggressive balloon dilatation to acquire optimal expansion. Nonetheless, in clinical practice, balloon dilatation is regularly performed either pre- or post-stent placement to prevent acute complications associated with severe malappositioning. [37] It seems conceivable that balloon dilatation may reduce some of the benefit related to self-expansion, but this remains speculative.

In the recent DEFER-STEMI trial, stent placement was deferred if TIMI 3 flow was obtained after thrombus aspiration with or without low-pressure balloon angioplasty. [38] This approach was governed by the hypothesis that immediate stent placement is associated with adverse effects such as MVO and no-reflow, whereas delayed stenting allows partial relief of thrombus burden and recovery of microvascular function. Indeed, delayed stenting reduced the rate of no-reflow, and improved myocardial salvage as compared to an immediate stenting strategy, paving the way for this novel approach, but also for dedicated stent platforms.

Procedural and adjunctive anticoagulation regimens

Aggressive anticoagulation regimens governed pharmacological adjunctive strategies in the acute setting of pPCI, due to the consideration of distal embolisation of thrombus fragments as the main determinant of MVO and no-reflow.

The use of fibrinolysis as a standalone therapeutic approach in STEMI has declined dramatically after extensive evidence showed inferiority to pPCI. However, the administration of low-dose intracoronary streptokinase immediately after pPCI was shown to improve TIMI flow grade and microvascular function, to limit infarct size, and to preserve left ventricular volumes and function. [39][40] These hypothesis-generating findings emphasise the

potential of adjunctive fibrinolytic therapy to improve microvascular function, and justify further exploration in more definitive trials. [41][42]

The potent inhibition of platelet aggregation with the concomitant use of glycoprotein IIb/IIIa inhibitors and heparin was found to reduce the incidence of ischaemic events over the use of heparin alone, albeit with concerns of haemorrhagic complications. [43][44][45] Consequently, the administration of a glycoprotein IIb/IIIa inhibitor should be considered for bail-out therapy if there is angiographic evidence of massive thrombus, slow or no-reflow, or a thrombotic complication according to the European guidelines [33], and the US guidelines consider it reasonable to administer glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing PCI, although they do not definitively recommend it as routine therapy. [32]

The direct thrombin inhibitor bivalirudin was suggested to provide potent anticoagulation similar to the combination of heparin and a glycoprotein IIb/IIIa inhibitor, but resulting in reduced rates of haemorrhagic complications, overall improving both early and long-term clinical outcomes. [46][47] Notwithstanding, recent trials have cast doubts on the efficacy of bivalirudin to improve outcome in contemporary practice using novel thienopyridines in combination with heparin or bivalirudin alone, and glycoprotein IIb/IIIa inhibition in a bail-out strategy. Interestingly, the INFUSE-AMI trial showed that, in patients with large anterior wall STEMI undergoing pPCI with bivalirudin anticoagulation, administration of a glycoprotein IIb/IIIa inhibitor directly to the infarct lesion site prior to pPCI was associated with a significant reduction in 30-day infarct size. [34]

Future strategies to protect the microvasculature

Amid the focus on preventing embolic and thrombotic complications of pPCI to protect the microvasculature, the observation of MVI has pertinent implications for adjuvant treatment strategies in STEMI, and could well explain the limited efficacy of contemporary treatment strategies focused on improving microvascular perfusion. The identification of a border zone of the infarct core comprising morphologically intact microvasculature containing microthrombi suggests an obstructive or at least thrombotic origin that might benefit from thrombus aspiration and aggressive anticoagulation therapy secondary to revascularisation. However, an infarct core without intact vasculature characterised by excessive extravasation suggests a haemorrhagic origin that might be aggravated by aggressive anticoagulation therapies. Additionally, the vulnerability of the hypoxic microvasculature could augment the loss of vessel integrity in response to the sudden restoration of perfusion pressure by pPCI, which corroborates the fact that reperfusion itself has been shown to induce expansion of myocardial necrosis. Moreover, inflammatory processes that go beyond the embolisation theory have been described as leading to infarct expansion. [48]

Many novel therapeutic strategies to protect the microvasculature have been evaluated in experimental and clinical models, most of them unfortunately without much success to date. In their review, Windecker et al concluded that reduction of treatment delays remains the cornerstone of preventing myocardial injury in view of the limited novel therapeutic options to reduce microvascular injury. [49] In addition, the cardioprotective effectiveness of interruption of reperfusion with short periods of ischaemia, also referred to as postconditioning, remains a subject of debate. The new insights into MVI together with previously documented benefits of gradual reperfusion indicate that the destructive force of abrupt restoration of perfusion pressure and the vulnerability of the ischaemic microvasculature could well be therapeutic targets for future treatment strategies. [50][51][52] The growing insights into the detrimental effects of the inflammatory response after STEMI provide another potential therapeutic target, even more so since it has been shown that early intravenous beta-blockade therapy reduces infarct size and increases left ventricular ejection fraction, likely due to alteration of the inflammatory response following ischaemia. [48][53]

CONCLUSION

Myocardial reperfusion goes beyond restoring epicardial patency. Advanced diagnostic modalities allow accurate assessment of microvascular function and the effects of reperfusion in the setting of STEMI, which allows the identification of patients who may benefit from adjuvant therapies after pPCI. Future therapeutic strategies should not limit their therapeutic target to resolving distal embolisation of the microvasculature, but should focus on protecting the microvasculature against the harmful effects of reperfusion and on enhancing healing of the injured microvasculature and myocardium in those patients who may benefit most.

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CHAPTER 9

Acute alterations in glucose homeostasis impact coronary microvascular function in patients presenting with ST-segment elevation myocardial infarction

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ABSTRACT

Background: Microvascular dysfunction in the setting of ST-segment myocardial infarction (STEMI) is thought to be related to stress-related metabolic changes, including acute glucose intolerance. The aim of this study was to assess the relationship between admission glucose levels and microvascular function in non-diabetic STEMI patients.

Methods: 92 consecutive patients with a first anterior-wall STEMI treated with primary percutaneous coronary intervention (PPCI) were enrolled. Blood glucose levels were determined immediately prior to PPCI. After successful PPCI, at 1-week and 6-month follow-up, Doppler flow was measured in culprit and reference coronary arteries to calculate coronary flow velocity reserve (CFVR), baseline (BMR) and hyperaemic (HMR) microvascular resistance.

Results: The median admission glucose was 8.3 (7.2–9.6) mmol/l respectively 149.4 mg/dl [129.6–172.8] and was significantly associated with peak troponin T (standardised beta coefficient [std beta] = 0.281; p = 0.043). Multivariate analysis revealed that increasing glucose levels were significantly associated with a decrease in reference vessel CFVR (std beta = –0.313; p = 0.002), dictated by an increase in rest average peak velocity (APV) (std beta = 0.216; p = 0.033), due to a decreasing BMR (std beta = –0.225; p = 0.038) in the acute setting after PPCI. These associations disappeared at follow-up. These associations were not found for the infarct-related artery.

Conclusion: Elevated admission glucose levels are associated with impaired microvascular function assessed directly after PPCI in first anterior-wall STEMI. This influence of glucose levels is an acute phenomenon and contributes to microvascular dysfunction through alterations in resting flow and baseline microvascular resistance.

INTRODUCTION

It is well recognised that even after rapid and successful revascularisation of ST-segment elevation myocardial infarction (STEMI), myocardial tissue perfusion remains compromised in 30–40% of patients despite restored epicardial patency. [1][2] This phenomenon is attributed to microvascular dysfunction in the setting of acute STEMI [3], which is observed in both the perfusion territory of the culprit artery, and in non-ischaemic regions remote from the infarcted myocardial tissue. [4] Whereas culprit vessel flow abnormalities have been ascribed to numerous pathophysiological mechanisms, it has partly been ascribed to metabolic consequences of the acute ischemic event. [5][6]

Major stress-related metabolic changes occur during the early hours of STEMI, which include the release of stress hormones such as noradrenaline and cortisol, increased concentration of free fatty acids, and the occurrence of glucose intolerance. [7] As a result, elevated glucose levels are frequently observed in (non-diabetic) STEMI patients, which have been associated with an increased risk of in-hospital mortality, congestive heart failure and cardiogenic shock in patients with and without diabetes. [8][9] Notably, in patients with STEMI, hyperglycaemia is associated with the no-reflow phenomenon in the culprit vessel, postulated to be a proxy of microvascular dysfunction. [10] It suggests that the acute metabolic changes in STEMI may contribute to microvascular dysfunction in this setting through alterations in glucose homeostasis.

The aim of this study was to assess the relationship between admission glucose levels and microvascular function in non-diabetic patients with first anterior-wall STEMI.

METHODS

A total of 100 consecutive patients with a first anterior-wall STEMI treated by primary percutaneous coronary intervention (PPCI) were enrolled. The initial results were reported previously. [4][11] STEMI was defined as chest pain lasting >30 minutes in the presence of persistent ST-segment elevation in ≥2 precordial leads. PPCI was performed within 6 hours after onset of symptoms according to standard clinical practice. The exclusion criteria were reported previously. [4] The study protocol was approved by the local ethics committee and all patients gave informed consent.

Cardiac catheterisation and periprocedural measurements

After successful reperfusion, intracoronary blood flow velocity was measured in the infarct-related artery (IRA) and an angiographic normal reference vessel (diameter stenosis

<30% on visual estimation) using a 0.014-inch sensor equipped guide wire (Volcano Corp., San Diego, CA). Reference vessel measurements were performed in the left circumflex coronary artery, or the right coronary artery if a stenosis of >30% was present. At 1-week and 6-month follow-up, patients underwent repeat angiography with assessment of intracoronary Doppler flow velocity. Hyperaemia was induced by an intracoronary bolus of 20–40 μg adenosine. Before and after PCI, coronary angiography suitable for quantitative coronary angiographic analysis was performed for offline analysis of thrombolysis in myocardial infarction (TIMI) flow and myocardial blush grade. Left ventricular function was evaluated by means of echocardiographic 16-segment Wall Motion Score Index (WMSI) performed immediately before PPCI.

Haemodynamic data analysis

Coronary flow velocity reserve (CFVR) was calculated as the ratio of hyperaemic average peak flow velocity (hAPV) to baseline average peak velocity (bAPV). In the absence of significant epicardial disease in the reference vessels, microvascular resistance was calculated at baseline and during hyperaemia, respectively the ratio between mean aortic pressure and mean distal flow velocity at baseline (baseline microvascular resistance—BMR), and during hyperaemia (hyperaemic microvascular resistance—HMR). The delta microvascular resistance from resting to hyperaemic conditions (dMR) was determined by calculating the absolute difference between BMR and HMR.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk test, and homogeneity of variance was tested with Levene's test. All continuous variables are presented as mean ± standard deviation or median [25th–75th percentile] according to their normal or non-normal distribution. Categorical variables are presented as counts and percentages. Univariate regression analysis was used to identify variables associated with reference vessel CFVR at the end of the PPCI procedure ($p_{\text{inclusion}} < 0.1$), with candidate variables including all baseline, laboratory and procedural covariates as listed in Table 1. Subsequent multivariate analysis was performed using a multivariate linear regression model with adjustments for these variables to identify the association of glucose levels with microvascular function parameters, which are presented as standardised coefficients to facilitate comparison. A p-value below the two-sided α-level of 0.05 was considered statistically significant.

RESULTS

In total, 92 patients were included in the study (Table 1). Median admission glucose was 8.3 mmol/l [7.2–9.6] respectively 149.4 mg/dl [129.6–172.8] and was significantly associated with infarct size (standardised beta coefficient [std beta] = 0.281; $p = 0.043$), as determined by peak troponin T levels. After PPCI, IRA TIMI 3 flow was achieved in 65 patients (70%). Intracoronary physiological measurements obtained in the IRA and reference vessel are presented in Table 2.

Association between admission glucose and microvascular function after PPCI

No association was found between admission glucose levels with $CFVR_{IRA}$, as well as $bAPV_{IRA}$ or $hAPV_{IRA}$ measured directly after revascularisation.

$CFVR_{reference}$ decreased significantly with increasing admission glucose levels (std beta = −0.381; $p < 0.001$). In addition, $bAPV_{reference}$ increased significantly with increasing admission glucose levels (std beta = 0.244; $p = 0.020$), and $BMR_{reference}$ decreased with admission glucose levels (std beta = −0.257; $p = 0.015$). Consequently, $dMR_{reference}$ decreased with increasing admission glucose levels (std beta = −0.325; $p = 0.002$) (Figure 1). $hAPV_{reference}$ as well as $HMR_{reference}$ did not show a significant association with admission glucose levels.

Univariate analysis of all candidate baseline, laboratory and procedural covariates as listed in Table 1. Age, heart rate, peak troponin T after 24 hours, WMSI assessed before PPCI, and the use of calcium antagonists were associated with $CFVR_{reference}$. After adjustment for these variables, admission glucose level remained independently associated with $CFVR_{reference}$ (std beta = −0.313; $p = 0.002$), $bAPV_{reference}$ (std beta = 0.216; $p = 0.033$), $BMR_{reference}$ (std beta = −0.225; $p = 0.038$) and $dMR_{reference}$ (std beta = −0.274; $p = 0.008$) (Table 3).

Association between admission glucose and microvascular function at 1-week and 6-month follow-up

At one week follow-up, intracoronary physiology measurements in the IRA and reference vessel were repeated in 62 patients (Table 2). No significant association was found between admission glucose levels and $CFVR_{IRA}$, $bAPV_{IRA,}$ as well as $hAPV_{IRA}$ measured at 1-week follow-up.

Univariate analysis revealed that admission glucose was significantly associated with $CFVR_{reference}$ (std beta = −0.284; $p = 0.025$), $BMR_{reference}$ (std beta = −0.280; $p = 0.029$), and $dMR_{reference}$ (std beta = −0.295; $p = 0.021$). However, after adjustment for the identified confounders, none of these variables retained a significant association.

Table 1. Baseline clinical and procedural characteristics ($n = 92$)

Demographics	
Age, y	56 ± 12
Male	74 (80)
Risk factors	
Smoking	49 (53)
Hypertension	23 (25)
Family history	39 (42)
Hyperlipidaemia	24 (26)
Prior medication use	
βBlocker	12 (13)
Calcium antagonist	8 (9)
Angiotensin-converting enzyme inhibitors	5 (5)
Nitrates	4 (4)
Lipid-lowering drugs	7 (8)
Aspirin	11 (12)
Laboratory assessment at admission	
CRP, mg/l	1.9 [1.1–5.2]
Glucose, mmol/l	8.3 [7.2–9.6]
Creatinine, μmol/l	70 [60–79]
NT-proBNP after reperfusion, pg/ml	93 [49–242]
Peak troponin T after 24 hours, ng/ml	4.58 [2.47–6.34]
Procedural characteristics	
Heart rate, bpm	79 ± 13
Systolic arterial pressure, mm Hg	119 ± 15
WMSI before reperfusion	1.9 ± 0.2
Time to reperfusion, h	2.9 [2.3–3.9]
ST-segment resolution after reperfusion ≥70%	40 (43)
Angiographic	
Final TIMI flow grade 3	56 (60)
Final myocardial blush grade 3	37 (40)

Data are presented as mean ± SD, median [25th–75th percentile], or frequency (%). CRP C-reactive protein, eGFR estimated glomerular filtration rate, NT-proBNP N-terminal pro-brain natriuretic peptide, TIMI thrombolysis in myocardial infarction, WMSI Wall Motion Score Index

Table 2. Haemodynamic characteristics

Infarct-related artery at admission (n =92)	
Final IRA CFVR	1.5 [1.3–1.7]
Baseline APV, cm per second	19 [14–24]
Hyperaemic APV, cm per second	29 [21–42]
Infarct-related artery at 1 week (n =62)	
Final IRA CFVR	1.9 [1.6–2.2]
Baseline APV, cm per second	21 ± 7
Hyperaemic APV, cm per second	37 [30–44]
Infarct-related artery at 6 months (n =61)	
Final IRA CFVR	2.8 ± 0.9
Baseline APV, cm per second	17 ± 7
Hyperaemic APV, cm per second	48 ± 19
Reference vessel haemodynamics at admission (n =91)	
Reference CFVR	2.3 [2.0–2.7]
Baseline APV, cm per second	16 [14–20]
Hyperaemic APV, cm per second	37 [31–45]
Baseline MR, mm Hg/cm per second	7.2 [6.2–8.8]
Hyperaemic MR, mm Hg/cm per second	3.1 [2.6–3.8]
Delta MR, mm Hg/cm per second	4.0 [3.3–5.4]
Reference vessel haemodynamics at 1 week (n =62)	
Reference CFVR	2.7 ± 0.5
Baseline APV, cm per second	17 [13–20]
Hyperaemic APV, cm per second	44 [35–53]
Baseline MR, mm Hg/cm per second	6.6 [5.4–8.4]
Hyperaemic MR, mm Hg/cm per second	2.5 [2.1–3.0]
Delta MR, mm Hg/cm per second	4.2 [3.4–5.4]
Reference vessel haemodynamics at 6 months (n =61)	
Reference CFVR	3.4 ± 0.6
Baseline APV, cm per second	15 [10–21]
Hyperaemic APV, cm per second	47 [39–60]
Baseline MR, mm Hg/cm per second	8.9 [6.2–11.3]
Hyperaemic MR, mm Hg/cm per second	2.5 [2.0–3.0]

Values are presented as mean±SD or median (25th–75th percentile). APV average peak flow velocity, CFVR coronary flow velocity reserve, IRA infarct-related artery, MR microvascular resistance.

Table 3. Association between reference CFVR and glucose by univariate and multi-variate analysis at admission, 1week and 6month follow-up

	At admission (n = 92)				At 1week follow-up (n = 61)		At 6month follow-up (n=61)	
	Univariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis	
	Std beta	P value	Std beta	P value	Std beta	P value	Std beta	P value
CFVR in reference vessel								
Glucose	−0.381	<0.001	−0.313	0.002	-	-	-	-
Age	−0.254	0.015	-	-	-	-	-	-
Heart rate	−0.225	0.034	-	-	−0.413	0.002	-	-
Peak troponin T (after 24 h)	−0.469	<0.001	−0.355	0.002	-	-	-	-
WMSI	−0.265	0.014	-	-	-	-	−0.278	0.042
Calcium antagonist	−0.381	<0.001	-	-	-	-	-	-
Baseline APV in reference vessel								
Glucose	0.244	0.02	0.216	0.033	-	-	-	-
Age	-	-	-	-	-	-	-	-
Heart rate	-	-	-	-	-	-	-	-
Peak troponin T (after 24 h)	0.241	0.026	-	-	-	-	-	-
WMSI	0.316	0.003	0.266	0.014	-	-	-	-
Calcium antagonist	0.349	0.001	0.385	<0.001	-	-	-	-
Baseline MR in reference vessel								
Glucose	−0.257	0.015	−0.225	0.038	-	-	-	-
Age	-	-	-	-	-	-	-	-
Heart rate	−0.262	0.02	−0.229	0.045	−0.269	0.044	-	-
Peak troponin T (after 24 h)	−0.228	0.038	-	-	−0.346	0.022	-	-
WMSI	−0.326	0.003	−0.246	0.035	-	-	-	-
Calcium antagonist	−0.295	0.006	−0.292	0.008	-	-	-	-
Delta MR in reference vessel								
Glucose	−0.325	0.002	−0.274	0.008	-	-	-	-
Age	-	-	-	-	-	-	-	-
Heart rate	−0.318	0.004	−0.244	0.023	−0.320	0.015	-	-
Peak troponin T (after 24 h)	−0.376	<0.001	-	-	−0.336	0.022	-	-
WMSI	−0.357	0.001	−0.223	0.041	-	-	-	-
Calcium antagonist	−0.299	0.005	−0.247	0.016	-	-	-	-

Std beta standardised beta coefficient, CFVR coronary flow velocity reserve, APV average peak velocity, MR microvascular resistance, WMS Wall Motion Score Index

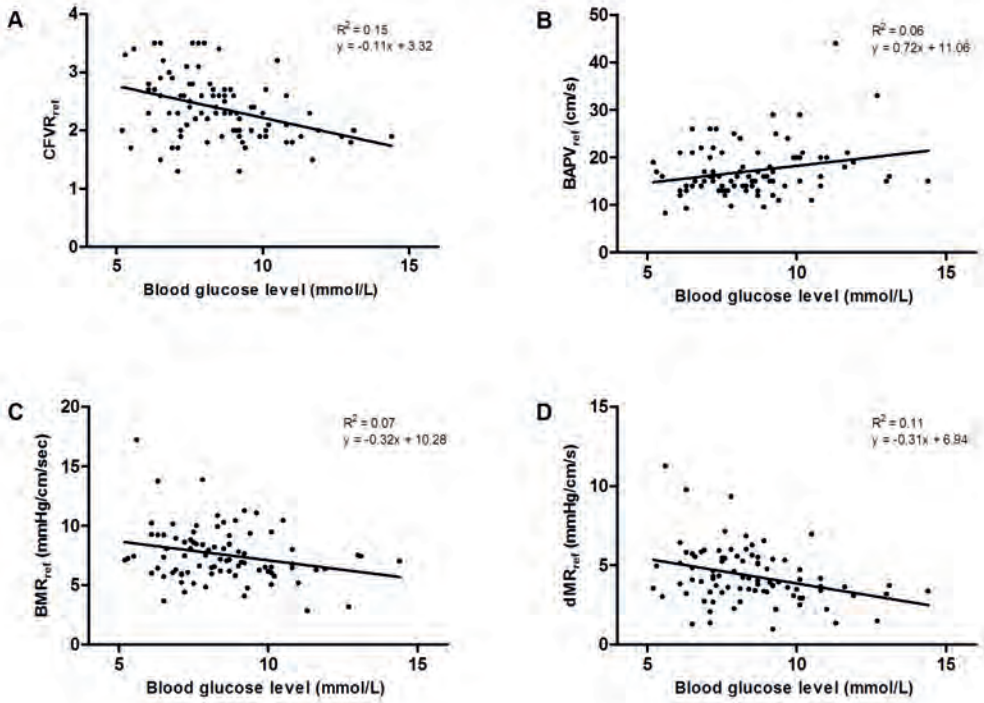

Figure 1. Scatterplots of admission glucose levels with microvascular function in the reference vessel after PPCI. Admission glucose levels were significantly associated with coronary flow velocity reserve (a), bAPV (b), BMR (c) and dMR (d) in the reference vessel in the acute setting of STEMI (*PPCI* primary percutaneous coronary intervention, $CFVR_{ref}$ reference vessel coronary flow velocity reserve, $bAPV_{ref}$ reference vessel baseline averaged peak velocity, BMR_{ref} reference vessel baseline microvascular resistance, dMR_{ref} reference vessel delta microvascular resistance)

At 6-month follow-up, intracoronary physiology measurements in the IRA and reference vessel were repeated in 61 patients (Table 2). Univariate analysis revealed that admission glucose at times of the PPCI was only associated with $CFVR_{reference}$ measured at 6-month follow-up, although this association was eclipsed after adjusting for the identified confounders. Univariate analysis revealed no association between admission glucose levels, BAPV, hAPV and CFVR at 6-month follow-up.

DISCUSSION

We observed that increased admission glucose levels in the acute setting of STEMI are independently associated with alterations in microvascular function, particularly during resting, autoregulated conditions. Increasing glucose levels were associated with progressive impairment of reference vessel CFVR measured directly after PPCI, which resulted from increased bAPV secondary to decreased BMR. At 1-week and 6-month follow-up, the existing associations present in the acute setting disappeared, suggesting recovery of coronary autoregulatory function at normalisation of glucose levels.

It has been reported that age, heart rate and infarct size affect myocardial blood flow by influencing myocardial microvascular function. [12][13][14][15] Our results confirm this, and add that blood glucose, likely secondary to acute metabolic changes in response to the infarction, plays a distinct role in the pan-myocardial microvascular dysfunction observed in the acute setting of first anterior STEMI.

We found no association between microvascular function and admission glucose levels in the IRA. The influence of admission glucose levels on the parameters of microvascular function was likely eclipsed by other physiological processes that alter microvascular function in the IRA during the acute setting of STEMI.

Microvascular function following STEMI: novelty of the present findings

Microvascular function assessed by Doppler flow velocity is known to be altered in the setting of STEMI, even in non-ischaemic regions at distance from the infarcted myocardium. [4] We previously reported that microvascular dysfunction in these regions is expressed in an impairment of reference vessel CFVR, which is independently associated with long-term fatal cardiac events. [11] We showed that the acute impairment of reference vessel CFVR in the setting of STEMI originates from a combination of decreased hAPV in the presence of increased HMR, and increased bAPV in the presence of decreased BMR. It has been hypothesised that a combination of mechanical and metabolic alterations due to the acute ischaemic event is responsible for the overall flow impairment at a distance of the infarcted myocardium. The increase in HMR leading to impairment of hyperaemic flow is generally attributed to neurohumoral overactivation. [5] A reduced BMR leading to an increased resting coronary flow may underlie a mechanical as well as a metabolic origin, which is yet to be elucidated. Our present results attribute at least part of the decrease in BMR, and the resulting increase in basal flow velocity, to metabolic changes in the setting of acute STEMI reflected in hyperglycaemia.

Glucose and insulin mediated microvascular dysfunction

Increased glucose levels are frequently observed in non-diabetic patients presenting with acute myocardial infarction. It reflects the conjoined effects of many interrelated stress mechanisms that influence glucose homeostasis secondary to the acute ischaemic event. [7][16] Relative insulin resistance is proposed as one of the contributing mechanisms, caused by antagonising effects of stress mediators that impair insulin-regulated glucose uptake. [17][18] Concomitantly, insulin plays an important role as a mediator in normal myocardial and systemic vascular function. [19] It has been demonstrated to increase myocardial blood flow, acting as a slow vasodilator inducing vasodilation in a time and dose dependent manner. [20][21][22] In patients with coronary artery disease, intracoronary insulin infusion increases coronary blood flow in the absence of an increase in myocardial oxygen demand. [20] The most important physiological mechanism that contributes to insulin-induced vasodilation is the L-arginine to nitric oxide pathway in the vascular endothelium. [23] Despite the effects of insulin resistance on glucose uptake and resulting hyperglycaemia, it has been shown that the insulin-induced coronary vasodilation still occurs in obese patients with insulin resistance. [24] Therefore, the association observed between myocardial microvascular function and admission glucose levels might reflect the effect of elevated plasma levels of insulin, secondary to acute relative insulin resistance, on myocardial vascular function. Unfortunately, plasma insulin levels were not measured in the present study and the proposed mechanism of action should be considered hypothesis-generating.

Concomitant causes of increased baseline flow velocity in STEMI

In addition to the influence of alterations in glucose homeostasis on microvascular function, and in particular bAPV and BMR, other factors may have had a concomitant effect on bAPV. Due to regional myocardial dysfunction, hyperkinesia of remote non-ischaemic myocardium may occur, leading to a predominant increase in bAPV due to an increase in local myocardial oxygen demand. [25][26] In addition, an increase in left ventricular end-diastolic pressure or stiffening of the myocardium because of hypoxic perfusion, may result in a restriction in myocardial capacitance, leading to an isolated increase in reference vessel bAPV. [27][28] Nonetheless, the association between admission glucose levels and the bAPV retained significance after adjusting for the identified confounders, including infarct size WMSI which can be considered important predictors for the magnitude of hyperkinesia, left ventricular end-diastolic pressure and hypoxic perfusion.

Implications for the present study

The present study implies that admission glucose levels are associated with reference vessel microvascular function in the acute setting of STEMI, influencing resting coronary vascular tone and increasing resting flow. Importantly, increased bAPV has previously been documented to be associated with impaired clinical outcomes in both stable coronary artery

disease and STEMI. [11][29] Due to the role of insulin in establishing glucose homeostasis and altering vascular tone, we hypothesise that high insulin levels, secondary to acute insulin resistance, are the mechanism of action responsible for the increase in bAPV. Recovery of this phenomenon at follow-up likely drives recovery of normal coronary autoregulatory function. The fact that larger myocardial infarctions, as determined by troponin T levels, were associated with higher glucose levels, as well as with higher resting flow levels, suggests that the severity of the acute ischaemic event determines the magnitude of metabolic disturbance, and is thereby indirectly related to the magnitude of pan-myocardial microvascular dysfunction.

Limitations

Accurate assessment of flow velocity depends on the operator's experience, and, furthermore, on the achievement of maximal vasodilation. The measurements in this study were performed by experienced operators. The amount of adenosine used in this study is considered sufficient. [30]

We only assessed reference vessel microvascular resistance in coronary arteries without angiographically significant epicardial narrowing using aortic pressure as a substitute for distal pressure.

In this study, glucose levels were only measured at admission and were not repeated at 1-week and 6-month follow-up. This did not allow for exploration of the time course of glucose levels in the period following myocardial infarction. In addition, insulin levels were not determined at any of the time points, resulting in the fact that the hypothesised mechanism could not be further elucidated. Subjects were excluded based on known pre-existing diabetes at the time of admission, however, information on the HbA1C levels was not available to reveal unknown pre-existing impaired glucose homeostasis. Additionally, the study population was relatively small, in particular at 6-month follow-up, and some statistical analyses may lack statistical significance because of a lack of statistical power.

CONCLUSION

Elevated glucose levels at admission for anterior STEMI are associated with impaired microvascular function in myocardial territories remote from the infarction, as assessed by CFVR in reference coronary arteries measured after PPCI. This influence of glucose levels is an acute phenomenon dominantly affecting coronary autoregulation, affecting BMR and bAPV, and contributes to the pan-myocardial microvascular dysfunction observed in acute STEMI.

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CHAPTER 10

Time course of coronary flow capacity impairment in ST-segment elevation myocardial infarction

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ABSTRACT

Background: Microvascular dysfunction in the setting of ST-elevated myocardial infarction (STEMI) plays an important role in long-term poor clinical outcome. Coronary flow reserve (CFR) is a well-established physiological parameter to interrogate the coronary microcirculation. Together with hyperaemic average peak flow velocity, CFR constitutes the coronary flow capacity (CFC), a validated risk stratification tool in ischaemic heart disease with significant prognostic value. This mechanistic study aims to elucidate the time course of the microcirculation as reflected by alterations in microcirculatory physiological parameters in the acute phase and during follow-up in STEMI patients.

Methods: We assessed CFR and CFC in the culprit and non-culprit vessel in consecutive STEMI patients at baseline (n = 98) and after one-week (n = 64) and six-month follow-up (n = 65).

Results: A significant trend for culprit CFC in infarct size as determined by peak troponin T ($p = 0.004$), time to reperfusion ($p = 0.038$), the incidence of final Thrombolysis In Myocardial Infarction 3 flow ($p = 0.019$) and systolic retrograde flow ($p = 0.043$) was observed. Non-culprit CFC linear contrast analysis revealed a significant trend in C-reactive protein ($p = 0.027$), peak troponin T ($p < 0.001$) and heart rate ($p = 0.049$). CFC improved both in the culprit and the non-culprit vessel at one-week (both $p < 0.001$) and six-month follow-up ($p = 0.0013$ and $p < 0.001$) compared with baseline.

Conclusion: This study demonstrates the importance of microcirculatory disturbances in the setting of STEMI, which is relevant for the interpretation of intracoronary diagnostic techniques which are influenced by both culprit and non-culprit vascular territories. Assessment of non-culprit vessel CFC in the setting of STEMI might improve risk stratification of these patients following coronary reperfusion of the culprit vessel.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is considered the cornerstone for treating ST-segment elevation myocardial infarction (STEMI), and the implementation of dedicated revascularization networks has resulted in a remarkable decline in cardiac morbidity and mortality. [1] Despite these advancements, a significant proportion of patients have a poor outcome, which is attributed to changes in the microvascular function and integrity due to the ischaemic event. [2] It is increasingly recognized that the impact of the acute ischaemic event on the functional and structural integrity of the microcirculation may yield opportunities to further enhance clinical outcomes in STEMI patients. [3]

Coronary flow reserve (CFR) is a well-validated index that assesses the contribution of obstructive, diffuse and microcirculatory involvement to coronary flow impairment in ischaemic heart disease. [4][5][6] In the past decades it has been extensively used to elucidate the role of microvascular dysfunction for the prognosis of myocardial infarction. However, assessing the coronary microcirculation solely by means of CFR is inherently cumbersome in STEMI patients, since residual effects of the ischaemic events and changes in (regional) cardiac workload may influence resting or hyperaemic flow and thereby obscure microvascular function assessment by CFR values. [7]

Recently the coronary flow capacity (CFC) concept has been validated as a cross modality platform for the diagnosis, prognosis and risk-stratification in ischaemic heart disease. [7] [8] It integrates both the coronary vasodilatory reserve as well as maximal achievable flow, thereby providing comprehensive insight into coronary haemodynamics. [9] Accordingly, CFC was documented to be less prone to alterations in systemic haemodynamics. [10] In the present study we aimed to document the impact of STEMI on CFC in 1) the ischaemic region of the myocardium and 2) in myocardial territories remote from the infarction at baseline, one-week and six-month follow-up.

METHODS

Between April 1997 and August 2000, 98 consecutive patients with a first anterior wall STEMI treated by primary PCI were enrolled in the study, for whom the initial results have been reported previously. [2][11] All patients were treated in the Amsterdam University Medical Centres – location AMC, a large tertiary referral centre in Amsterdam, The Netherlands.

Anterior STEMI was defined as chest pain lasting >30 min in the presence of persistent ST-segment elevation in ≥ 2 precordial leads. Primary PCI was performed within 6 hours after the onset of symptoms according to standard clinical practice, with provisional bare metal stent implantation. Major exclusion criteria comprised prior anterior wall myocardial infarction, acute left-side heart failure (Killip class >II), prior coronary artery bypass grafting, known left ventricular ejection fraction of <40%, left ventricular hypertrophy, absence of thoracic windows for echocardiography, three-vessel coronary artery disease, Thrombolysis In Myocardial Infarction (TIMI) grade 2 or 3 flow at initial angiography before PCI, or unsuccessful PCI defined as TIMI grade 0 or 1 flow or >50% residual stenosis in the infarct-related artery after PCI. The study protocol was approved by the local ethics committee and all patients gave informed consent.

Cardiac catheterization and periprocedural measurements

Five to 10 minutes after successful reperfusion, intra- coronary blood flow velocity was measured in the infarct related artery using a 0.014-inch sensor equipped guide wire (Philips/Volcano, Rancho Cordova, California, USA). Additionally, measurements were performed in an angiographic normal non-culprit coronary artery, defined as a coronary artery with <30% diameter stenosis on visual estimation. Non-culprit vessel measurements were performed in the left circumflex coronary artery, unless a stenosis of >30% was present, in which case the right coronary artery was used. At one-week and six-month follow-up, 64 and 65 respectively patients underwent repeat angiography with assessment of intracoronary Doppler flow velocity, of which the initial results have been reported previously. [2] [11] The flow diagram in Figure 1 shows the number of patients included in the analysis at each time frame. Hyperaemia was induced by an intracoronary bolus of adenosine (40 μg). Before and after PCI, coronary angiography suitable for quantitative coronary angiographic analysis was performed for offline analysis of TIMI flow and myocardial blush grade. Left ventricular function was evaluated by means of echocardiographic 16-segment wall motion score index performed immediately before primary PCI.

CFC

From the recorded data, CFR was calculated as the ratio of hyperaemic average peak flow velocity (hAPV) to baseline average peak flow velocity (bAPV). The CFC concept was applied according to that recently derived for invasive coronary flow measurements. Normal CFC was defined as a CFR ≥2.8, with its corresponding hAPV ≥49.0 cm/s. [12] Mildly reduced CFC was defined as a CFR <2.8 but >2.1, and corresponding hAPV <49.0 and >33.0 cm/s, respectively. Moderately reduced CFC was defined as CFR ≤2.1 and >1.7, and the corresponding hAPV ≤33.0 and >26.0 cm/s, respectively. [13] Finally, severely reduced CFC was defined as a CFR ≤1.7, and a corresponding hAPV ≤26.0 cm/s. [5]

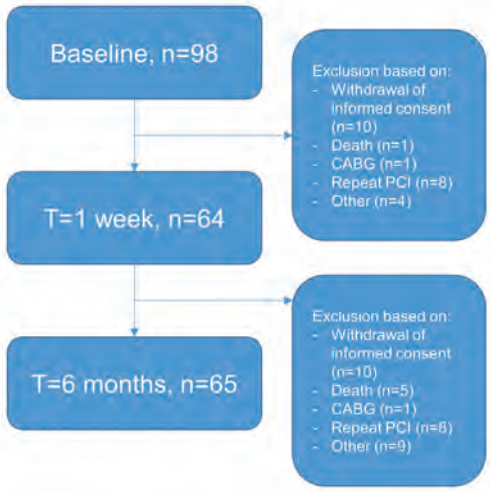

Figure 1. Flow diagram. CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

Haemodynamic data analysis

Microvascular resistance was calculated at baseline and during hyperaemia, respectively the ratio between mean aortic pressure and mean distal flow velocity at baseline (BMR), and during hyperaemia (HMR), in the culprit and in the absence of significant epicardial disease in the non-culprit vessel. The delta microvascular resistance from resting to hyperaemic conditions (dMR) was determined by calculating the absolute difference between BMR and HMR.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk test, and homogeneity of variance was tested with Levene's test. All continuous variables are presented as percentile) according to their normal or non-normal mean±standard deviation or median (25th to 75th distribution. Categorical variables are presented as counts and percentages. Analyses of linear trends across CFC categories were performed with polynomial contrasts.

Improvement of CFC in the culprit and non-culprit vessel between baseline, one week and six months was assessed by a Kruskal–Wallis test with pairwise post hoc correction for multiple comparisons. A p-value <0.05 was considered statistically significant.

The STATA version 13.1 (StataCorp, College Station, Texas, USA) software package was used to perform statistical analyses.

RESULTS

In total, 98 patients were included in the study at baseline, for which characteristics are listed in Table 1. The mean age of this cohort was 56±12 years, and 81% were male. Repeat coronary angiography and intracoronary measurements at one-week and six-month follow-up have been performed in a total of 64 and 65 patients respectively.

Table 1. Baseline characteristics

Demographics	
n	98
Age, y	56±12
Male	80 (81)
Risk factors	
Smoking	52 (53)
Hypertension	24 (24)
Family history	40 (40)
Hyperlipidemia	26 (26)
Diabetes mellitus	6 (6)
Prior medication use	
β-Blocker	13 (13)
Calcium antagonist	8 (8)
Angiotensin-converting enzyme inhibitors	5 (5)
Nitrates	4 (4)
Lipid-lowering drugs	8 (8)
Aspirin	11 (11)

Data are presented as mean±SD or frequency (%).

Relationship of CFC with procedural characteristics

Across CFC groups determined in the culprit vessel directly after primary PCI, linear contrast analysis revealed a significant trend in infarct size as determined by peak troponin T ($p=0.004$), time to reperfusion ($p=0.038$), the incidence of respectively final TIMI 3 flow ($p=0.019$) and systolic retrograde flow ($p=0.043$) (Supplemental file 1 online). For CFC determined for the non-culprit vessel linear contrast analysis revealed a significant trend in C-reactive protein ($p=0.027$), peak troponin T ($p<0.001$) and heart rate ($p=0.049$) across the different groups of CFC (Supplementary file 2).

Time course of culprit vessel CFC

Figure 2(a) to (c) shows the scatterplots of the time course of CFC in the culprit vessel. At this stage of the procedure, 10% of the patients showed a normal CFC, 29% a mildly reduced

CFC, 19% a moderately reduced CFC and 42% a severely reduced CFC (Supplementary file 3). A significant linear trend across CFC groups was observed for CFR, bAPV, hAPV, BMR, HMR and dMR ($p<0.001$ for all measurements except for dMR, $p=0.002$).

At one-week follow-up, measurements in the culprit artery were obtained in 64 patients. In 28% of patients a normal CFC was found, in 44% a mildly reduced CFC, in 19% a moderately reduced and in 9% a severely reduced CFC. A significant linear trend across CFC groups was observed for CFR, bAPV and hAPV ($p=0.004$, $p<0.001$ and $p<0.001$, respectively), but not for BMR ($p=0.183$), HMR ($p=0.163$) and dMR ($p=0.279$). At six-month follow-up measurements in the culprit artery were obtained in 65 patients. In 69% of patients a normal CFC was found, in 20% a mildly reduced CFC, in 6% a moderately reduced and in 5% a severely reduced CFC (Supplementary file 3). A significant linear trend across CFC groups was observed for CFR, bAPV ($p<0.001$), hAPV ($p<0.001$), HMR ($p<0.001$) and dMR ($p=0.02$), but nor for BMR ($p=0.142$).

Time course of non-culprit vessel CFC

Figure 2(d) to (f) shows the scatterplots of the time course of CFC in the non-culprit vessel. At the index procedure, CFC was also determined post PCI in a non-culprit vessel derived from measurements obtained in 97 patients with angiographically normal coronary arteries (<30% diameter stenosis): the left circumflex coronary artery was assessed in 87 patients (90%) and the right coronary artery in 10 patients (10%) (Supplementary file 4). CFC in the non-culprit vessel was normal in 27%, mildly reduced in 45%, moderately reduced in 25% and severely reduced in 3% of patients. A significant trend was observed for CFR and hAPV ($p<0.001$ and $p<0.001$), but not for bAPV ($p=0.160$). In addition, linear trend analysis of microvascular resistance parameters revealed a significant trend in HMR as well as in dMR ($p<0.001$ and $p<0.001$), but not in BMR ($p=0.428$).

At one-week follow-up, CFC was derived from measurements obtained in 64 patients: the left circum- flex coronary artery was assessed in 60 patients (94%), and the right coronary artery in four patients (6%). One week after acute myocardial infarction (AMI), CFC in the non-culprit vessel was normal in 45%, mildly reduced in 52%, and moderately reduced in 3% of patients. A statistically significant difference between normal and mildly reduced CFC was observed for CFR ($p<0.001$) and hAPV ($p<0.001$), but not for bAPV ($p=0.077$). At six-month follow-up, non-culprit vessel measurements were obtained in the same non-culprit vessel as during one-week follow-up: in 65 patients. Six months after AMI, CFC in the non-culprit vessel was normal in 92% and mildly reduced in 8% of patients. A statistically significant difference between normal and mildly reduced CFC was observed for CFR ($p=0.003$), hAPV ($p=0.003$) and HMR ($p<0.001$).

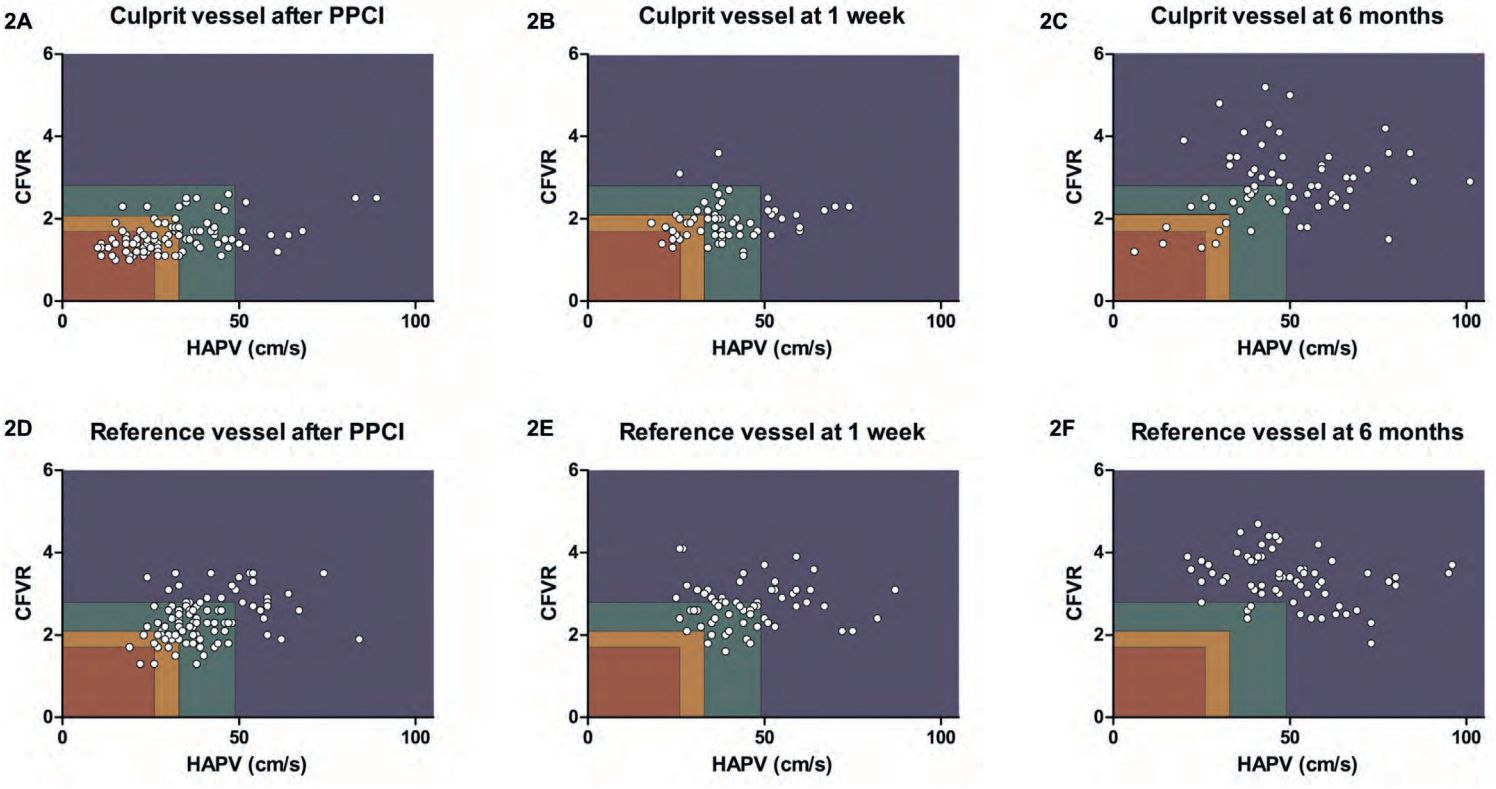

Figure 2. Scatterplot of the time course of coronary flow capacity (CFC) in the culprit vessel ((a), (b) and (c)) and non-culprit vessel ((d), (e) and (f)) after primary percutaneous coronary intervention, at one-week follow-up and six-month follow-up. The rectangles represent CFC categories; blue: normal CFC; green: mildly reduced CFC; orange: moderately reduced CFC; red: severely reduced CFC. CFVR: coronary flow velocity reserve; hAPV: hyperaemic average peak flow velocity; PPCI: primary percutaneous coronary intervention.

CFC improved significantly both in the culprit and the non-culprit vessel, when compared at baseline post PCI with one-week follow-up (p=0.036 and p<0.001), and one-week follow-up compared with six-month follow-up (p=0.0013 and p<0.001) (Figure 3; Supplementary file 5).

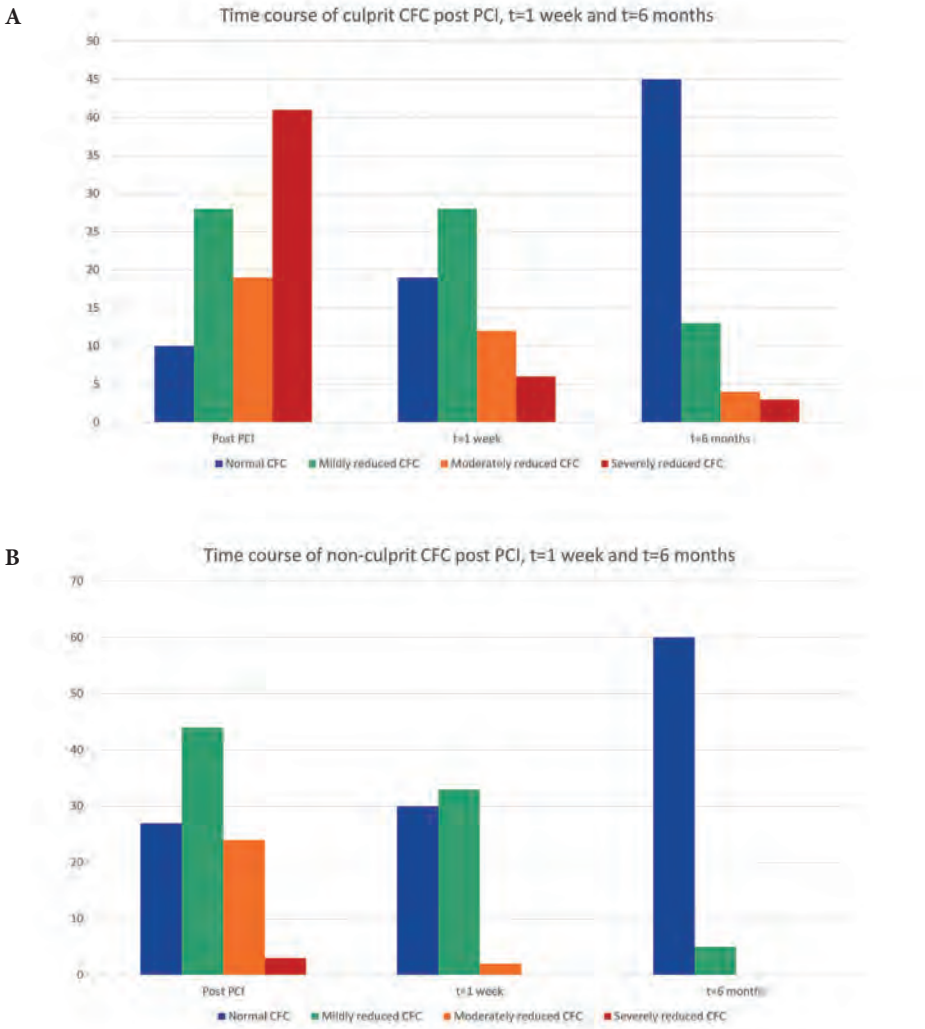

Figure 3. Time course of coronary flow capacity (CFC) in the culprit (a) and the non-culprit vessel (b) post primary percutaneous coronary intervention (PCI), at one-week and at six-month follow-up. In the culprit vessel, CFC improved significantly post PCI compared with one-week and six-month follow-up ($p < 0.001$) and one-week compared with six-month follow-up ($p = 0.0013$). In the non-culprit vessel, CFC improved post PCI compared with one-week and six-month follow-up, and one-week compared with six-month follow-up (all $p < 0.001$).

DISCUSSION

The present study is one of the first to document the impact of STEMI on myocardial perfusion using the validated CFC framework to comprehensively assess the consequences of focal obstructive, diffuse and microcirculatory causes of myocardial blood flow impairment. We have previously reported that micro- vascular function assessed by Doppler flow velocity is altered in the setting of STEMI, even in non-ischaemic regions at distance from the infarcted myocardial tissue and the independent association with long-term fatal cardiac events.

We observed a trend in infarct size for both the culprit vessel post PCI as well as the non-culprit vessel across CFC groups. In addition, an increase in time to reperfusion was associated with worsening of CFC determined after primary PCI in the both the culprit and the non-culprit vessel. CFC at the different time points resulted from an alternating contribution of the individual components that determine CFC group allocation; CFR, hAPV and bAPV. Of note, bAPV showed a significant trend across culprit vessel CFC groups after primary PCI and at one-week and six-month follow-up, but did not differ between groups in the non-culprit vessel.

CFC in the acute setting

First derived from positron emission tomography, the CFC concept integrates CFR with maximal hyperaemic flow velocity. [7][9][14] It thereby captures all components of coronary flow physiology and provides a comprehensive tool to depict myocardial blood flow impairment due to a combination of obstructive, diffuse and microcirculatory involvement of the coronary vasculature. Hence, in the absence of epicardial disease the CFC concept provides insights into the microvascular function. In addition, it has been shown to provide an improvement in risk discrimination for adverse clinical outcomes compared with CFR alone. [9]

This concept is of particular interest when assessing microvascular function in the acute setting of STEMI, where mechanical and neurohumoral factors can have an effect on both resting and hyperaemic coronary flow, [11] resulting in prolonged activation of the sympathetic nervous system, [15][16] subsequently inducing a vasoconstrictive response of the coronary resistance vessels by upregulated catecholamines. [3] The current study utilized the CFC concept to document the time course of microvascular function in the setting of STEMI in both the culprit and the non-culprit arteries.

It also revealed that despite restored epicardial patency of the culprit, a substantial number of patients remained having a severely reduced CFC, which improved over time. As previ-

ously documented for CFR, we also observed an impaired CFC in the non- culprit artery remote from the ischaemic region. However, compared with the culprit vessel, CFC in the non-culprit vessel was less impaired in the acute setting and improved more rapidly over time.

Previous studies on microvascular function in STEMI

Myocardial tissue perfusion remains compromised in 30–40% of STEMI patients despite rapid and successful mechanical revascularization. [17][18] Whereas culprit vessel flow abnormalities have been ascribed to numerous pathophysiological mechanisms, including reperfusion injury, distal embolization of plaque and thrombus material, endothelial dysfunction, leucocyte plugging and external compression of the microvasculature, the pan-myocardial nature of microvascular dysfunction is less well-understood, but has partly been ascribed to metabolic consequences of STEMI. [3][19] Microvascular dysfunction in the infarct related artery as well as remote regions from the infarct related myocardium observed after primary PCI are associated with a significantly increased long-term clinical outcome and mortality. [11][20][21][22][23] In addition, CFR obtained directly after primary PCI is an independent predictor of long term global as well as regional recovery of left ventricular function. [24][25] However, microvascular dysfunction in the setting of STEMI is often disclosed as a decrease in hyperaemic flow and increase in resting flow. The ratio of these, that is, the coronary flow reserve, does not provide insights into the relative contribution of both components.

Clinical implication

Risk stratification in the setting of AMI has long remained to be elucidated, and recent findings of large clinical trials have led to a revived interest in the approach to STEMI patients with multivessel disease. Revascularization of multivessel disease in STEMI patients roughly has three different approaches: angiography, optical coherence tomography (OCT) and invasive coronary physiology assessment. The COMPLETE (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI) trial suggests complete revascularization in STEMI patients with multivessel disease based on angiography, independent of infarct size. [26] A sub study of the COMPLETE trial and several other studies suggest OCT assessment of obstructive non-culprit lesions containing complex vulnerable plaque morphology and subsequent treatment of these lesions. [27][28][29] Coronary physiology assessment by using Fractional Flow Reserve (FFR) in STEMI patients with multivessel disease has been evaluated in several trials, and showed a decrease in major adverse cardiac events for FFR-guided PCI of the non-culprit; however, this effect is mainly driven by the complete revascularization at baseline and subsequent prevention of inevitable revascularization at a later stadium. [30][31] Additionally, non-culprit instantaneous wave-free ratio (iFR) has been assessed in the iSTEMI trial, during the acute ischaemic event

and ≥16 days post-STEMI. IFR was significantly lower during the acute ischaemic event compared with follow-up, potentially due to a higher baseline flow in the setting of STEMI, resulting in a potential overtreatment of these lesions compared with FFR. [32] The ongoing trials iModern (iFR Guided Multi-vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction, NCT03298659) and FRAME- AMI (FFR Versus Angiography-Guided Strategy for Management of AMI With Multivessel Disease, NCT02715518) both evaluate non-culprit lesions with iFR and/or FFR in the setting of AMI. However, certainly FFR, and potentially to a lesser extent iFR, are affected by the coronary microcirculation and microvascular resistance in particular, so these indices have to be interpreted cautiously if these are assessed in the setting of STEMI. [33][34] On the contrary, non-culprit vessel CFR has important prognostic value as reflected by a 4.09-fold increase in long-term cardiac mortality if non-culprit vessel CFR <2.0 in STEMI patients with multivessel disease. [11] Non-culprit vessel CFC assessment post primary PCI of the culprit has a significant benefit to determine long term prognosis and clinical outcome. Hence, patients with lower CFC in the non- culprit vessel after primary PCI of the culprit in the setting of STEMI require more intensive treatment and monitoring.

Limitations

There has been an extensive debate on the amount of adenosine needed to achieve a maximally vasodilated state. More recently, the dose–response relationship of intracoronary hyperaemia has been investigated, and no significant differences in FFR-values between low and high dose intracoronary adenosine were documented. [35] In this study we used an intracoronary bolus of 40 mg adenosine, which induced a sufficient state of hyperaemia to allow accurate assessment of coronary flow characteristics.

The acquisition of coronary flow velocity was performed by a sensor-equipped guidewire that assessed only coronary flow. We assessed only non-culprit vessel haemodynamics in coronary arteries without significant epicardial narrowing and assumed distal pressure to equal aortic pressure. Therefore, a potential role of subclinical atherosclerosis of the conduit artery in the absence of focal narrowing in the impairment of non- culprit vessel flow and pressure cannot be excluded. However, resting coronary flow is unlikely to be disturbed by coronary stenoses up to 85% of the vessel diameter, without interference of compensatory vasodilation of the distal vascular bed. [36]

CONCLUSION

These observations underline the impact of the coronary microcirculation both in the culprit and non- culprit vessel in the setting of STEMI on intracoronary diagnostic techniques. The coronary microcirculation recovers over time at six-month follow-up, as shown by an improvement in CFC. Both culprit and non-culprit vessel CFC assessment in the setting of STEMI might provide valuable insight into the recovery of the coronary circulation, emphasizing the importance of intracoronary physiology assessment following primary PCI in AMI.

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Supplementary file 1. Procedural and hemodynamic characteristics according to culprit vessel coronary flow capacity groups determined directly after PPCI

	CORONARY FLOW CAPACITY							
	Overall	**Normal**	**Mildly reduced**	**Moderately reduced**	**Severely reduced**	**p value for normality**	**p value for Levene test**	**p value for linear trend**
N	**98 (100)**	**10 (10)**	**28 (29)**	**19 (19)**	**41 (42)**	.	.	.
Laboratory assessment at admission								
CRP, mg/L	2.21 [1.17-5.41]	1.33 [1.06-1.6]	2.55 [1.58-5.03]	1.40 [1.06-4.2]	2.92 [1.41-6.53]	<0.001	0,041	0,095
Creatinine, µmol/l	69 [50-79]	71 [65-79]	67 [58-76]	66 [56-75]	72 [62-86]	<0.001	0,483	0,134
NT-proBNP after PPCI, pg/mL	92 [49-242]	79 [32-172]	94 [53-173]	79 [39-199]	139 [56-280]	<0.001	0,119	0,203
Peak CK-MB, µg/L	465 [298-666]	399 [240-584]	478 [259-720]	468 [283-752]	516 [311-666]	0,32	0,597	0,151
Peak Troponin T, µg/L	4.80±2.91	2.66±1.29	4.51±2.54	4.58±2.63	5.73±3.30	0,008	0,09	0,004
Procedural characteristics								
Heart rate, bpm	80±14	73±9	81±13	79±16	83±14	0,518	0,364	0,094
Systolic arterial pressure, mm Hg	119±15	119±11	114±15	117±13	123±17	0,06	0,384	0,058
WMSI before PPCI	1.89±0.23	1.93±0.19	1.91±0.21	1.81±0.19	1.90±0.26	0,302	0,404	0,689
Time to reperfusion, h	2.89 [2.3-3.9]	2.2 [2-2.94]	2.63 [2-3.35]	3.02 [2.34-3.59]	3 [2.45-4.08]	<0.001	0,756	0,038
ST resolution after PPCI ≥70%	41	3	13	8	17	.	.	0,396
Angiographic								
Final TIMI 3	60 (61)	9	19	14	18	.	.	0,019
Final blush grade 3	38 (38)	4	11	11	12	.	.	0,968
DDT before PPCI	200 [120-300]	260 [220-380]	200 [110-330]	200 [160-240]	200 [120-280]	<0.001	0,155	0,133
SRF present	20 (20)	1	4 (4)	5 (5)	10 (10)	.	.	0,043

In case Levene's test was significant ($p<0.05$) p-value for contrast analysis for a linear trend is shown that does not assume equal variances. CRP, C-Reactive Protein; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; CK-MB, Creatine Kinase MB; WMSI, Wall Motion Score Index; TIMI, Thrombolysis In Myocardial Infarction; DDT, Diastolic Deceleration Time; SRF, Systolic Retrogade Flow.

Supplementary file 2. Procedural and hemodynamic characteristics according to reference vessel coronary flow capacity groups determined directly after PPCI

	CORONARY FLOW CAPACITY							
	Overall	**Normal**	**Mildly reduced**	**Moderately reduced**	**Severely reduced**	**p value for normality**	**p value for Levene test**	**p value for linear trend**
N	98 (100)	27 (28)	44 (45)	24 (24)	3 (3)	.	.	.
Laboratory assessment at admission								
CRP, mg/L	2.21 [1.17-5.41]	1.81 [0.64-2.74]	2.21 [1.27-4.71]	2.74 [1.39-6.27]	5.86 [5.06-6.53]	<0.001	0,013	0,027
Creatinine, µmol/l	69 [60-69]	67 [63-67]	69 [58-69]	71 [63-71]	66 [53-66]	<0.001	<0.001	0,23
NT-proBNP after PPCI, pg/mL	92 [49-242]	91 [32-242]	75 [50-157]	154 [57-300]	93 [85-205]	<0.001	0,003	0,413
Peak CK-MB, µg/L	475 [298-666]	471 [299-814]	468 [255-638]	484 [342-694]	779 [653-895]	0,32	0,229	0,064
Peak Troponin T, µg/L	4.6±2.90	3.67±2.58	4.26±2.49	6.1±3.19	6.84±3.08	0,008	0,4	<0.001
Procedural characteristics								
Heart rate, bpm	80±14	76±12	81±15	83±12	87±26	0,518	0,169	0,049
Systolic arterial pressure, mm Hg	119±15	124±11	118±13	119±21	114±10	0,06	0,025	0,214
WMSI before PPCI	1.89±0.23	1.88±0.21	1.84±0.25	1.94±0.20	1.99±0.17	0,302	0,808	0,186
Time to reperfusion, h	2.9 [2.3-3.9]	3.07 [2.25-4.08]	2.82 [2.21-3.9]	3 [2.31-3.4]	4.07 [2.39-5.2]	<0.001	0,255	0,809
ST resolution after PPCI ≥70%	41	12	17	11	1	.	.	0,225

In case Levene's test was significant ($p<0.05$) p-value for contrast analysis for a linear trend is shown that does not assume equal variances. CRP, C-Reactive Protein; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; CK-MB, Creatine Kinase MB; WMSI, Wall Motion Score Index; TIMI, Thrombolysis In Myocardial Infarction; DDT, Diastolic Deceleration Time; SRF, Systolic Retrogade Flow.

Supplementary file 3. Time course of coronary flow capacity in the culprit vessel determined directly after PPCI, at 1-week and 6-months

	CORONARY FLOW CAPACITY							
	Overall	**Normal**	**Mildly reduced**	**Moderately reduced**	**Severely reduced**	**p value for normality**	**p value for Levene test**	**p value for linear trend**
Culprit vessel, after PPCI								
n	98 (100)	10 (10)	28 (29)	19 (19)	41 (42)	.	.	.
CFVR	1.5 [1.3-1.7]	1.7 [1.4-2.4]	1.7 [1.5-2.3]	1.7 [1.3-1.9]	1.4 [1.2-1.5]	<0.001	<0.001	<0.001
BAPV, cm/s	19 [14-24]	37 [32-40]	24 [19-28]	19 [15-22]	15 [11-18]	<0.001	0,163	<0.001
HAPV, cm/s	29 [21-39]	60 [52-68]	40 [36-44]	29 [27-32]	21 [15-24]	<0.001	0,001	<0.001
BMR, mmHg/cm/s	4.59 [3.26-6.37]	2.52 [1.98-2.75]	3.49 [2.91-4.45]	4.56 [3.93-5.95]	6.36 [5.04-8.14]	<0.001	0,006	<0.001
HMR, mmHg/cm/s	2.74 [1.92-3.76]	1.44 [1.23-1.58]	1.95 [1.74-2.11]	2.74 [2.47-2.93]	3.85 [3.5-5.41]	<0.001	<0.001	<0.001
dMR, mmHg/cm/s	1.84 [0.86-2.82]	0.83 [0.43-1.14]	1.88 [0.92-2.53]	1.70 [0.87-2.46]	2.53 [1.29-3.07]	<0.001	0,165	0,002
Culprit vessel, 1-week follow up								
n	65 (100)	19 (29)	28 (43)	12 (18)	6 (9)	.	.	.
CFVR	1.9 [1.6-2.2]	1.8 [1.6-2]	2.3 [2.2-2.5]	2 [1.9-2]	1.6 [1.5-1.7]	0,006	0,05	<0.001
BAPV, cm/s	20 [15-26]	33 [31-34]	17 [15-23]	19 [15-24]	23 [16-27]	0,08	0,06	<0.001
HAPV, cm/s	37 [30-44]	55 [52-60]	38 [36-51]	37 [30-43]	35 [25-39]	0,013	<0.001	<0.001
BMR, mmHg/cm/s	4.35 [3.27-6.19[	3.63 [3.27-5.31]	4.55 [3.84-6.08]	4.90 [3.02-7.89]	3.76 [3.18-8.1]	<0.001	0,107	0,183
HMR, mmHg/cm/s	1.87 [1.47-2.32]	1.60 [1.40-2.29]	1.92 [1.60-2.15]	2.44 [1.57-2.93]	1.76 [1.47-2.32]	0,07	0,08	0,163
dMR, mmHg/cm/s	2.45 [1.27-4.35]	2.22 [1.41-3.35]	2.65 [1.70-4.27]	2.13 [0.99-5.58]	2.45 [2.36-6.34]	<0.001	0,002	0,279
Culprit vessel, 6-month follow up								
n	64 (100)	45 (69)	13 (20)	4 (6)	3 (5)	.	.	.
CFVR	2.8 [2.3-3.3]	3.1 [2.7-3.6]	2.5 [2.3-2.6]	1.8 [1.6-1.9]	1.3 [1.2-1.4]	0,193	0,004	<0.001
BAPV, cm/s	17 [12-22]	18 [12-24]	15 [14-17]	18 [13-20]	10 [5-19]	0,604	0,028	0,04
HAPV, cm/s	45 [26-59]	54 [43-65]	38 [34-39]	30 [22-31]	14 [6-25]	0,676	0,026	<0.001
BMR, mmHg/cm/s	5.24 [4.24-7.82]	4.96 [4.14-7.73]	5.78 [5.17-6.5]	4.84 [4.40-6.81]	10.4 [4.26-17.8]	<0.001	0,035	0,142
HMR, mmHg/cm/s	1.98 [1.57-2.51]	1.77 [1.39-2.04]	2.28 [2.10-2.71]	3.19 [2.50-4.20]	7.43 [3.24-14.8]	<0.001	<0.001	<0.001
dMR, mmHg/cm/s	3.23 [2.41-4.53]	3.41 [2.46-5.47]	3.49 [3.05-3.98]	1.91 [1.64-2.87]	2.97 [1.02-1.12]	<0.001	0,061	0,02

In case Levene's test was significant ($p<0.05$) p-value for contrast analysis for a linear trend is shown that does not assume equal variances. CRP, C-Reactive Protein; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; CK-MB, Creatine Kinase MB; WMSI, Wall Motion Score Index; TIMI, Thrombolysis In Myocardial Infarction; DDT, Diastolic Deceleration Time; SRF, Systolic Retrogade Flow.

Supplementary file 4. Time course of coronary flow capacity in the reference vessel determined directly after PPCI, at 1-week and 6-months

	CORONARY FLOW CAPACITY							
	Overall	**Normal**	**Mildly reduced**	**Moderately reduced**	**Severely reduced**	**p value for normality**	**p value for Levene test**	**p value for linear trend**
Culprit vessel, after PPCI								
n	97 (100)	26 (27)	44 (45)	24 (25)	3 (3)	.	.	.
CFVR	2.3 [2.0-2.7]	2.95 [2.7-3.4]	2.3 [2.2-2.6]	1.9 [1.8-2.0]	1.3 [1.3-1.7]	0,308	<0.001	<0.001
BAPV, cm/s	16 [14-20]	18 [15-22]	15 [13-18]	16 [15-20]	16 [11-20]	<0.001	0,009	0,16
HAPV, cm/s	37 [31-45]	54 [45-58]	37 [33-42]	32 [29-36]	22 [19-26]	<0.001	<0.001	<0.001
BMR, mmHg/cm/s	7.21 [6.15-8.63]	7.24 [6-8.81]	7.47 [6.15-9.21]	7.09 [6.43-8]	6.94 [5.95-9.36]	<0.001	0,022	0,428
HMR, mmHg/cm/s	3.10 [2.57-3.81]	2.41 [2.17-2.86]	3.06 [2.81-3.67]	3.64 [3.27-4.32]	5.05 [4.58-5.42]	0,005	0,621	<0.001
dMR, mmHg/cm/s	3.99 [3.28-5.33]	4.79 [3.72-5.96]	4.41 [3.48-5.41]	3.39 [3.08-3.72]	1.89 [1.37-3.94]	<0.001	0,002	<0.001
Culprit vessel, 1-week follow up								
n	64 (100)	30 (46)	33 (51)	2 (3)	0	.	.	.
CFVR	2.7 [2.35-3.05]	3 [2.7-3.1]	2.6 [2.3-2.8]	2.15 [2.1-2.2]	.	0,369	.	<0.001
BAPV, cm/s	17 [13-20]	18 [12-22]	16 [13-19]	14 [13-14]	.	<0.001	.	0,077
HAPV, cm/s	44 [35-53]	53 [35-63]	40 [36-45]	30 [28-32]	.	<0.001	.	<0.001
BMR, mmHg/cm/s	6.57 [5.53-8.46]	6.37 [5.32-8.64]	6.61 [5.911-8.36]	7.01 [6.38-7.64]	.	<0.001	.	0,497
HMR, mmHg/cm/s	2.48 [2.09-3.0]	2.12 [1.94-2.82]	2.51 [2.32-3.06]	3.15 [2.96-3.34]	.	0,009	.	0,106
dMR, mmHg/cm/s	4.24 [3.33-5.44]	4.28 [3.33-5.85]	4.20 [3.12-5.27]	3.86 [3.42-4.29]	.	<0.001	.	0,133
Culprit vessel, 6-month follow up								
n	65	60 (92)	5 (8)	0	0	.	.	.
CFVR	3.4 [3.0-3.8]	3.4 [3.05-3.8]	2.6 [2.5-2.7]	.	.	0,886	.	0,003
BAPV, cm/s	15 [10-21]	15 [10-21]	15 [12-15]	.	.	<0.001	.	0,544
HAPV, cm/s	47 [39-59]	49 [41-60]	38 [32-39]	.	.	<0.001	.	0,003
BMR, mmHg/cm/s	8.78 [6.23-11.28]	8.54 [6.06-11.22]	11.01 [9.75-13.68]	.	.	0,002	.	0,254
HMR, mmHg/cm/s	2.49 [2.04-2.99]	2.45 [1.97-2.91]	4.44 [3.86-5.07]	.	.	<0.001	.	<0.001
dMR, mmHg/cm/s	7.78 [5.23-10.28]	7.54 [5.06-10.22]	10.01 [8.75-12.68]	.	.	0,002	.	0,254

In case Levene's test was significant ($p<0.05$) p-value for contrast analysis for a linear trend is shown that does not assume equal variances. CRP, C-Reactive Protein; NT-proBNP, N-Terminal pro B-type Natriuretic Peptide; CK-MB, Creatine Kinase MB; WMSI, Wall Motion Score Index; TIMI, Thrombolysis In Myocardial Infarction; DDT, Diastolic Deceleration Time; SRF, Systolic Retrogade Flow.

Supplementary file 5. Patient level time course of coronary flow capacity

		CORONARY FLOW CAPACITY				
	Overall	**Normal**	**Mildly reduced**	**Moderately reduced**	**Severely reduced**	**p value**
CFC at 1 week compared to after primary PCI						
Culprit vessel						<0.001
Decreased	8 (13)	3	4	1	.	
Equal	18 (28)	4	7	4	3	
Improved	38 (59)	.	8	6	24	
Reference vessel						<0.001
Decreased	6 (9)	6	.	.	.	
Equal	33 (52)	14	17	2	.	
Improved	25 (39)		12	11	2	
CFC at 6 months compared to 1 week follow up						
Culprit vessel						0.001
Decreased	13 (20)	2	5	1	1	
Equal	22 (34)	15	7	.	.	
Improved	30 (46)	.	15	10	5	
Reference vessel						<0.001
Decreased	4 (7)	3	1	.	.	
Equal	29 (47)	25	4	.	.	
Improved	28 (46)	.	26	2	.	

Values are displayed as n or n (%) of total per vessel.

CHAPTER 11

Summary

This thesis addresses coronary physiology's complexity in acute and chronic coronary syndromes. It is well recognized that microvascular perfusion remains compromised in a large number of STEMI patients, despite rapid and successful mechanical revascularization, both in the culprit and non-culprit vascular territories. This phenomenon is associated with larger post-infarction myocardial necrosis and is a determinant for the prognosis of STEMI survivors. More recently, insights have progressed on the role of the microvascular function in the contribution of ischemia in chronic coronary syndromes. Therefore, a comprehensive understanding of the involvement of the different levels of coronary circulation is warranted to guide optimal treatment selection. This can be obtained by using sensor-equipped guidewires to measure a multitude of parameters derived from intracoronary pressure and/or flow. Therefore, Part A of this thesis covers microvascular function in chronic coronary syndromes, starting with addressing several procedural considerations and looking into different approaches to assess microvascular function. Part B of this thesis outlines novel insights in the behavior of microvascular function in the setting of acute coronary syndromes.

PART A: CORONARY PHYSIOLOGY IN CHRONIC CORONARY SYNDROMES

In Chapters 2 and 3, we outline procedural considerations when it comes to assessing coronary physiology invasively using pressure and flow measurements. In **Chapter 2**, we outline that the use of resting indices for evaluating coronary stenosis severity is not always as simple as it seems. They are more vulnerable to drift, resulting in a marked and clinically significant misclassification, particularly when indices are close to their cutoff value. Therefore, physiological assessments should be performed meticulously to prevent procedural and technical sources from drifting and ensure optimal measurement conditions for clinical decision-making. **Chapter 3** provides a brief overview of the methodological considerations for the coronary-wedge-pressure-based correction of microvascular resistance for the assumed contribution of collateral flow. In stenoses with a wedge pressure <25 mmHg and/or FFR >0.6, the coronary wedge pressure is determined by the chronotropic and inotropic properties of the heart than collateral flow. Applying a wedge-pressure-based correction of microvascular resistance in these cases will generally lead to underestimating actual resistance.

Chapters 4, 5 and 6 look at the comprehensive diagnosis of chronic coronary syndromes and the insights provided by combined pressure and flow measurements into the underlying disease pattern and prognosis. In **Chapter 4**, the debate on the role of microvascular function in treatment decisions of epicardial stenoses is sparked by presenting a controversial

case study. A discordant diagnostic finding with normal fractional flow reserve (FFR) and abnormal coronary flow reserve (CFR) suggested the presence of a depleted vasodilatory reserve secondary to microvascular disease in conjunction with mild epicardial stenosis. Restoring epicardial patency in this patient was hypothesized to have restored part of the vasodilatory reserve by alleviating the strain on the compensatory autoregulatory vasodilatation, resulting in a decrease in angina symptoms at follow-up. In **Chapter 5** novel concepts of pressure-derived CFR were evaluated against Doppler flow and thermodilution derived CFR for diagnostic and prognostic purposes that were introduced to simplify comprehensive assessments. It was found that these pressure-derived parameters of CFR poorly agree with Doppler flow and thermodilution derived CFR, which may explain the inferior association with long-term MACE as compared to flow-derived CFR. **Chapter 6** investigates the prognostic impact of normal or abnormal microvascular function in conjunction with epicardial stenoses in a large cohort. The results of this study indicated that in stenoses with discordant CFR and FFR results, the status of the microvasculature, as determined by CFR, was an important determinant of long-term clinical outcome.

In the last chapter of Part A, we look at the impact of the treatment of stenosis with discordant results for the CFR and FFR. **Chapter 7** assesses the impact of the percutaneous coronary intervention (PCI) on resolving myocardial ischemia in discordant stenoses based on the novel coronary-flow-capacity (CFC) concept. It shows that in patients with FFR>0.80 and CFR<2.0, myocardial ischemia is frequently present according to the CFC concept. Additionally, PCI improves flow parameters to non-ischemic levels, whereas in patients with FFR≤0.80 and CFR≥2.0, myocardial ischemia is infrequent, and PCI does not improve the ischemic status.

PART B: MICROVASCULAR FUNCTION IN ACUTE CORONARY SYNDROMES

Chapter 8 provides an overview of the pathophysiology, diagnostic armamentarium, and treatment strategies related to microvasculature in patients with ST-segment elevation myocardial infarction (STEMI). It emphasizes that myocardial perfusion goes beyond restoring epicardial patency in the setting of STEMI, and adjuvant therapies should be considered in patients suspected of infarct-related microvascular dysfunction.

In Chapter 9 and Chapter 10, the microvascular function was investigated in the acute event of myocardial infarction and how it restores following a successful primary percutaneous intervention. The results described in **Chapter 9** advance the understanding of the impact of stress-related metabolic changes on microvascular function in patients with first

anterior-wall STEMI. It showed that elevated admission glucose levels are associated with impaired microvascular function assessed directly after PPCI. This influence of glucose levels is an acute phenomenon and contributes to microvascular dysfunction through alterations in resting flow and baseline microvascular resistance. The observations in **Chapter 10** underline the impact of the coronary microcirculation in the culprit and non-culprit vessel in the setting of STEMI based on intracoronary diagnostic techniques. Additionally, it provides insights into the time course of microcirculatory disturbances post primary PCI, showing microvascular function recovery over time at a six-month follow-up, as assessed by an improvement in CFC. Both culprit and non-culprit vessel CFC assessment in the setting of STEMI might provide valuable insight into the recovery of the coronary circulation, emphasizing the importance of intracoronary physiology assessment following primary PCI in acute myocardial infarction.

CHAPTER 12

Samenvatting

Dit proefschrift behandelt de complexiteit van de coronaire fysiologie bij acute en chronische coronaire syndromen. Het is algemeen erkend dat microvasculaire perfusie gecompromitteerd blijft bij een groot aantal STEMI-patiënten, ondanks snelle en succesvolle mechanische revascularisatie, zowel in de infarct gerelateerde en niet-infarct gerelateerde perfusie gebieden. Dit fenomeen wordt in verband gebracht met grotere myocardnecrose na een infarct en is bepalend voor de prognose van STEMI-overlevenden. Meer recentelijk is er meer inzicht gekomen in de rol van de microvasculaire functie bij het ontstaan van ischemie in chronische coronaire syndromen. Daarom is een alomvattend begrip van de betrokkenheid van de verschillende niveaus van coronaire circulatie nodig om richting te geven aan de keuze voor de optimale behandeling. Dit kan worden bereikt door gebruik te maken van met sensoren uitgeruste voerdraden om in de kransslagaderen een groot aantal parameters te meten die zijn afgeleid van druk en/of flow. Daarom behandelt deel A van dit proefschrift de microvasculaire functie bij chronische coronaire syndromen, te beginnen met het behandelen van verschillende procedurele overwegingen en het onderzoeken van verschillende benaderingen om de microvasculaire functie te beoordelen. Deel B van dit proefschrift schetst nieuwe inzichten in het gedrag van de microvasculaire functie in de setting van acuut coronair syndroom.

DEEL A: CORONAIRE FYSIOLOGIE IN CHRONISCH CORONAIR SYNDROMEN

In Hoofdstuk 2 en 3 worden de procedurele overwegingen uiteengezet als het gaat om het invasief meten van de coronaire fysiologie door middel van druk- en doorstromingsmetingen. In **Hoofdstuk 2** wordt beschreven dat het gebruik van rust parameters voor de evaluatie van de ernst van epicardiale vernauwing niet zo makkelijk is als het lijkt. Deze parameters zijn gevoelig voor drift wat resulteert in klinisch significante misclassificatie, met name wanneer het resultaat van deze parameters zich nabij de afkapwaarde bevindt. Daarom dienen fysiologische metingen altijd zorgvuldig te worden gedaan om procedurele en technische bronnen van drift te voorkomen en zo te zorgen voor optimale meetcondities voor de klinische besluitvorming. **Hoofdstuk 3** geeft een overzicht in methodologische overwegingen voor op coronaire wiggedruk gebaseerde correctie van microvasculaire weerstand voor de aanwezige collaterale bloeddoorstroming. In vernauwingen met een wiggedruk <25 mmHg en/of FFR>0.6 wordt deze wiggedruk echter niet bepaald door de aanwezige collaterale bloeddoorstroming, maar voornamelijk door chronotropische en inotropische eigenschappen van het hart. Het toepassen van een op wiggedruk gebaseerde correctie van de microvasculaire weerstand in deze gevallen resulteert in een onderschatting van de daadwerkelijke weerstand.

In Hoofdstuk 4, 5 en 6 kijken we naar de volledige diagnose van het chronisch coronair syndroom en de inzichten die invasieve gecombineerde druk- en doorstromingsmetingen geven in het onderliggende ziektepatroon en prognose. In **Hoofdstuk 4** wordt het debat gestart over de rol van de microvasculaire functie op behandeling van vernauwingen in de kransslagaderen op basis van een controversiële casus presentatie. Een discordante diagnose met een normale Fractionele Flow Reserve (FFR) en abnormale Coronaire Flow Reserve (CFR) suggereert een uitgeputte vasodilatoire reserve secundair aan de aanwezigheid van abnormale microvasculaire functie bovenop de impact van een milde epicardiale vernauwing. Er wordt verondersteld dat het herstellen van de doorstroming in de epicardiale vaten bij deze patiënt de vasodilatoire reserve verbeterde door het verminderen van de compensatoire autoregulatoire vasodilatatie, wat resulteerde in een afname in angina klachten tijdens het vervolg van de patiënt. In **Hoofdstuk 5** worden nieuwe concepten van druk-afgeleide CFR geëvalueerd tegen Doppler-flow en thermodilutie-afgeleide CFR voor diagnostische en prognostische doeleinden. Gevonden wordt dat deze van druk afgeleide parameters van CFR slecht overeenkomen met van Doppler-flow en thermodilutie afgeleide CFR. Dit verklaart mogelijk de inferieure associatie met klinische lange termijn uitkomsten in vergelijking met de van flow afgeleide CFR. In **Hoofdstuk 6** wordt de prognostische impact van de normale en abnormale microvasculaire functie bij vernauwingen in de kransslagaderen onderzocht in een groot cohort. De resultaten van deze studie geven aan dat in vernauwingen met discordante resultaten voor de CFR en FFR, de microvasculaire functie een belangrijke determinant is voor de klinische lange termijn uitkomsten.

In het laatste hoofdstuk van Deel A kijken we naar de impact van behandeling van vernauwingen met discordante resultaten voor de CFR en FFR. In **Hoofdstuk 7** wordt de impact van Percutane Coronaire Interventie (PCI) op het oplossen van myocardischemie in discordante vernauwingen beoordeeld op basis van het nieuwe concept van de coronaire flowcapaciteit (CFC). Het laat zien dat bij patiënten met FFR>0.80 en CFR <2.0, myocardischemie vaak aanwezig is volgens het CFC-concept en dat PCI de flowparameters verbetert tot niet-ischemische niveaus. Bij patiënten met een FFR≤0.80 en CFR≥2.0 is myocardiale ischemie daarentegen zeldzaam en verbetert PCI de ischemische status niet.

DEEL B: MICROVASCULAIRE FUNCTIE IN ACUUT CORONAIR SYNDROMEN

Hoofdstuk 8 geeft een overzicht van de pathofysiologie, diagnostische armamentarium en behandelstrategieën gerelateerd aan de microvasculatuur bij patiënten met een ST-segment elevatie myocardinfarct (STEMI). Het benadrukt dat myocardiale perfusie verder gaat dan het herstellen van de epicardiale doorgankelijkheid in de setting van STEMI en dat adjuvante

therapieën overwogen dienen te worden bij patiënten die verdacht worden van infarctgerelateerde microvasculaire disfunctie.

In Hoofdstuk 9 en Hoofdstuk 10 is beschreven hoe de microvasculaire functie onderzocht is in STEMI en hoe deze herstelt na succesvolle primaire PCI. De resultaten beschreven in **Hoofdstuk 9** bevorderen het begrip van de impact van stressgerelateerde metabole veranderingen op de microvasculaire functie bij patiënten die voor de eerste keer een voorwandinfarct doormaken. Het toont aan dat verhoogde glucosespiegels bij opname geassocieerd zijn met een verminderde microvasculaire functie die direct na primaire PCI wordt gemeten. Deze invloed van glucosespiegels is een acuut fenomeen en draagt bij aan microvasculaire disfunctie door veranderingen in de bloeddoorstroming en weerstand in rust. De observaties in **Hoofdstuk 10** onderstrepen de impact van de coronaire microcirculatie, zowel in de infarct als niet-infarct gerelateerde coronairen in de setting van STEMI, gebaseerd op intracoronaire diagnostische technieken. Bovendien geeft het inzicht in het tijdsverloop van microcirculatiestoornissen na primaire PCI op basis van CFC. Zowel de CFC-beoordeling van infarct als niet-infarct gerelateerde kransslagaderen in de setting van STEMI, kan waardevolle inzichten verschaffen in het herstel van de coronaire circulatie en onderstreept het belang van intracoronaire fysiologische metingen na primaire PCI bij acuut myocardinfarct.

CHAPTER 13

Future perspectives

Over the past decades, physiological guidance to assess the functional severity of coronary stenoses in percutaneous coronary interventions has become established in clinical practice. It is becoming increasingly recognized that a comprehensive assessment of functional severity goes beyond epicardial stenoses and includes analysis of microvascular dysfunction. With the digitization of functional assessments by computational fluid dynamics, advancements in comprehensive and accessible diagnostic tools are on the horizon. In this chapter, this field's future perspectives will be discussed, with a particular focus on moving towards more comprehensive decision-making in patients with both obstructive and non-obstructive coronary artery disease (CAD).

THE EVOLUTION OF CORONARY PHYSIOLOGY TO DATE

The adoption of physiology-guided decision-making for epicardial stenoses has increased over the past decades and is now at the stage that it is incorporated in daily interventional cardiology practice. It has received the highest class of recommendation (1 A) in guidelines making it a state-of-the-art clinical decision-making tool.

The founder of interventional cardiology, Andreas Grüntzig, already used the trans-stenotic pressure gradient to assess the impact of angioplasty in 1979. In his landmark paper introducing his percutaneous transluminal coronary angioplasty technique, he reported a reduction in the mean gradient of 58 to 19 mm Hg after successful balloon dilatation. [1] In addition, he identified the relationship between the pressure gradient and diameter stenosis, and showed that a reduction in pressure gradient was a useful indicator of angiographic outcome. [2] Initially, angiographic means using the mean transit time during hyperemic conditions were used to assess coronary lesion severity on myocardial perfusion. [3] The clinical application of this novel technique was rather cumbersome and, as a result, new methods were developed utilizing sensor-equipped guidewires to study coronary hemodynamics. These wires were equipped with Doppler crystals to assess intracoronary blood flow velocity or pressure sensors to measure coronary pressure distal to coronary narrowings. [4][5][6] Clinical trials using Doppler wires to assess coronary flow reserve (CFR) were the first to reveal the discrepancy between anatomic and functional stenosis severity, and they introduced the concept of safe physiology-based deferral of percutaneous coronary intervention. The DEBATE trial showed that a distal CFR after angioplasty > 2.5 with residual diameter stenosis ≤ 35% identified lesions with a low incidence of adverse events at follow-up, and suggested that it be used to identify eligible patients for stent implantation. [7] This strategy was later confirmed by the randomized controlled trial, DESTINI, which showed comparable MACE rates at 12 months of 17.8% in the elective stenting group and 18.9% in an intervention group with CFR (<2.0) and diameter stenosis (≤ 35%) guided angioplasty. [8]

CFR assesses both epicardial disease severity and the distal coronary microvasculature. The pressure-derived Fractional Flow Reserve (FFR) was introduced to simplify the concept and the procedural workflow of invasive Doppler measurements. [9][10][11] Using pressure sensor-equipped guide wires, FFR was calculated as the ratio of aortic pressure to the pressure distal to the stenosis under hyperemic conditions. It took almost a decade for FFR to progress from introduction and validation in canine studies to the first large clinical trial. The DEFER trial randomly assigned patients with a negative FFR, less than 0.75, to either the deferral group or performance of PCI group. Both groups showed similar event-free survival (89% and 83% respectively) rates and a similar number of patients free from angina (70% and 51%) at 2-year follow-up. [12] The FAME 1 trial further enforced the superiority of physiology-guided PCI over angiography only guided PCI, indicating a lower event rate in the physiology group compared to the angiography guided group (13.2% versus 18.3%), despite a lower number of stents used (1.9±1.3 versus 2.7±1.2). [13] The subsequent FAME 2 trial, which randomized patients with a positive FFR of 0.80 or less, showed significantly lower major adverse cardiac events in the group that underwent PCI versus the group on medical therapy. [14] The randomized controlled FAME trials made FFR guided PCI an accepted tool in the interventional community, although adoption in daily clinical practice was still relatively low.

The use of vasodilatory agents to induce hyperemia, the cost, and patient discomfort were still significant barriers to adopting physiology-guided PCI for many interventional cardiologists. This led to the development of resting indices, introducing the instantaneous wave-free ratio (iFR), for which, unlike FFR, there is no need to induce hyperemia by looking at a particular segment of the pressure gradient during the diastolic phase. [15] Although the close correlation between resting Pd/Pa and FFR was already recognized at the time of the FAME trial, the widespread acceptance of resting indices was triggered by the validation of iFR in more than 3,500 patients in two randomized controlled trials. [16] The iFR SWEDEHEART trial compared an iFR- and FFR-guided revascularization strategy on patients with stable angina or acute coronary syndrome. The trial showed non-inferior MACE rates of the iFR-guided revascularization strategy. [17] The DEFINE FLAIR trial also showed non-inferiority of an iFR-guided versus FFR-guided strategy and that it was associated with less procedural time and fewer adverse events. [18] The development in coronary physiology led to the introduction with many other resting indices for evaluation of coronary lesion severity.

Hence, by moving from visual to functional assessment, flow velocity to pressure measurements, hyperemic to resting conditions, and focusing on the epicardial component rather than the full coronary vasculature, physiology-guided decision-making for the assessment of epicardial stenoses has emerged towards a powerful diagnostic method in daily interventional cardiology practice.

DIGITIZATION OF THE ASSESSMENT

The use of coronary angiography to assess myocardial perfusion by mean transit time was introduced 30 years. [3] The next stage in the evolution of coronary physiology that will push the field towards is advanced digitization, automation and standardization by using again coronary angiography for analysis of coronary hemodynamics. It will incorporate advanced computational hemodynamic models to estimate the functional significance of coronary artery stenoses as a standard tool in the catheterization laboratory. A pressure drop along the vessel can be calculated by feeding a geometric model obtained from a medical image (e.g., angiography or computed tomography) into the hemodynamic models. Although the field of image-derived coronary physiology was initiated by the introduction of CT-FFR for non-invasive assessment of coronary narrowings, angiographic derived parameters quickly followed. The angiographic-based solutions currently available perform single vessel assessments based on vessel geometry obtained from a quantified, three-dimensional coronary analysis. However, other solutions allow for the unilateral assessment of the entire coronary tree using computational fluid dynamics.

A substantial body of clinical evidence, showing excellent accuracy against invasive reference standards, already backs up commercially available solutions. A systematic review and meta-analysis comprising 1,842 vessels and multiple image-derived physiology methods reported a pooled sensitivity of 89% and specificity of 90%, using invasive wire-based FFR assessments as the reference standard. [19] However, in the absence of outcome-based validation of image-derived physiology, the results of randomized controlled trials like the FAVOR III Europe-Japan (NCT03729739) and FAVOR China (NCT03656848) are eagerly awaited. These trials aim to prove non-inferiority of the Quantified Flow Ratio (QFR) to FFR and superiority to the visual assessment of coronary stenosis severity, respectively.

Image-derived assessment will address the remaining barriers of current wire-based epicardial assessments and provide a shorter procedural time, decreased invasiveness, and reduced equipment costs. It will lead to a further increase in the adoption of physiology-guided PCI, potentially extends its use to acute coronary syndromes, and make it more accessible on a global scale. However, the current technology is still in its early stages, and there are still limitations to overcome to live up to its promise. Angiographic-derived assessment of coronary narrowings is readily available in the catheterization laboratory. However, its workflow is still labor-intensive and still requires many manual interactions. The computational processing time required to perform these assessments is reported to be several minutes, excluding manual corrections of segmentation and lesion identification, but using resting indices rather than hyperemic wire-based assessments, paves the way of workflow advantage for angiography-derived assessments. [20] To overcome the remaining

barriers, these diagnostic tools should become fully automated without the need for any user interaction. The first results of such a tool were recently published; the artificial intelligence-based AutocathFFR solution reported an accuracy level of 90% and an area under the curve of 0.91 using wire-based FFR as a reference, without any need of user interaction on the angiograms. [21]

It is also essential to recognize that these models require assumptions concerning boundary conditions for aortic pressure, branching outflow patterns and microvascular function. Although it is expected that these tools will gain a dominant place in the armamentarium of the interventional cardiologist, their reliance on population-based assumptions, e.g., status of the microvascular function constitute the Achilles heel in their current diagnostic performance. [22][23][24] Therefore, current tools should be applied with caution if the patient on whom the tools are being used does not match the characteristics on which the hemodynamic model was validated. Nevertheless, it will only be a matter of time before advanced artificial intelligence image-analysis will derive more detailed physiological information from the angiogram and image-derived physiology becomes a robust substitute for wire-based assessment in numerous coronary syndromes. When image-derived physiology techniques reach maturity, they will become the armamentarium of choice over wire-based assessment for physiological assessment of lesion severity in the catheterization laboratory.

BEYOND EPICARDIAL CORONARY ANGIOGRAPHY

With functional lesion severity assessment becoming nested in clinical practice, the time has come to introduce a more comprehensive diagnostic approach, encompassing structure and function beyond the epicardial stenosis. An increasing interest is emerging to expand routine assessment beyond the epicardial stenosis to re-introduce the assessment of coronary microvascular function, particularly in patients without obstructive coronary artery disease. [25] [26] A so-called invasive functional coronary angiography (FCA) comprises an assessment of coronary vasomotor function by administrating adenosine using intracoronary flow measurements to assess non-endothelial dependent vasodilation and a spasm provocation test using acetylcholine to assess endothelial dependent vasodilation. [27] Although invasive flow measurements utilizing sensor-equipped guidewires are still considered cumbersome, and for research settings only, advancements are being made to minimize learning curves and allow their ad-hoc use in a diagnostic procedure.

A pivotal trial in this field's resurrection was the CorMicA trial, the first randomized controlled trial in this area. [26] In this trial, 151 patients were randomized to stratified medical therapy guided by an interventional diagnostic procedure, including acetylcho-

line-induced endothelial and adenosine-induced vascular function assessments, versus standard care. The study results showed an improvement in angina score and quality of life score in the intervention group over the control group at 6-month follow-up; an effect that was sustained at 1-year follow-up. [26][28] The study resulted in a change in the recommendation for guidewire based microvascular assessment in patients with suspected microvascular angina from class IIb to IIa, now on a par with intracoronary provocations tests. This means that the weight of evidence is in favor of efficacy. [25]

Despite equality in guideline recommendations between coronary vasomotor tests and endothelial function assessments, they will not reach widespread adoption into clinical practice simultaneously.

Adenosine-based vasomotor function assessments will likely be the first to gain a more widespread adoption compared to acetylcholine-induced function testing. Contrary to endothelial function assessments, thresholds and clinical protocols are well established for vasomotor function assessments, alongside widespread familiarity with the required drugs to induce vasodilation. The emerging angiography-derived microvascular function testing will further accelerate the awareness and adoption of vasomotor function assessment in the interventional community. A subset of the methods currently under investigation follows a mean transit time approach, equivalent to the thermodilution-derived framework for the index of microvascular resistance (IMR). [29] An estimate of distal coronary pressure can be obtained by multiplying the aortic pressure by the image-derived FFR results. Together with the 'contrast' based estimate of the mean transit time, dividing the frame count under hyperemia by the frame rate at rest, a similar value is obtained as compared to thermodilution based mean transit time to calculate an image-derived substitute for IMR. An exploratory study in 45 STEMI patients found a significant correlation between angio-derived IMR and invasive IMR, and revealed an overall area under the curve of 0.96 to detect an invasive IMR > 40U, a sensitivity of 83%, and a specificity of 100%. [30] Another study applied a similar framework to assess angio-derived IMR in 57 patients presenting with stable or unstable angina in the absence of obstructive coronary artery disease. The study found an area under the curve of 0.92 to detect an invasive IMR > 25U, with a sensitivity of 86% and a specificity of 81%. [31] Remarkably, angio-derived IMR uses contrast propagation under resting conditions and does not require hyperemic image acquisition by assuming a fixed increase from resting to hyperemic flow of 2.1. Despite this simplification, angio-derived IMR still achieved high diagnostic performance, but this method should be handled with caution when abnormal CFR values are expected.

Endothelial function assessment faces more considerable barriers to its adoption, with one of the most important being the ophthalmic indication for the use of acetylcholine and the

off-label use of it in the coronary setting, making it a tedious administrative process getting started with these kind of procedures. The lack of a standardized protocol and the fear of complications are also significant factors impeding its adoption. Despite continuing insights into the complications with procedures using acetylcholine and attempts to harmonize protocols for endothelial function assessment, it will still take considerable time before these procedures will be used beyond an academic or specialized hospital setting. [27][32][33][34]

NOVEL THERAPEUTIC OPTIONS

In search of definitive treatment, the therapeutic value of providing a diagnosis itself should not be underestimated. A diagnosis of the underlying pathophysiological microvascular or vasospastic endotypes will lead to effective medical therapy management changes between the two endotypes. [27] Moreover, providing patients with a diagnosis of their symptoms motivates patients to implement lifestyle changes and will increase therapy compliance. These, together with tailored medical therapy, go hand-in-hand in improving patient symptoms. The CorMiCa trial showed that patient participation in cardiac rehabilitation was significantly higher in the intervention group, 40% versus 16%. [28]

Implantable device options for microvascular dysfunction are emerging, but validation is still ongoing. The coronary sinus reducer is an hourglass-shaped stent-like device that can be implanted in the coronary sinus. Upon endothelialization of the device, it obstructs the venous coronary sinus flow, resulting in increased venous backpressure that recruits collateral flow, with redistribution from the epicardium to the endocardium. [35][36][37] After a successful first-in-man study, the coronary sinus reducer was evaluated in patients presenting with refractory angina in the COSIRA trial, a phase II randomized, blinded, sham-controlled clinical trial. [38] While the COSIRA trial did not show any significant differences between the control and the intervention group in exercise time and wall-motion index, there was a significant reduction in anginal complaints and improvement in quality of life in the intervention group. The REDUCER-I trial (NCT02710435), REDUCER trial (NCT04523168), and COSIMA trial (NCT04606459) are currently enrolling to assess the effect of the coronary sinus reducer on established coronary indices, like the coronary flow reserve and microvascular resistance.

Pharmacological therapies are also emerging and focus on angiogenesis of the microvasculature to improve its function. One of these investigational therapies utilizes naturally occurring endothelial progenitor cells, so-called CD34+ stem cells, to stimulate angiogenesis. By administrating growth factors for five days to the patient, CD34+ cells are

mobilized from the bone marrow to the peripheral circulation and obtained through leukapheresis. Cells are then manufactured to isolate and concentrate the CD34+ cells and are then infused in the same patient directly into the coronary arteries through a single infusion. The recent open-label, phase II trial ESCAPE-CMD (NCT03508609) showed that, in a cohort of 20 patients with non-obstructive coronary artery disease, CFR increased from 2.08±0.3 at baseline to 2.68±0.8 at 6-month follow-up. It also showed a significant improvement in angina and quality of life. Its successor, the randomized control FREEDOM trial (NCT04614467), is currently recruiting and aims to explore the efficacy and safety of autologous CD34+ cells in 105 subjects using the change in coronary flow reserve at six months as its primary outcome measure. Another pharmacological angiogenic therapy is looking into vascular endothelial growth factor A (VEFG-A) mRNA administration hypothesizes to improve cardiac perfusion through vasodilation, improved endothelial cell function, and capillary angiogenesis. [39] The advantage over the aforementioned autologous stem cell therapy is the lack of induction of innate immune responses through growth factors and large-scale manufacturability. However, this technology is currently still in the very early stages of development. The endothelin receptor antagonist, Zibotentan, from the same manufacturer as the VEGF-A mRNA, is also being assessed for its impact in patients presenting with microvascular angina in the PRIZE trial (NCT04097314). [40] It is hypothesized that in patients with a chronic elevation of circulating ET-1, a suspected contributor to vasospasm episodes, endothelin receptor antagonists can decrease microvascular angina.

ONGOING TRIALS ASSESSING THE IMPACT OF A COMPREHENSIVE ASSESSMENT

As a follow-up on the work described in this thesis, the DEFINE FLOW trial was performed to investigate if patients with a preserved CFR but abnormal FFR could be safely deferred for PCI. Unfortunately, this hypothesis-generating exploratory study missed its primary endpoint in showing non-inferiority in 2-year MACE of stenoses with an abnormal FFR and normal CFR compared to stenoses with both normal FFR and CFR. Interestingly, this discordant group of abnormal FFR and normal CFR showed similar MACE rates as the group with abnormal FFR and CFR after PCI. A sub-analysis investigates the differences in reported angina and antianginal medication at 2-year follow-up, particularly important in this era where soft clinical endpoints gain relevance. The results of the DEFINE FLOW study are in line with the data from the ILLIAS Registry that includes a 5-year follow up period. [41] Concordant normal lesions have a lower event rate then non-revascularized discordant lesions. However, the non-revascularized discordant lesions have a similar MACE rate then lesions that were revascularized.

The ILIAS-ANOCA trial is currently enrolling and aims to harmonize and simplify the protocol of coronary reactivity tests, including both endothelial and non-endothelial dependent functional assessments. The primary endpoint of the trial will be an improvement in angina symptoms at six months. Secondary endpoints include assessing the effects of nitroglycerine on test outcomes, standardized medical treatment and the impact on the health economic burden of the disease.

CONCLUSION

Over the past decades the field of physiology-guided PCI has gone through a process of simplification, narrowing down to the assessment of epicardial stenoses using substitutes of coronary flow. With image-derived methodologies for functional assessment of coronary stenosis severity on the horizon, efforts associated with these assessments of coronary hemodynamics are reduced to a minimum. This gives space for physiological assessments to revert to their original scope, including both epicardial and microvascular function assessment. Returning to performing a comprehensive assessment beyond the coronary stenosis will be accelerated by advancements in guideline recommendations, diagnostic techniques and therapeutic options. Microvascular assessment will benefit from the innovations that contributed to the success of coronary stenosis severity analysis. It is expected that functional coronary angiography will emerge as a standard tool in the diagnostic workup of patients presenting with anginal symptoms.

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Appendices

AUTHOR CONTRIBUTIONS

Chapter 2 Draft manuscript: MAvL; Reviewed manuscript: JJP

Chapter 3 Draft manuscript: MAvL, TPvdH; Reviewed manuscript: JJP

Chapter 4 Data collection: MAvL, KDS, JJP; Analysis and interpretation: MAvL, TPvdH; Draft manuscript: MAvL, KDS, TPvdH, AF, BdB, KLG. Reviewed manuscript: JJP, KDS

Chapter 5 Study concept and design: MAvL, GWMW, TPvdH, MEP, JJP; Data collection: MEP, MM, JE, JJP; Analysis and interpretation: MAvL, GWMW, TPvdH, MEP; Draft manuscript: MAvL, GWMW; Reviewed manuscript: TPvdH, MEP, JJP, JE, TM, VES, MM.

Chapter 6 Study concept and design: TPvdH, MAvL, JAS, MS, JJP; Data collection: MAP, SAC, MV, JPSH, KTK, RJdW; Analysis and interpretation: TPvdH, MAvL, JAS, MS, JGT, MM, JJP; Draft manuscript: TPvdH, MAvL; Reviewed manuscript: PD, RD, JAS, MS, JGT, MM, JJP

Chapter 7 Study concept and design: GWMW, MAvL, YK, JJP; Data collection: MAvL, GWMW, RP, SSN, GAdW, SS, MEP, VES, TM, HMR, MM, DI, PK, JE, JED, JJP, TPvdH; Analysis and interpretation: MAvL, YK, GWMW, TPvdH, MEP; Draft manuscript: MAvL, YK, GWMW, CKMB; Reviewed manuscript: RP, SSN, GAdW, SS, MEP, VES, TM, HMR, MM, DI, PK, JE, JED, JJP, TPvdH

Chapter 8 Study concept and design: MAvL, TPvdH, JJP; Draft manuscript: MAvL; Reviewed manuscript: TPvdH, JJP

Chapter 9 Study concept and design: MAvL, KDS, JJP, MB; Data collection: MB, RJdW, KTK, JPSH, MM, JJP; Analysis and interpretation: MAvL, MB, VES, KDS, TPvdH; Draft manuscript: MAvL, VES, KDS; Reviewed manuscript: MB, TPvdH, GWMW, RJdW, KTK, JPSH, MM, JJP

Chapter 10 Study concept and design: MAvL, TPvdH, MEP, MB, JJP; Data collection: MB, RJdW, KTK, JPSH, MM, JJP; Analysis and interpretation: MAvL, VES, TPvdH, MEP; Draft manuscript: MAvL, VES; Reviewed manuscript: MB, TPvdH, GWMW, RJdW, KTK, JPSH, MM, JE, JJP

PHD PORTFOLIO

Name PhD student: Martijn A. van Lavieren
PhD period: 2013-2023
Name PhD supervisor: Prof. dr. Jan J. Piek

PhD training

	Year	Workload (ECTS)
General courses		
Pubmed	2013	0.1
BROK Course	2013	0.9
Practical Biostatistics	2013	1.1
Leadership in Science	2016	0.6
(Inter)national conferences & presentations		
European Society for Cardiology Congress	2013	
Trans Catheter Therapies • Presented Challenging Case "Intravenous administration of adenosine for physiological lesion severity assessment: How stable is maximal hyperemia?"	2013	
Advanced Physiology Summit	2013	
American College for Cardiology Congress • Poster presentation "Basal Versus Hyperemic Conditions for Physiological Stenosis Severity Assessment" • Poster presentation "Fractional Flow Reserve is Unlikely to be Abnormal in the Presence of High Microvascular Resistance."	2014	
Coronary Physiology and Intravascular Imaging Symposium	2014	
European Society for Cardiology Congress	2014	

- Poster presentation "Pressure-derived coronary flow reserve cannot be used as an alternative for coronary flow velocity reserve."
- Poster presentation "The resistance in the coronary microvasculature substantially impacts the assessment of epicardial stenosis severity by fractional flow reserve"

EuroPCR 2014
- Validation of pressure-derived coronary flow reserve as an estimate of coronary flow velocity reserve.

Trans Catheter Therapies 2014
- Challenging case "Refractory angina and a single stenosis with normal FFR but abnormal CFR: treating a depleted vasodilatory reserve"
- Challenging case "Non flow limiting stenoses: deffering revascularization in stenoses with positive fractional flow reserve"
- Poster presentation "Validation of pressure-derived coronary flow reserve as an estimate of Doppler flow velocity and thermodilution derived coronary flow reserve."

American College for Cardiology Congress 2015
- Poster presentation "Clinical Implications of a Cross-Modality Invasively Derived Coronary Flow Capacity concept"
- Poster presentation "The Influence of Ageing on Microvascular Resistance and Its Effect on FFR and CFR Discordance"

CVG Galway meeting 2015
- Oral presentation "Invasive coronary flow reserve"

Stent for Life Congress 2015

EuroPCR 2015

- Poster presentation "Heart rate dependence of baseline physiological index Pd/Pa for coronary lesion severity assessment"

Advances in Coronary Physiology 2015
- Challenging case "Refractory angina and a single stenosis with normal FFR but abnormal CFR: treating a depleted vasodilatory reserve"

Trans Catheter Therapies 2015

Stent for Life Congress 2016

EuroPCR 2016
- Oral presentation "The impact of acute alterations in glucose homeostasis on myocardial microvascular function in the setting of STEMI"

Advances in Coronary Physiology 2016
- Oral presentation "Case examples"

Teaching

	Year	Workload (ECTS)
Lecturing		
• Introduction into exercise physiology	2013	3.0
• Clinical Flow Training for Volcano Corp.	2014	2.0
Supervising		
• Bachelor assignment J. De Bruijn	2014	1.0
• Bachelor assignment E. Niewenhuis	2014	1.0
• Bachelor assignment H. Struik	2014	1.0
• Master assignment R. Feenstra	2015	2.0

Parameters of esteem

	Year
Organization	
Chairman of the board "Nederlandse Vereniging voor Technische Geneeskunde" • Organization of 40 persons, representing 300 technical physicians in The Netherlands.	2013-2015
Committee member on the working group on Medical Technology commissioned by the Netherlands Federation of University Medical Centres (NFU) and Dutch Hospital Organization (NVZ)	2015
Committee member on the evaluation of clinical quality assurance laws (Wet BIG) committee commissioned by the Dutch Ministry of Health (VWS)	2015

LIST OF PUBLICATIONS

[1] **van Lavieren MA**, Wijntjens GWM, Boerhout CKM, Kikuta Y, Petraco R, Nijjer SS, de Waard GA, Sen S, Echavarría-Pinto M, Stegehuis VE, Murai T, Mejía-Rentería H, Meuwissen M, Danad I, Knaapen P, Escaned J, Davies JE, van de Hoef TP, Piek JJ. Coronary Flow Capacity after Percutaneous Coronary Interventions in concordant and discordant lesions. *Submitted*

[2] **van Lavieren MA**, Stegehuis VE, Bax M, Echavarría-Pinto M, Wijntjens GW, de Winter RJ, Koch KT, Henriques JP, Escaned J, Meuwissen M, van de Hoef TP, Piek JJ. Time course of coronary flow capacity impairment in ST-segment elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2020 May 26:2048872620918706. doi: 10.1177/2048872620918706. Epub ahead of print. PMID: 32450714.

[3] **van Lavieren MA**, Bax M, Stegehuis VE, van de Hoef TP, Wijntjens GWM, de Winter RJ, Koch KT, Henriques JPS, Meuwissen M, Sjauw KD, Piek JJ. Acute alterations in glucose homeostasis impact coronary microvascular function in patients presenting with ST-segment elevation myocardial infarction. Neth Heart J. 2020 Mar;28(3):161-170. doi: 10.1007/s12471-020-01366-5. PMID: 31953778; PMCID: PMC7052118.

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[6] Wijntjens GWM, **van Lavieren MA**, van de Hoef TP, Echavarría-Pinto M, Meuwissen M, Stegehuis VE, Murai T, Escaned J, Piek JJ. Pressure-derived estimations of coronary flow reserve are inferior to flow-derived coronary flow reserve as diagnostic and risk stratification tools. Int J Cardiol. 2019 Mar 15;279:6-11. doi: 10.1016/j.ijcard.2018.11.013. Epub 2018 Nov 7. PMID: 30482445.

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[8] Vlastra W, Piek M, **van Lavieren MA**, Hassell MEJC, Claessen BE, Wijntjens GW, van de Hoef TP, Sjauw KD, Beijk MA, Delewi R, Piek JJ. Long-term outcomes of a Caucasian cohort presenting with acute coronary syndrome and/or out-of-hospital cardiac arrest caused by coronary spasm. Neth Heart J. 2018 Jan;26(1):26-33. doi: 10.1007/s12471-017-1065-1. PMID: 29236216; PMCID: PMC5758456.

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[13] **van Lavieren MA**, Piek JJ. Resting Indices of Coronary Lesion Severity: Not Always as Simple as It Seems. Circ Cardiovasc Interv. 2016 Apr;9(4):e003747. doi: 10.1161/CIRCINTERVENTIONS.116.003747. PMID: 27076572.

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[15] Nijjer SS, de Waard GA, Sen S, van de Hoef TP, Petraco R, Echavarría-Pinto M, **van Lavieren MA**, Meuwissen M, Danad I, Knaapen P, Escaned J, Piek JJ, Davies JE, van Royen N. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. Eur Heart J. 2016 Jul 7;37(26):2069-80. doi: 10.1093/eurheartj/ehv626. Epub 2015 Nov 26. PMID: 26612582; PMCID: PMC4940452.

[16] Echavarría-Pinto M, van de Hoef TP, **van Lavieren MA**, Nijjer S, Ibañez B, Pocock S, Quirós A, Davies J, Meuwissen M, Serruys PW, Macaya C, Piek JJ, Escaned J. Combining Baseline Distal-to-Aortic Pressure Ratio and Fractional Flow Reserve in the Assessment of Coronary Stenosis Severity. JACC Cardiovasc Interv. 2015 Nov;8(13):1681-91. doi: 10.1016/j.jcin.2015.09.002. PMID: 26585618.

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[18] Nijjer SS, Petraco R, van de Hoef TP, Sen S, **van Lavieren MA**, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, Al-Lamee R, Foin N, Sethi A, Malik IS, Mikhail GW, Hughes AD, Mayet J, Francis DP, Di Mario C, Escaned J, Piek JJ, Davies JE. Change in coronary blood flow after percutaneous coronary intervention in relation to baseline lesion physiology: results of the JUSTIFY-PCI study. Circ Cardiovasc Interv. 2015 Jun;8(6):e001715. doi: 10.1161/CIRCINTERVENTIONS.114.001715. PMID: 26025217; PMCID: PMC4943523.

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[20] **van Lavieren M**, Veelenturf J, Hofhuizen C, van der Kolk M, van der Hoeven J, Pickkers P, Lemson J, Lansdorp B. Dynamic preload indicators decrease when the abdomen is opened. BMC Anesthesiol. 2014 Oct 14;14:90. doi: 10.1186/1471-2253-14-90. PMID: 25337036; PMCID: PMC4203872.

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[23] Petraco R, van de Hoef TP, Nijjer S, Sen S, **van Lavieren MA**, Foale RA, Meuwissen M, Broyd C, Echavarria-Pinto M, Foin N, Malik IS, Mikhail GW, Hughes AD, Francis DP, Mayet J, Di Mario C, Escaned J, Piek JJ, Davies JE. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). Circ Cardiovasc Interv. 2014 Aug;7(4):492-502. doi: 10.1161/CIRCINTERVENTIONS.113.000926. Epub 2014 Jul 1. PMID: 24987048.

[24] van de Hoef TP, **van Lavieren MA**, Damman P, Delewi R, Piek MA, Chamuleau SA, Voskuil M, Henriques JP, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Meuwissen M, Piek JJ. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. Circ Cardiovasc Interv. 2014 Jun;7(3):301-11. doi: 10.1161/CIRCINTERVENTIONS.113.001049. Epub 2014 Apr 29. PMID: 24782198.

[25] **van Lavieren MA**, van de Hoef TP, Piek JJ. Coronary wedge pressure and collateral flow contribution: not a dichotomy! EuroIntervention. 2014;9(12):1485-8. doi: 10.4244/EIJV9I12A250. PMID: 24755391.

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[27] van de Hoef TP, Nolte F, Echavarría-Pinto M, **van Lavieren MA**, Damman P, Chamuleau SA, Voskuil M, Verberne HJ, Henriques JP, van Eck-Smit BL, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Meuwissen M, Piek JJ. Impact of hyperaemic microvascular resistance on fractional flow reserve measurements in patients with stable coronary artery disease: insights from combined stenosis and microvascular resistance assessment. Heart. 2014 Jun;100(12):951-9. doi: 10.1136/heartjnl-2013-305124. Epub 2014 Apr 11. PMID: 24727867.

[28] van de Hoef TP, **van Lavieren MA**, Henriques JP, Piek JJ, Claessen BE. Fractional flow reserve-guided percutaneous coronary intervention: does coronary pressure never lie? Curr Treat Options Cardiovasc Med. 2014 Apr;16(4):294. doi: 10.1007/s11936-014-0294-5. PMID: 24515354.

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Abel, paranimf, van gezonde rivaliteit op de Oude Markt toen, tot samen peuter zwemmen nu. Het is bijzonder hoe onze tijd in het bestuur van de NVvTG en in het AMC is uitgegroeid tot een hechte vriendschap. Je staat altijd klaar op het juiste moment, in goede, maar ook in uitdagende tijden. Er zijn weinigen die zo oprecht, maar ook principieel zijn als jij, ik bewonder je normen en waarden en hoe sterk je hiervoor staat. En dan die glimlach van je, een magische glimlach waarmee je van alles voor elkaar krijgt, bewonderenswaardig, maar ook een teken van je hartelijke en open karakter. Ik denk nog vaak terug aan de vele 'koffies' in het AMC, waar we de wereld bespraken, onze promotie perikelen, en onze NVvTG hobby. Ik kijk uit naar nog vele bezoekjes aan Artis met onze kinderen.

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CURRICULUM VITAE

Martijn Anne van Lavieren was born on February 19th, 1987, in Harlingen, The Netherlands, as the son of Martje Anna van der Veen and Teunis Willem van Lavieren. In 2005 he graduated high school (VWO) at the RSG Simon Vestdijk and, over the summer, moved to Enschede to start his study Technical Medicine at the University of Twente. During the early years of the Bachelor's study, Martijn got involved in the Experimental Center for Technical Medicine as a student assistant, where the interest in hemodynamic physiology sparked off. In 2010 he received his Bachelor of Science and continued his education by enrolling in the Master of Science track 'Medical Signaling'. He gained experience through internships at the Medisch Spectrum Twente, Radboud UMC, University of Florida, and VU Medical Center, where cardiopulmonary physiology developed as a central theme across his internships. Martijn completed his master thesis at the intensive care department of Radboud UMC in Nijmegen under the supervision of dr. Joris Lemson, dr. Charlotte Hofhuizen and dr. ir. Benno Lansdorp. On January 31st, 2013, he received his Master of Science degree cum laude with his thesis entitled 'The development of a clinical decision support method to improve the applicability of dynamic indices in the intensive care unit'.

Martijn started his Ph.D. in 2013 under the supervision of Professor Jan J. Piek and dr. Tim P. van de Hoef at the department of Cardiology in the Academic Medical Center in Amsterdam, The Netherlands. The topic of his Ph.D. was coronary physiology and the role of the microcirculation. He was involved in numerous commercial and academic clinical trials as well as acted as a consultant to industry partners. Concomitant to his Ph.D. appointment, Martijn was elected as the board's chair for the Dutch Association for Technical Medicine ('Nederlandse Vereniging voor Technische Geneeskunde'). He represented Technical Physicians as a committee member on the working group on Medical Technology commissioned by the Netherlands Federation of University Medical Centres (NFU) and Dutch Hospital Organization (NVZ), as well as a committee member on the evaluation of clinical quality assurance laws (Wet BIG) committee commissioned by the Dutch Ministry of Health (VWS).

In 2016 he joined the business unit of Image-Guided Therapies Systems in Philips in the role of venture manager, leading a project on the future of coronary physiology. In 2017 he continued his assignment at the Advanced Development department of Image-Guided Therapies Devices as program lead for the coronary and peripheral business segment. In 2018 he became senior manager of strategy and market development for the coronary segment and in 2020 took on the assignment of senior upstream global product manager

responsible for the roadmap and delivery of future coronary physiology solutions. In 2021 Martijn became a member of the Image Guided Therapies Innovation leadership team responsible for driving transformations in the cardiology innovation portfolio.

After many years in Amsterdam, Martijn and his wife Katinka Davy moved to Abcoude in 2017. There they became the proud parents of Alexander van Lavieren, born in 2018, and Benjamin van Lavieren, born in 2020.