Comprehensive assessment of ischaemic heart disease with invasive pressure and flow measurements

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COMPREHENSIVE ASSESSMENT OF **ISCHAEMIC HEART DISEASE** WITH INVASIVE PRESSURE AND FLOW MEASUREMENTS

Mauro Echavarría Pinto

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Comprehensive assessment of ischaemic heart disease with invasive pressure and flow measurements

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A mi esposa, hijos y padres

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CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

More than 40 years ago, it was shown that reductions in coronary artery diameter ≥50% limited maximum coronary flow. This landmark experimental demonstration was rapidly translated and incorporated into clinical cardiology practice.[1] A "sine qua non" relationship between obstructive coronary artery disease (CAD), myocardial ischaemia and adverse cardiovascular events progressively matured, and became the governing paradigm on the genesis and prognosis of ischaemic hear disease (IHD).[2] As a consequence—and in a logical attempt to fulfil criteria for causality[3]— the mechanical resolution of such epicardial stenosis (either by surgical or percutaneous approaches) became one of the ultimate objectives of IHD therapy. Cumulative evidence now clearly suggests, however, that such direct relationship between obstructive CAD and IHD represents a simplistic view of the leading cause of worldwide death.[2,4-6] Indeed, many studies have shown how numerous patients with objective evidence of myocardial ischaemia do not have obstructive CAD, and conversely, that many patients with obstructive CAD neither experience anginal symptoms nor have objective evidence of abnormal myocardial blood supply.[7-10] Following this rationale, it is increasingly recognized that the unitary "stenosis-centred" theory of IHD has important limitations; with the coronary microcirculation and myocardial cell envisaged as the next diagnostic and therapeutic steps.[2]

Fractional flow reserve (FFR) has become the standard method to assess IHD in the catheterization laboratory following the demonstration that revascularization decisions based on FFR results in better patient outcomes than revascularization decisions based on angiography.[11-13] However and by definition, FFR is a stenosis-centred technique, that uses the hyperaemic trans-stenotic pressure ratio as a surrogate of myocardial flow impairment.[14] FFR theory do acknowledges that non-obstructive causes of IHD, such as coronary microcirculatory dysfunction (CMD), can modulate FFR values, but faultily assumes that since CMD will not be solved by revascularisation, further understanding on the microcirculatory function is not physiologically relevant nor have clinical implications and can be thus left unattended.[15] Nevertheless, a growing body of evidence is convincingly showing how CMD is significantly associated with a noteworthy and quantifiable risk for cardiovascular morbidity and mortality.[6,8-10] These additional coronary abnormalities beyond the FFR domain might help to explain why patients with normal FFR values in randomised trials were not free from long-term cardiac events (21% mayor adverse cardiovascular event rate in DEFER trial,[11] 33% and 20% long-term angina at 5 and 2 years of follow-up in DEFER[11] and FAME[12] trials, respectively) and, conversely, why some patients with abnormal FFR values but with preserved coronary flow supply have a low rate of cardiovascular adverse events at follow-up.[6] Consequently and above its recognized clinical value, the theoretical FFR

framework seems insufficient to face the complexity of IHD that involves the epicardial vessel but also the microcirculatory domains of the coronary circulation.

This thesis focusses first on the physiological assessment of coronary stenosis under non-hyperaemic and hyperaemic conditions, and from there, proposes a combined non- and hyperaemic coronary pressure diagnostic approach to assess stenosis severity. Second, the thesis provides some novel insights on the systemic effects of hyperaemic agents and their impact on the physiological assessment of coronary stenosis, and also proposes an operational definition of the FFR more close to its theoretical framework. The third focus of the thesis is the influence of the coronary microcirculation on the invasive assessment of IHD. Particularly, how does the ageing process, stenosis location and non-invasive ischaemia influences microcirculatory resistance appraisal. Finally, a more comprehensive invasive physiological assessment of IHD is proposed in the fourth part of the thesis, where FFR, coronary flow reserve and microcirculatory resistance are viewed as complementary rather than competing techniques. Finally, two complementary physiology indices (the coronary flow capacity and the coronary flow reserve predicted from pre-interventional measurements) were explored, including their potential clinical and prognostic implications.

OUTLINE OF THE THESIS

Part A. Physiological assessment of coronary stenosis under non-hyperaemic and hyperaemic conditions

The functional assessment of the coronary circulation has clearly lead to an improvement in patient care. The FFR is the most widely physiology index used for the latter purpose, and its fundamental basis and clinical applications are discussed in detail un *Chapter 2* and *3*. However and in spite of a high level recommendation in clinical practice guidelines, the worldwide use of FFR has remained low, with the cost of vasodilator agents and some uncertainty on the achievement of "true maximum" hyperaemia as some of the proposed reasons for its low use. Non-hyperaemic coronary physiology indices have been proposed to tackle such issues. *Chapters 4 and 5* describe the main results of the ADVISE II Study (ADenosine Vasodilator Independent Stenosis Evaluation II), that sought to assess in a rigorous manner the diagnostic performance of two non-hyperaemic indices, the instantaneous wave free ratio and the baseline distal to aortic pressure ratio, against the FFR. *Chapter 6* proposes a combined non-hyperamic and hyperaemic coronary stenosis assessment approach, where baseline and hyperaemic pressure indices are viewed as complementary rather than competing techniques. Finally, *Chapter 7* describes a meta-analytical effort on the safety of revascularization deferral of left main disease based on FFR or intravascular ultrasound.

Part B. Systemic effects of adenosine and its impact on the physiological assessment of coronary stenosis

FFR is largely considered independent of systemic haemodynamics. However, in *Chapter 8,* we describe how the hypotensive effect of intravenous adenosine infusion is positively associated with coronary microcirculatory resistance and lower FFR values. *Chapter 9* explores from a different angle the influence of the fluctuations in aortic pressure and the development of the hyperaemic plateau on the FFR. These analyses show that the FFR value commonly used in clinical practice slightly differs from the original FFR framework, and also describes a pragmatic operational definition for the index.

Part C. Influence of the coronary microcirculation on the invasive assessment of ischaemic heart disease

Part C of this thesis sought to underscore the importance of the coronary microcirculation. Firstly in a review on the use of intracoronary physiology indices in acute coronary syndromes (*Chapter 10*), that is largely focused on the prognostic role of the coronary flow reserve and microcirculatory resistance indices, and then on an analyses of the influence of the ageing process on the stenosis and microcirculatory resistance indices in *Chapter 11*. A theoretical concern for the clinical use of microcirculatory resistance and relative flow indices to assess microcirculatory function was comprehensively addressed in *Chapter 12*. Namely, the physiologically expected increase in estimated coronary resistance across the branching structure of the coronary tree.

Part D. Comprehensive invasive physiological assessment of ischaemic heart disease

Part D of this thesis sought to propose how does a comprehensive invasive physiological assessment of IHD can significantly enrich information and might have prognostic implications. *Chapters 13* and *14* describes the simultaneous use of FFR, coronary flow reserve and the index of microcirculatory resistance in the invasive diagnosis of IHD, and in *Chapters 15* and *16*, two complementary physiology indices derived from invasive pressure and flow data were explored. First, in *Chapter 15*, the coronary flow capacity concept, that soughs to overcome some of the acknowledged limitations of the coronary flow reserve in describing the flow characteristics of the coronary circulation. Then, in *Chapter 16*, the coronary flow reserve predicted from pre-interventional measurements, that takes advantage of FFR theory and aims to predict the physiological impact of percutaneous coronary intervention on the coronary flow reserve. This novel diagnostic approach was comprehensively teste by meta-analytic and individual means.

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Part A

Physiological assessment of coronary stenosis under non-hyperaemic and hyperaemic conditions

CHAPTER 2

Use of fractional flow reserve in contemporary scenarios of coronary revascularization

Echavarría-Pinto M, Escaned J

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ABSTRACT

Fractional flow reserve (FFR), an invasive pressure-derived index of stenosis severity, can be performed easily, rapidly, and safely in patients with coronary artery disease as a surrogate of non-invasive detection of ischemia. Over the last decades, profound clinical and scientific evaluation has demonstrated that FFR is one of the few diagnostic modalities that improve patient outcome and, at the same time, are cost-effective and cost-saving. The increasing use of PCI to treat multivessel disease and complex anatomical subsets has created new demands for accurate, "per stenosis" assessment, since revascularisation should be performed only in those stenosis that are ischaemia generating. Recent studies have demonstrated that this attitude results in better patient outcomes. Altogether, current evidence clearly supports the measurement of FFR in catheterization laboratories in order to provide objective and complementary data to coronary angiography. The purpose of this review is to discuss the value of FFR in the diagnosis and treatment of patients with different anatomical subsets, including intermediate stenosis, multivessel disease, left main disease, serial stenosis, ostial and bifurcation lesions, saphenous vein graft disease and in-stent restenosis, as well as in those presenting with acute coronary syndromes.

INTRODUCTION

Coronary angiography remains the most frequently used imaging technique for the assessment of epicardial coronary arteries. However, images provided by coronary angiography have well-recognized limitations. Perhaps the most important, is the poor association between angiographic stenosis severity and hemodynamic relevance.[1] Over the last decade, intracoronary physiology techniques have become powerful diagnostic tools to establish the haemodynamic impact of coronary stenoses and have been pivotal in promoting ischaemia-driven coronary revascularization. Several indices for the assessment of stenotic severity based on intracoronary measurements of pressure, flow velocity or both, have been proposed. Many of them have clinically important limitations. The fact that an ideal physiological test has to be accurate, independent of changing haemodynamic conditions, easy to perform, safe, and easy to interpret[2] probably explains why fractional flow reserve (FFR), a pressure-derived index of coronary flow reserve, has become accepted as the intracoronary technique of choice by most interventional cardiologists.[3]

The link between percutaneous coronary interventions (PCI) and intracoronary physiology stems from the fact that establishing stenotic relevance is a pre-requisite for setting the indication of treatment. There are multiple specific scenarios of PCI where the importance of FFR has to be highlighted in which specific comments relevant to the technique and interpretation of the results have to be made. The present review will focus on the current evidence for FFR-guided revascularization and will discuss those specific clinical and anatomical scenarios that have received more attention in the literature and that, in our experience, are of special relevance for those involved in treating patients with coronary artery disease.

HISTORICAL PERSPECTIVE. IMAGING VERSUS PHYSIOLOGY

In late 80´s, technical easiness boosted percutaneous revascularization. However, the decision to perform percutaneous coronary intervention (PCI) was frequently based on visual assessment, especially in presence of non-conclusive non-invasive tests and stenosis of intermediate severity. Little after, several studies depicted incorrect individual angiographic stenosis judgment and a high inter- and intraobserver variability.[1,4,5] Also, anatomical and intravascular ultrasound (IVUS) studies demonstrated that coronary lesions are highly complex and often exhibited distorted or eccentric luminal shapes.[6,7] This lead to major developmental progresses in analytical angiography software and X-ray imaging technology and finally, quantitative digital coronary analysis (QCA) emerged. However, it soon became evident that despite a much better

interobserver variability and reliability in the geometric measurements obtained, QCA was frequently not capable of discriminating between hemodynamically severe and non-severe stenoses leaving this pivotal question unanswered.[8-10]

Pressure measurements to assess stenosis severity were first used soon after the introduction of over-the-wire coronary angioplasty balloons. First, the trans-stenotic pressure gradient was measured, using large lumen guide catheters to determine the aortic pressure and the guidewire lumen of balloon catheters to measure the post-stenotic pressure, to infer stenosis haemodynamic severity prior and after balloon dilatation.[11] However, several influencing variables systematically falsified this gradient analysis. Due to their large cross-sectional area, balloon catheters limited correct pressure deduction and precluded its guidance into smaller arteries or through high degree stenosis. Also, the transducer system could only receive low-frequency impulses with fluid-filled catheters. These problems remained when using dedicated thin intracoronary catheters and, as a consequence, determination of the trans-stenotic gradient was not widely implemented as a diagnostic technique.[12] Later, PCI-compatible pressure wires were incorporated in the early 90´s. Given its low profile, the interference of these guidewires with the interrogated haemodynamic conditions was very low, and the introduction of an extremely sensitive micro-transducer allowed, finally, accurate measurements of trans-stenotic pressure gradient.

However, the definitive step forward in intracoronary physiology was not a technical one but, rather, the development of a new theoretical framework for interpreting pressure drop across the stenosis. This new concept was fractional flow reserve, in which pressure-derived estimates of coronary blood flow could be obtained.[3] In the next section we will review briefly key physiological aspects from which FFR is derived.

FROM PRESSURE TO FLOW. THE CORNERSTONE OF FFR

In order to understand the theory of FFR, it is essential to recognise some key aspects of the coronary pressure-flow relationship. First of all, at rest, the relationship between pressure and flow in the coronary arteries is non-lineal and its characteristics vary with the metabolic status of the heart.[13] Second, during maximum coronary hyperemia (which occurs as a response to intense metabolic myocardial demand or to the administration of vasodilator agents) resistance is minimised and the relation between coronary blood pressure and flow becomes linear.[14] This linear relation, is the cornerstone for obtaining information on coronary flow from coronary pressure measurements (figure 1).

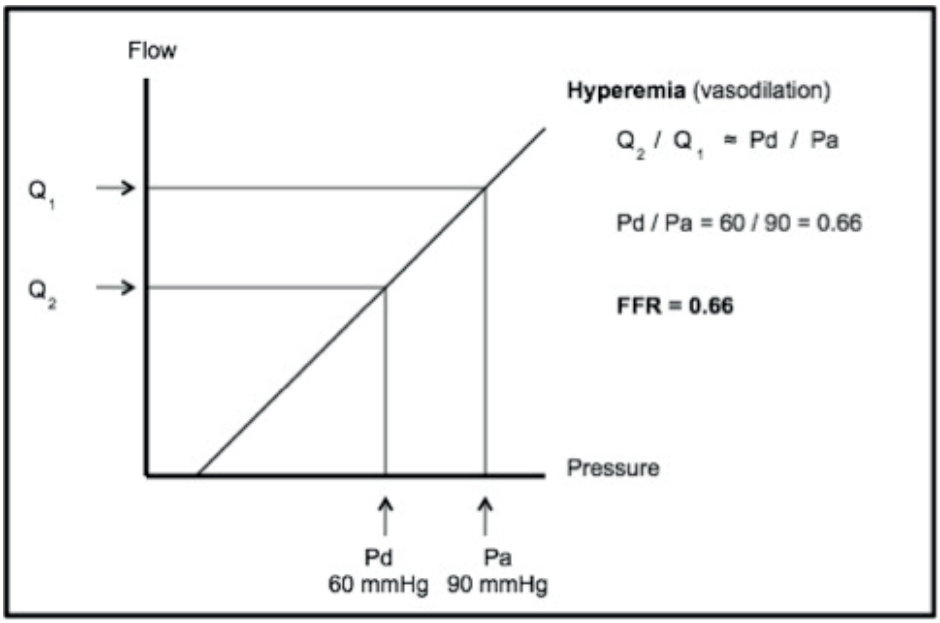

Figure 1 | Fractional flow reserve is estimated on the grounds of the existing lineal relationship between pressure and flow that takes place in the coronary arteries during maximal hyperemia. The graphic illustrates two coronary pressures that correspond to those used for FFR calculation: Pa (aortic pressure, obtained from the guiding catheter), and Pd (pressure distal to the interrogated stenosis, obtained with the pressure guidewire). Their corresponding flow values, Q1 and Q2, are also shown. Being a linear relationship, the ratio between pressures is equivalent to the ratio between flow values. The obtained FFR value of 0.66 expresses that blood flow to the myocardium in the area of distribution of the vessel is 66% of that expected if the stenosis is completely removed.

FFR calculation requires two pressures: the aortic pressure (Pa) and the pressure distal to an interrogated stenosis (Pd). Since the pressure flow relationship is linear during maximal hyperaemia, the ratio of pressures Pd/Pa is proportional to the ratio of flows. Consequently, pressure can be used as a surrogate of flow. FFR is simply derived from pressure (Pd/Pa) and is defined as the ratio of maximal flow in a stenotic artery to the flow in the same artery in the theoretic absence of the stenosis.[3] For example, if FFR is 0.70, it means that the myocardium in the area of distribution of the interrogated vessel receives only 70% of the expected flow in the absence of that stenosis; or, conversely, it causes a 30% impairment of blood supply to the subtended myocardium. As a ratio, the highest possible value is 1.0 and denotes an epicardial vessel with completely normal epicardial conductance. This means that epicardial arteries do not contribute to the total resistance of coronary blood flow. Any FFR value < 1.0 indicate some degree of intracoronary pressure/flow loss, and the critical threshold for myocardial hypoperfusion was stipulated at an FFR value of 0.75. Stenoses with an FFR <0.75, are almost invariably associated with myocardial ischaemia while those with an

FFR >0.80 are almost never associated with this condition.[15] This leaves a "grey zone" for FFR between 0.75 and 0.80 that will be discussed in the following paragraphs.

There is little doubt in that the success of FFR was due in large part to the simplification of coronary haemodynamics, but also to other clinically important worth-nothing characteristics (figure 2).[16] First, FFR measurements are extremely reproducible and are not influenced by systemic haemodynamics (though animal studies suggested an influence of heart rate, blood pressure and contractility, such unwanted interference could not be verified clinically in humans).[17] Second, FFR allows to specifically relate myocardial mass to the severity of the stenosis, since the larger the myocardium perfused, the larger the flow normally provided. This explains why two stenosis with the same minimal cross sectional area have a totally different haemodynamic impact, for example, in the left main artery or a diagonal branch. Third, FFR reflects not only antegrade flow, but also that provided by collaterals and, if it is the case, by surgical grafts distal to the interrogated stenosis. As a matter of fact, the first term used by Pijls et al for the hyperaemic ratio Pd/Pa was "myocardial fractional flow reserve" since it conveys both, antegrade and retrograde coronary artery flow.[18] Fourth, it has a uniform normal value of 1.0 for every coronary artery and there is no need for a control artery. Finally, FFR provides an instantaneous assessment of flow that during a pull-back, allows a very high spatial resolution analysis. Altogether, these characteristics of FFR have created unprecedented expectations and has boosted the interest in intracoronary physiology among interventional and non-interventional cardiologists alike.

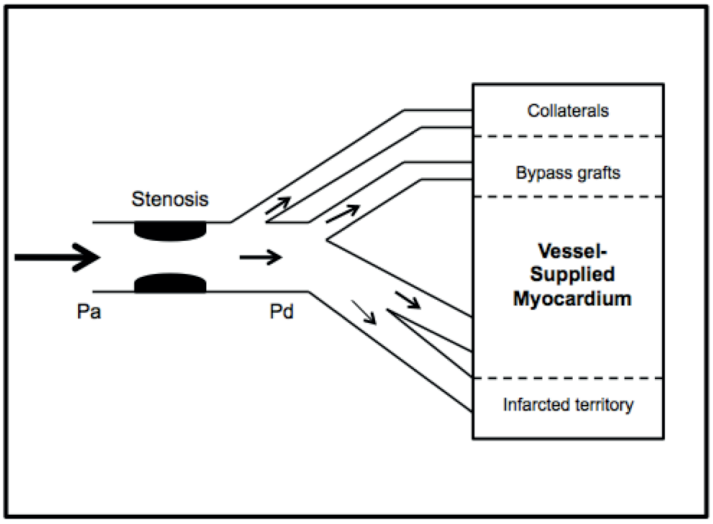

Figure 2 | This graphic illustrates how FFR takes into account the contribution of coronary antegrade flow, collateral circulation, bypass grafts (if present) and the amount of viable myocardial mass. Pa: aortic pressure; Pd: pressure distal to the interrogated stenosis.

RELEVANT DIFFERENCES IN MYOCARDIAL ISCHAEMIA ASSESSMENT WITH NON-INVASIVE FUNCTIONAL TESTS AND FFR

The validation of FFR as an index capable of identifying haemodynamically severe stenosis has been based in comparison with non-invasive tests of myocardial ischaemia. This first studies (Table 1) established that FFR values <0.75 were consistently associated with ischaemia, with high sensitivity (88%), specificity (100%), positive predictive value (100%) and overall accuracy (93%).[3] Conversely, negative ischaemic results were expected with FFR values >0.80 with an overall accuracy of 95%. More recently, a meta-analysis of diagnostic studies that compared FFR with QCA and/or non-invasive imaging for the evaluation of myocardial ischaemia found a more complex association.[10] Across 18 studies (1,522 lesions), QCA had a random effects sensitivity of 78% and specificity of 51% against FFR. Overall concordance was high (95%) for low-degree stenoses (<30%), 61% for intermediate stenoses (30% to 70%) and 67% for high degree stenoses (>70%). Compared with non-invasive imaging (21 studies, 1,249 lesions), FFR had a sensitivity of 76% and specificity of 76% by random effects. From these results we can conclude that QCA does not predict the functional impact of coronary stenosis and, that probably, the concordance between FFR and non-invasive functional tests is not as strong as we previously tough. These discordant results can be partially explained by the differences in the information provided by non-invasive functional tests and FFR that will be discussed in the next paragraph.

Table 1 | Validation studies for fractional flow reserve

Author	n	Reference test	OCV	Sn	Sp
Pijls et al.[18]	45	ETT+SPECT+SE	0.75	88	100
Abe et al. [88]	46	SPECT	0.75	83	100
Erhard et al.[87]	47	SPECT	0.75	83	77
Chamuleau et al.[86]	127	SPECT	0.74	65	85

OCV:optimal cutoff value; Sn:sensitivity; Sp:specificity; ETT:exercise tolerance test; SPECT: single photon emission computed tomography; SE: stress echocardiography

In the clinical evaluation of patients with suspected coronary artery disease (CAD), functional imaging tests play a crucial role in the assessment of myocardial ischaemia and viability. A worth-noting characteristic of non-invasive functional tests (such as myocardial perfusion imaging (MPI) studies, dobutamine stress echocardiogram and more recently, stress magnetic resonance imaging), is their proven capacity to measure the extent and severity of inducible myocardial ischaemia.[19,20] Ischaemic burden is a major prognostic factor in CAD patients, as recently highlighted by the COURAGE (Clinical Outcomes Utilising Revascularization and Aggressive Drug Evaluation) Trial Nuclear Sub-study.[21] This sub-study stated that the magnitude of residual ischaemic burden

was proportional to the risk for cardiac events, indicating that the survival benefits of PCI are only produced when the stenosis-to-be-treated is the cause if significant myocardial ischaemia (≥5% myocardium). This extremely important information cannot be completely inferred from a FFR measurement and therefore the ischaemic area has to be estimated from the size, length and distribution of the coronary vessel downstream the FFR interrogated stenosis. On the other hand, non-invasive functional test have a limited spatial resolution, as observed by the trichotomized result obtained from an exercise electrocardiogram test (positive, negative or non-conclusive), or the "per artery" resolution of MPI studies. Non-invasive functional tests commonly fail in the assessment of multivessel coronary disease (these aspects will be discussed in detail in section 7.2). In this regard, FFR has a much better spatial resolution and allows an instantaneous assessment of the interrogated artery with a spatial resolution of only a few millimetres. These differences in the information provided by non-invasive functional tests and FFR have to be stressed, recognised as complementary, and properly integrated in the decision-making process.

SAFETY OF CLINICAL DECISION-MAKING BASED ON FFR

We have already discussed that stenosis geometry correlates poorly with stenosis relevance. In the following paragraphs, we will discuss a more important premise: that cardiovascular outcomes are best predicted by the functional severity of a stenosis and that, as a corollary of that statement, functional assessment plays an important role in assessing the prognosis of patients coronary artery disease (CAD) patients. This concept has been highlighted in large MPI studies showing an excellent long-term prognosis after a normal scan[22,23] and a very large body of evidence[19] suggesting a poor prognosis in patients with a high-risk profile according to MPI, with an annualised rate of major adverse cardiac events of 5.9%, in contrast to a 0.6% in case of a normal result.[19] Furthermore, several influential randomised clinical trials support the safety of coronary physiological assessment in clinical decision-making. The results of the COURAGE trial underlined the fact that percutaneous coronary intervention (PCI) is capable of reducing death or major cardiovascular events only in patients with stable coronary heart disease (CHD) with significant proven ischaemia.[21,24] The DEFER trial (Deferral of Percutaneous Coronary Intervention) demonstrated that in patients with documented epicardial stenosis that are not functionally significant, the annual rate of myocardial infarction and death is <1% and was not decreased with stenting.[25] Finally, the FAME trial (Fractional Flow Reserve versus Angiography for Guiding PCI in Patients with Multivessel Coronary Artery Disease) showed that in patients with stenosis in

more than one coronary artery, a tailored revascularization approach based in FFR measurements resulted in a better clinical outcome and reduces costs.[26,27]

As a conclusion, the safety of deferring coronary intervention for coronary stenosis with normal physiology has been reported in several studies with remarkable and consistently low clinical outcomes (Table 2).[18,27-32] This is of particular importance at a time when the SYNTAX trial (Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease), which compared PCI with paclitaxel eluting stents and CABG, reported similar death and myocardial infarction rates in patients randomised to CABG and percutaneous intervention arms,[33] anticipating an increase in the number of patients with multivessel stenosis to be treated with PCI. In the following sections, we review those clinical and anatomical subsets more widely studied with FFR and will discuss pros and caveats of FFR-driven revascularization.

Table 2 | Studies on safety of clinical decision making based on FFR

Author	n	clinical scenario	Study design
Bech et al.[29]	100	intermediate stenosis	SC / R
DEFER trial [28]	350	intermediate stenosis	MC / R
Wongpraparut et al.[85]	137	intermediate stenosis	SC / R
Chamuleau et al. [39]	107	intermediate stenosis	SC / NR
Ozdemir et al. [84]	51	intermediate stenosis	SC / NR
Wijpkema et al. [83]	61	intermediate stenosis	SC / NR
Rieber et al. [82]	56	intermediate stenosis	SC / NR
Legalery et al.[81]	407	intermediate stenosis	SC / NR
Verna et al.[32]	112	multivessel disease	SC / NR
Jiménez-Navarro et al.[80]	38	multivessel disease	SC / NR
Berger et al.[79]	102	multivessel disease	SC / NR
Chamuleau et al.[38]	191	multivessel disease	MC / NR
FAME trial [27]	1005	multivessel disease	MC / R
Bech et al. [46]	54	left main coronary artery	SC / NR
Jiménez-Navarro et al. [47]	27	left main coronary artery	SC / NR
Lindstaedt et al. [48]	51	left main coronary artery	SC /NR
Legutko et al. [49]	38	left main coronary artery	SC / NR
Suemaru et al. [78]	15	left main coronary artery	SC / NR
Courtis et al. [51]	142	left main coronary artery	SC / NR
Hamilos et al. [50]	213	left main coronary artery	SC / NR
Dominguez-Franco et al.[77]	42	diabetic patients	SC / NR
Lopez-Palop et al. [72]	62	in-stent restenosis	SC / NR

SC: single center; MC: multicenter; NR: non-randomised; R: randomised.

FFR AND SAFETY OF CLINICAL DECISION MAKING IN SPECIFIC SCENARIOS

Outcomes of FFR guided-revascularization in stenosis of intermediate severity

By far, the most frequent indication of FFR is (and will remain) the assessment of intermediate stenosis (40-70% luminal narrowing by angiography). As discussed previously, recurrent or constant hypoperfusion of the supplied myocardium is suspected below the commonly used cut-off value of 0.75 for FFR[18] and PCI is justified[34] Values between 0.76 and 0.79 represent a "grey zone" where further considerations should be taken into account to decide upon treatment. These considerations comprise morphological and anatomical lesion criteria (e.g. access to the lesion, lesion composition, additional serial stenosis) as well as patient characteristics (e.g. diabetes, comorbidities, overall prognosis, typical vs. atypical angina) and results from non-invasive ischaemia testing (e.g. localisation and extent of ischaemia). An FFR-value ≥ 0.80 is a surrogate parameter for non-ischaemia generating, and PCI most likely will neither affect the patient's complaints nor his prognosis. Instead - according to the long-term results of the DEFER study - the patient is exposed to the risk of sustaining a procedure-related adverse event.

The DEFER-study randomised 325 patients scheduled for PCI into 3 groups according to FFR-measurement.[25] The reference group consisted of 144 patients with a FFR-value < 0.75 and was designated to PCI. Patients with a FFR-value ≥ 0.75 were randomly assigned to the deferral group (n=71), that received medical therapy only, or the PCI performance group (n=90), that received stent implantation plus medical therapy. Recently, the 5-year outcomes have been published (follow-up completion rate 98%) showing similar event-free survival for the deferral and the performance group (80% and 73%, p = 0.52), both proving superior to the reference group (63%, p = 0.03). Another key conclusion of the DEFER-study was that in patients with a FFR > 0.75, the risk of cardiac death or myocardial infarction related to the stenosis was < 1 % per year and not decreased by stenting. This low event rate is comparable to those observed in patients with normal MPI tests.[19] These results and others,[29,31,35-39] strongly supports the use of FFR in the decision making process of intermediate lesions (Figure 3).

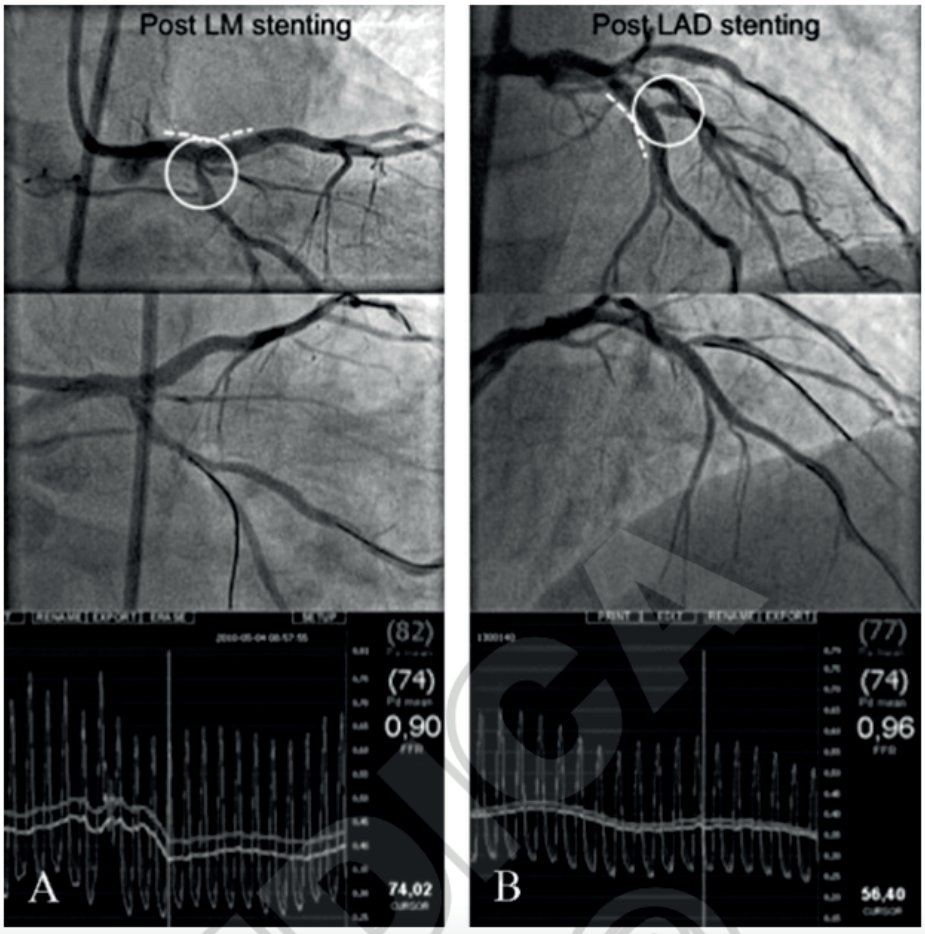

Figure 3 | This figure shows the value of FFR in the assessment of the jailed side branches during PCI. Panel A: After implantation of a drug-eluting stent in a left main stenosis (dotted line), an angiographic narrowing (60% DS) became evident in the jailed circumflex branch. An FFR of 0.90 was documented and no further intervention was performed at this level. Panel B: A mid LAD stenosis was the treated at a bifurcation with a diagonal branch. After stent implantation (dotted line) an angiographic stenosis developed at the ostium of the jailed diagonal branch with TIMI III flow. A pressure guidewire was crossed through the stent struts and FFR was measured. On the grounds of the result obtained (FFR 0.96), no additional action was taken regarding the diagonal branch. The patient evolved favourably during hospital stay and remained free of angina at follow-up. Reprinted with permission from: Escaned, J., Serruys, PW. "Assessment of stenosis severity with intracoronary pressure and thermodilution measurements". Coronary Stenosis Imaging, Structure and Physiology. Toulouse: PCR Publishing, Europa Edition, 2010. 355-376.

FFR in multivessel coronary intervention

With the advent of drug eluting stents the likelihood of restenosis after PCI decreased markedly. This paved the way to the vast field of multivessel coronary intervention and,

consequently, the total amount of stents implanted worldwide escalated. This situation should lead to the rationalization of PCI, in terms of minimising the amount of stents, peri-interventional and long-term complications and health care costs. In this regard, it is logical that only perfusion-limiting stenosis should be treated – a theorem called stenosis selection.[40] However, assessment of patients with multivessel disease, either noninvasive or with angiography, is more complex than in patients with single vessel narrowings, and represent one of the most frequent problems faced by interventional cardiologist in current practice. In this setting, existing non-invasive modalities used for MPI may fail to correctly identify areas of hypoperfusion because they rely on relative flow heterogeneity.[41] Masking of significant local ischaemia by another superimposed most ischaemic area or false negative studies due to balanced ischaemia are mechanisms explaining this diagnostic insufficiency.[2] For example, in a study by Melikian et al., MPI compared with FFR, underestimated in 36% and overestimated in 22% the number of ischaemic territories of patients with multivessel disease.[41] Moreover, a recent study that evaluated the change in strategy if the decision to intervene was based on FFR rather than angiography, found that the incidence of significant three-vessel disease dropped from 27% to 9%, two-vessel disease from 43% to 17% and single-vessel disease increased from 30% to 60% using FFR.[42] The results of that study highlights the limitations of MPI in the assessment of patients with multivessel disease and therefore strengths the importance of FFR measurement in order to achieve a correct revascularization.

Over the last 10 years an important body of evidence has been gathered on the safety of tailored treatment based on FFR measurements in patients with multiple stenosis in the coronary tree.[11,71-75] The more robust and influencing of these studies is the FAME randomised clinical trial, which investigated the clinical outcome of 1,005 patients with multivessel coronary stenosis undergoing PCI with drug-eluting stents.[27] Compared to patients treated on the basis of angiography only, patients with FFR-guided PCI (non-ischaemic threshold 0.80) reached significantly less often the composite endpoint of death, nonfatal myocardial infarction, and repeat revascularization at 1 year (13.2% vs. 18.3%; P=0.02). The mean number of angiographic stenosis per patient was similar in both groups (2.8 vs. 2.7), but 37% of stenoses in the FFR-guided group were considered non-ischaemic (FFR >0.8). Consequently, significantly fewer drug-eluting stents were used in the FFR-guided group (1.9 vs. 2.7, P<0.001), which lead to significantly lower costs (US $5332 vs. US$6007; P<0.001). It is important to state that costs with FFR guidance remained lower than without it at 1 year ($14,315 vs. $16,700), reflecting the benefit of fewer repeat revascularization procedures.[26] After two years, still a significant advantage for FFR-guided PCI was observed concerning the composite endpoint of death or myocardial infarction (34% reduction) and the stand-alone endpoint myocardial infarction (37% reduction).[43] These findings stresses the utility of physiologic assessment in refining decision making during multivessel-PCI, in

terms of minimising the amount of stents, health care costs and peri-interventional and long-term complications.

Left main coronary artery stenosis

Stenoses in the left main coronary artery (LMCA) disease and proximal left anterior descending artery (LAD) position are located in a critical anatomical location with pivotal prognostic importance.[44] Apart from high degree, critical LMCA stenosis, angiography is incapable of discriminating between therapy requiring and subclinical stenosis (Figure 4). Also, in this context, MPI studies frequently fail to identify significant hypoperfusion due to balanced ischaemia, especially, when the right coronary artery is also diseased.[45] Clinical complications resulting from untreated left main disease as well as complications during or after unnecessary revascularization therapy are feared due to coherent high morbidity. In this context, an exact identification of lesion morphology and haemodynamic significance is crucial for decision-making.

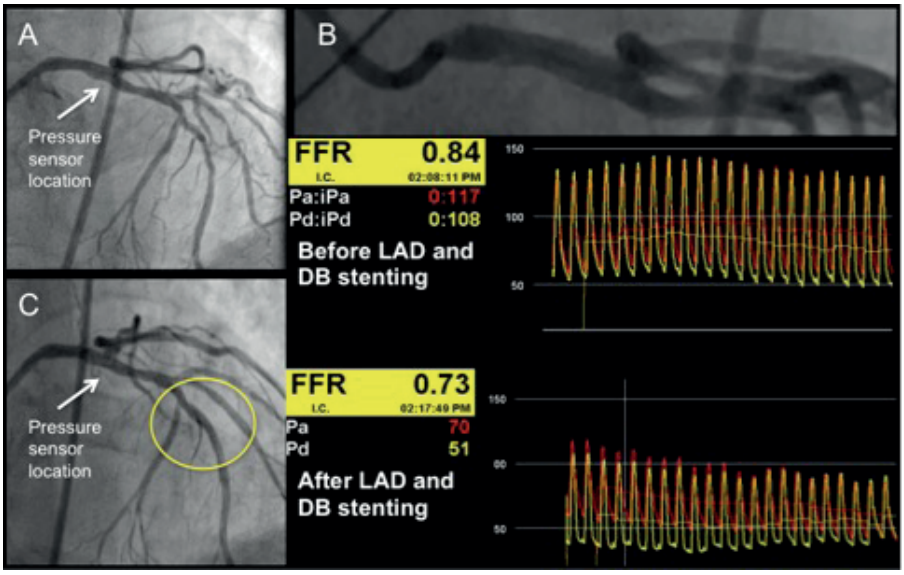

Figure 4 | A patient with an acute inferior myocardial infarction had multiple stenosis in the left coronary artery tree. After successful treatment of the infarct-related artery (RCA)(not shown), the question of whether the stenosis in the middle LAD, first DB (A) and ostial LMCA (B) required revascularization was raised. Assessment with FFR was performed in in the distal third of the LAD and distal to the LMCA (arrow), documenting FFR values of 0.70 and 0.84, respectively. Drug eluting stents were implanted in the LAD and first DB stenosis without complications (C, circle). In order to correctly assess the LMCA stenosis after the removal of those distal, a final FFR reassessment was performed in the same position as previously, distal to the LMCA (arrow). FFR interrogation documented then a new value of 0.73 (previously 0.84). Finally, a drug eluting stent was successfully implanted to treat the LMCA stenosis. This case exemplifies the importance of taking into account downstream stenoses when assessing a stenosis in the LMCA.

Several studies have shown that FFR can be used safely as a tool to decide whether coronary revascularization or a conservative attitude should be taken in ambiguous LMCA stenosis.[46-50] (Table 2). In a prospective single-center study, 51 patients with intermediate LMCA stenosis were treated using FFR.[46] A threshold of <0.75 was applied below which bypass surgery was appointed; medical treatment was recommended with values >0.80 and, in case of a "grey zone" value, the treatment was individualized. It was substantiated that the prognosis of patients deferred from revascularization and receiving medical management only, was excellent with comparable major adverse cardiovascular event rates during long-term follow-up. Another prospective study followed the same strategy in 142 consecutive patients with LMCA intermediate stenosis.[51] Remarkably, no significant differences in major cardiac events were noted during the 14-months follow-up period. Finally, Hamilos et al. reported the long term follow up in 213 patients with angiographically equivocal LMCA stenosis.[50] When FFR was ≥0.80, patients were treated medically (nonsurgical group; n=138) and when FFR was <0.80, coronary artery bypass grafting was performed (surgical group; n=75). The 5-year survival estimates were 89.8% in the nonsurgical group and 85.4% in the surgical group (P=0.48). Also, the 5-year event-free survival estimates were similar in the nonsurgical and surgical groups, (74.2% and 82.8%, respectively) (P=0.50). Importantly, the stenosis was haemodynamically significant by FFR in 23% of patients with a LMCA diameter stenosis <50%. Therefore, patients with an intermediate LMCA stenosis are optimal candidates for physiologic assessment and FFR can safely identify those patients suitable for revascularization or continued medical treatment.

Some technical considerations should be taken into account when performing FFR measurements in LMCA or ostial stenosis. Since guiding catheter potentially influences the blood flow in a narrowed left main, pressure equalisation should be performed before engaging the coronary ostium. The catheter pressure waveform should be careful monitored during hyperemia and the use of intravenous adenosine appears mandatory, since it allows complete de-engagement of the guiding catheter from the ostium. It also has to be kept in mind that in LMCA stenosis causing ostial narrowing in the LAD and / or circumflex artery (LCX), it is important to perform separate pressure measurements in both branches. In addition, it is important to remember that stenosis located in the main branches of the LAD or LCX arteries may influence FFR measurements at LMCA level if untreated, and may therefore cause false negatives (Figure 4). This phenomenon is further discussed in the following section on the assessment of sequential stenosis.

Sequential stenosis

The presence of serial stenosis constitutes an additional challenge in the interpretation of coronary angiographic findings. Also, MPI studies cannot determine which narrowing

in an artery with sequential stenosis is responsible for ischaemia. Although theoretically feasible,[52] FFR assessment of the individual severity of two stenosis in series is not performed in clinical practice since it requires documentation of coronary wedge pressure for the calculation. However and beside these limitations, the concept of FFR is still valid to assess the effect of all stenoses together.

The occurrence of flow disturbances when two stenosis are separated by a distance equivalent to six-fold the vessel diameter or shorter, may increase the hemodynamic impact of individual stenosis.[53] However, the problem of FFR assessment of serial stenosis rely in the fact that the distal one limits maximal flow, and thereby interferes with the basic assumptions of FFR theory when assessing the proximal one. These theoretically influencing variables can practically be objectified by hyperaemic pull-back curves using a pressure wire to obtain a "physiologic roadmap" of the coronary artery. Pressure roadmapping can be easily performed. First, the pressure wire is positioned in a distal location of the vessel. Second, steady-state hyperemia is pharmacologically induced and then, the pressure wire is slowly retrieved under fluoroscopic guidance. During all the manouver the flow profile is monitored and the stenosis with the most significant pressure gradient may be identified. When the combined effect causes an FFR >0.80, PCI may be deferred. When FFR is <0.80, the most frequent attitude is treatment of the most severe stenosis (as assessed with angiography or intracoronary imaging) followed by FFR and reassessment of the second stenosis (Figure 4).

Diffuse coronary narrowings

Diffuse atherosclerosis in the coronary artery tree is a major prognostic factor in CAD patients.[54] Once again, coronary angiography has important limitations in the evaluation of diffuse coronary stenosis. In the assessment of percent diameter stenosis, a reference "healthy" segment is required, but the true size of an artery is often not visible during angiography since this method allows only the assessment of the arterial lumen and the remodelling of the vessel cannot be evaluated.[55,56] Consequently, coronary angiography severely underestimates mild or diffuse coronary atherosclerosis and may overestimate >50% diameter stenosis.[54,57] Compared to normal vasculature, diffuse coronary atherosclerosis cause a graded, continuous pressure fall along arterial length due to variation of lumen diameter. This resistance to flow may contribute to myocardial ischaemia and in approximately 10% of patients may be the cause of reversible defects.[16] Pressure roadmapping is the only available method to demonstrate the epicardial resistance produced by diffuse epicardial disease. No studies on FFR guidance in the treatment of patients with diffuse narrowing have been reported.

Assessment of stenosis after acute coronary syndromes

The pathophysiology of the acute coronary syndromes (ACS) is a dynamic one. The use of FFR in this context has, therefore, some theoretical limitations derived from the presence of microvascular obstruction, vasoconstriction and changes in stenosis geometry caused by thrombus or plaque haemorrhage. However, several groups have investigated FFR in the recovery phase of myocardial infarction (>6 days) with relevant and interesting findings.[58-60] After a myocardial infarction, the viable myocardial tissue decreases and consequently, hyperaemic flow and hyperaemic pressure gradient will both decrease.[58] Thus, the exact value of FFR for a given coronary narrowing depends on the mass of viable myocardium. FFR has been shown to be capable of distinguishing patients with positive from those with negative SPECT imaging after a myocardial infarction as demonstrated by De Bruyne et al., who compared FFR and MPI studies in 57 patients with a prior myocardial infarction (mean 20 days).[58] The sensitivity and specificity of FFR of <0.75 to detect a defect on MPI were 82% and 87% respectively. Remarkably, when only truly positive and negative MPI studies were considered, the corresponding values were 87% and 100% ($p<0.001$) suggesting that FFR can accurately identify the haemodynamic severity of a coronary stenosis despite the damaged microvascular circulation in the infarcted territory. Also, Leesar et al. investigated the role of FFR-based treatment in patients with recent unstable angina or non-ST-segment elevation myocardial infarction and compared it with a management based on MPI studies.[59] They found that FFR markedly reduces the duration (11 ± 2 h vs. 49 ±5 h, $p<0.001$) and cost (U.S. $1,329 ± $44 vs. $2,133 ± $120, $p<0.05$) of hospitalisation, with no increase in procedure time, radiation exposure, or clinical event rates.

Another important aspect refers to the applicability of FFR to other stenosis located in the non-culprit coronary arteries of patients with ACS. A recent study by Ntalianis et al, has shown that during the acute phase of ACS, the severity of non-culprit coronary artery stenosis can reliably be assessed by FFR.[61] They studied whit FFR 112 non-culprit stenosis in 101 patients with ACS (75 with STEMI and 26 with non-ST-segment elevation myocardial infarction) and found that after 35±4 days, the FFR value of the non-culprit stenosis did not change. This opens the possibility of an early physiological assessment of patients with ACS and multivessel stenosis but, in spite of this, the available data on the use of FFR in this context is limited as to make any recommendations.

Assessment of PCI results

A key aspect in PCI is the correct assessment of the final result of the procedure. This is currently facilitated by the compatibility of pressure guidewires with PCI equipment. The relationship between FFR after stenting and outcome has gone through several stages. A large international registry reported the adverse cardiac events of 750 patients in which FFR was performed after angiographically apparently satisfactory bare-metal

stent implantation.[62] At 6 months, cardiac event rates varied from 4.9% in patients with final FFR >0.95, to 29.5% in those with final FFR <0.80. By multivariate analysis, FFR immediately after stenting was the most significant independent variable related to all types of cardiac events.[62] This study could not provide clues on whether final FFR was a result of suboptimal stent implantation or concomitant disease. Klauss et al, reported the predictive value of FFR in relation to cardiac events after stent implantation.[63] In this study, 119 consecutive patients had a stent implanted with the use of a pressure wire as a guidewire and were followed for at least six months. Final FFR was significantly higher in patients without than in patients with a cardiac event (0.95 vs 0.88 respectively, p = 0.001) and, remarkably, multivariate logistic regression analysis identified only final FFR and left ventricular ejection fraction as determinants of patient outcome at follow-up. A recent study performed in the DES era, documented as predictors of cardiac events after PCI variables like baseline FFR, stent diameter, stent length, and minimal lumen diameter. The fact that in that study post-interventional flow reserve was related to baseline FFR-measurements and to the diameter of the implanted stent seems to reflect the impact of concomitant diffuse narrowing of the treated vessel.[64]

The current paradigm, born of the new requirements of DES implantation, negates that FFR alone can provide all the information required to ensure that stent implantation has been optimal. In the BMS era, a comparison between optimal bare metal deployment as assessed with IVUS and FFR has been reported, showing that an FFR<0.96 was observed in all cases that did not fulfil IVUS criteria.[65] The authors stressed, however, that an FFR>0.96 did not ensure optimal stent deployment. In the DES era, the association of stent underexpansion with stent thrombosis is a matter of concern. Incomplete stent apposition or malapposition are common, occurring in 10-20% of DES and probably linked with stent thrombosis.[66] Roy et al. published the largest available registry on IVUS-guided PCI with DES. A total of 884 patients (1296 lesions) underwent IVUS-guided DES implantation and were compared with 884 propensity-score matched patients who underwent DES implantation with lone angiographic guidance.[67] Definite stent thrombosis was more common in the lone angiographic guidance group (0.5 vs 1.4%; p=0.046) and, regarding target vessel revascularization, a trend in favour of the IVUS-guided group was observed (5.1 vs 7.2%; p=0.07). Little information about the utility of FFR is available in this context. A recent study reported the 1 year follow up of 80 patients who underwent a FFR measurement after DES implantation.[68] Patients were divided into 2 groups: low and high FFR using >0.90 as a cut-off value. The rate of cardiac events was 12.5% in the low-FFR group versus 2.5% in the high-FFR group (p<0.01) stating the possible utility of FFR in this clinical situation.

Notwithstanding the complementarity of FFR and intracoronary imaging techniques, like IVUS and optical coherence tomography, there are subsets of cases where the accessibility of pressure guidewires makes possible an assessment of PCI result that would not be

feasible with the former. These situations highlights the importance of the combination of imaging and physiology assessment when deciding upon treating coronary stenosis.

Side branches and bifurcations assessment

The correct assessment by angiography of bifurcations lesions or ostial narrowing in side branches is particularly difficult due to vessel overlapping and image foreshortening. Although clinical evidence is limited, a growing number of interventionalists find that FFR can be particularly useful in this scenario. Koo et al evaluated 91 jailed side-branch stenosis with FFR and intervention was performed only when FFR was <0.75.[69] Mean percent stenosis of jailed side-branch lesions was 79 ± 11% but only 30.7% were functionally significant, demonstrating that these stenosis are clearly overestimated by angiography. In 26 of 28 stenosis that were functionally significant, balloon angioplasty was performed and an FFR >0.75 was achieved in 92% despite a residual stenosis of 69 ± 10%. At 6 month follow-up, there were no changes in side-branch FFR and functional restenosis (FFR <0.75) was observed in only 8%. Thus, FFR assesment of ostial and side branch stenosis is feasible and this strategy results in good functional outcomes (Figure 3).

FFR in secondary coronary revascularization

Patients undergoing secondary revascularisation procedures typically present a high-risk profile due to a more extensive atheromatosis, left ventricular dysfunction, renal failure, risk factor clustering, and older age.[70] These factors often are causative in the long-term failure of their first coronary revascularisation, either due to surgical graft occlusion, native disease progression or stent restenosis. In the following paragraphs we will discuss the role of FFR in the assessment of in-stent restenosis and in patients with previous coronary artery bypass grafting (CABG).

Assessment of in-stent restenosis

In-stent restenosis is a significant clinical problem and its treatment remains a technical challenge. This is true, even in the DES era, due to the increasing number of patients undergoing PCI and the use of stents in more complex clinical and anatomic scenarios.[71] In patients with typical anginal symptoms, proven ischaemia and severe ISR, there is little discussion that an intervention is required. However, it is not uncommon to find in clinical practice patients with recurrent angina and only mild or moderate neointimal proliferation in control angiography. This leaves unanswered the pivotal question whether this hyperplasia or ISR is responsible for the symptoms and/or ischaemia. Lopez-Palop et al., studied 65 ISR lesions of moderate severity with QCA and FFR.[72] FFR was used in the treatment decision and an FFR value <0.75 was considered significant. This study provides two key conclusions. First, that QCA is inappropriate for assessing

the physiological significance of moderate ISR, since only half of stenosis >50% were haemodynamically significant; and second, that decision making based on FFR in these patients is safe: after a 12 months follow-up, not a single death or myocardial infarction occurred in relation to any of the deferred stenosis and only one patient (2%) required revascularization. This strategy avoided unnecessary treatment and its associated risks in an already stented artery.

Assessment of stenosis in venous or arterial conduits after surgical coronary revascularization

Many operators feel puzzled by the use of FFR in the complex coronary circulation of CABG patients, which includes not only the native vessels but also the surgical grafts. As a matter of fact, FFR constitutes an excellent tool to provide clear answers in complex coronary circuits since, as discussed above, it provides an estimate of hemodynamic relevance that incorporates any source of blood to the myocardium. Thus, either stenoses located in the surgical grafts or in the native circulation can be studied in these patients. Besides, the angiographic assessment of grafts is also fraught with major limitations (Figure 5).

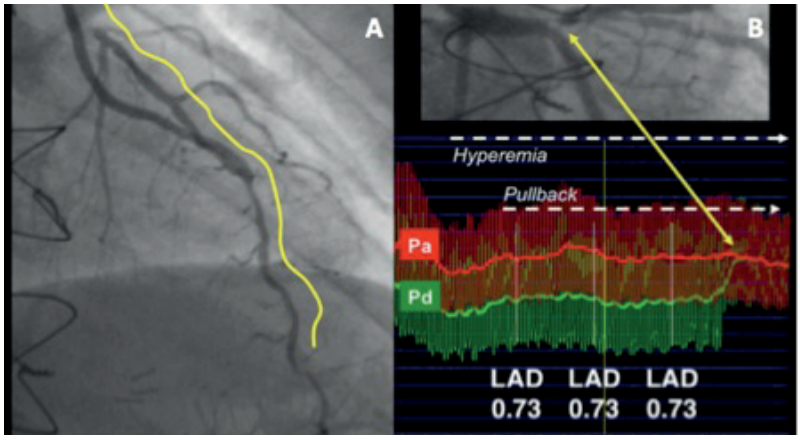

Figure 5 | This figure shows the pressure roadmap tracing obtained in the LAD of a patient with prior coronary artery revascularization to this vessel with a left internal mammary artery (LIMA) graft due to a ostial LAD stenosis. The patient was investigated due to the persistence of symptoms within the first 3 months of the operation, and presented an angiographiocally normal graft to the LAD (left panel). The pressure guidewire was crossed through the ostial stenoses. Once steady state of maximal hyperaemia was obtained with intravenous adenosine infusion, the pressure transducer, located in a distal location of the LAD, was slowly pulled back while the infusion of the adenosine continued (A). During the pullback, a constantly impaired epicardial conductance is observed (FFR 0.73). When the ostial stenosis was crossed by the transducer back to the left main, the pressure gradient disappears abruptly (Pd and Pa curves converge), ensuring that adequate calibration was maintained throught the procedure (B). This example shows that in spite of adequate arterial conduit patency, optimal functional revascularization was not achieved.

In addition to this, FFR might prove useful to investigate whether a vessel should receive a graft during CABG. In standard practice, CABG is subjectively recommended for all eligible arteries with >50% diameter narrowing in patients with multivessel disease. However, the hypothesis that grafting of less critical stenosis may increase the risk of early bypass graft failure has recently gained supporting evidence. Botman et al. studied 164 patients eligible for CABG.[73] FFR was measured in all lesions to be grafted and the surgeon was blinded to these results. Coronary angiography was performed 1 year after the surgery to assess the patency of a total of 450 CABGs. Remarkably, only 8.9% of the bypass grafts on functionally significant stenosis were occluded versus 21.4% of those grafted on non haemodynamically significant stenosis. Although the exact mechanisms of graft closure remains under study, it is postulated that coronary blood flow favors the relatively non-physiologically-obstructed native artery rather than the graft, promoting competitive flow and premature graft closure.[74] Thus, patients with coronary multivessel disease could benefit from FFR-derived prognostic information upon future bypass patency. Though profound clinical data is missing, also functional assessment of bypass stenosis and anastomoses might post a future routine indication for FFR-measurement.[75,76]

CONCLUSIONS

With the recent progress in pressure wire technology, FFR-measurement can be performed easily, rapidly, and safely in patients with coronary artery disease. Over the last decades, profound clinical and scientific evaluation of FFR demonstrated the feasibility and validity of the method, and supported the safety of clinical decision-making based on FFR findings in different clinical and anatomical subsets. From the point of view of healthcare economics, FFR is a cost-effective diagnostic tool than can contribute to reduce healthcare costs while improving quality. Altogether, current evidence clearly support the measurement of FFR in all catheterization laboratories in order to provide objective and complementary data to coronary angiography for the decision-making process.

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CHAPTER 3

Physiological assessment of coronary restenosis

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ABSTRACT

The limitation of coronary angiography to assess the functional significance of coronary restenosis has been well recognized. Therefore, the decision to proceed with repeat intervention is usually based on angiographic findings rather than using physiological measurements. With the potential of procedural complications, both short and long term, it is essential to have objective evidence of myocardial ischemia prior proceeding with repeat intervention. In this chapter the potential of physiological assessment of coronary artery restenosis is discussed.

INTRODUCTION

Over the last decades an important body of evidence has been gathered on the relevance of physiological assessment of ischemic heart disease.[1,2] Randomized and non-randomized trials have consistently shown that most of the benefit of mechanical strategies targeting myocardial flow restoration - i.e., surgical or percutaneous coronary revascularisation-- is confined to the treatment of those coronary stenosis associated with objective signs of significant myocardial ischemia in downstream area.[3,4] In this regard, intracoronary physiology techniques have become powerful diagnostic and adjuvant tools to establish the hemodynamic relevance of epicardial stenoses, and have been pivotal in promoting ischemia-driven coronary revascularization.[5] These notions are of utmost importance when investigating coronary restenosis (ISR), as the risk and benefit ratio of further interventions in this particular scenario is already influenced by the presence of the latter entity. In the following paragraphs, we firstly describe the hemodynamic consequences of coronary stenosis; then briefly discuss the concept of fractional flow reserve (FFR), and finally we outline the contributions of intracoronary physiology to the ISR field.

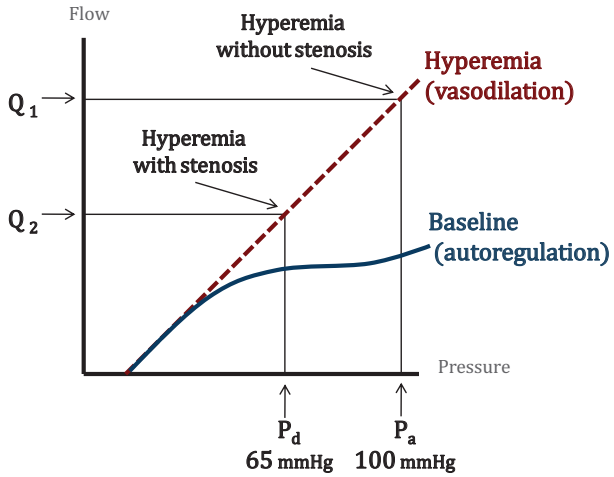
PHYSIOLOGICAL CONSEQUENCES OF AN EPICARDIAL STENOSIS

The anatomical impediment to flow imposed by an epicardial stenosis (including ISR) is determined by the stenosis geometry and the magnitude of trans-stenotic flow; which is governed by the amount of functional myocardium supplied by the epicardial vessel.[5] Physiologically, epicardial stenosis generate pressure drops; that are the sum of pressure losses due to viscous friction (when blood passes through the stenosis) and to flow separation (due to transformation of normal flow first to high velocity flow in the stenosis and then to turbulent non-laminar flow that eddies at the exit throat).[6,7] It has been established that this complex interaction can be expressed in the form of a quadratic equation as follows: $\Delta P = fQ + sQ2$; where ΔP is the trans-stenotic pressure drop, Qis flow, and the constants f and s (which are functions of stenoses geometry) represent for pressure losses due to the viscous friction and to passive expansion (flow separation), respectively.[8] Ultimately, if the total trans-stenotic pressure drop is significant, distal perfusion pressure will be limited, and therefore flow to distal myocardium.

FRACTIONAL FLOW RESERVE AS THE MOST WIDELY USED INDEX TO ASSESS THE ISCHEMIC POTENTIAL OF AN EPICARDIAL STENOSIS

Several indices for the assessment of stenoses severity based on intracoronary measurements of pressure, flow, or both, have been proposed.[9,12] Many of them have clinically important limitations. In this regard, FFR has become accepted as the technique of choice because of its accuracy and relatively easiness to perform and interpret.[1,9] In order to understand the theoretical framework of FFR, it is important to recognize some key aspects of the coronary pressure-flow relationship (*figure 1*). First of all, at rest, the relationship between pressure and flow in the coronary arteries is non-lineal and its characteristics vary with the metabolic status of the heart. Second, during coronary hyperaemia (which occurs as a response to intense metabolic myocardial demand or to the administration of vasodilator agents) resistance is minimised and the relation between coronary pressure and flow is assumed to be linear[9] (full detail is beyond the scope of this chapter and the interested reader is referred to specialized literature[5]). This linear relation is the cornerstone for obtaining information on coronary flow from coronary pressure measurements. FFR calculation requires two pressures: the aortic pressure (P_a) and the pressure distal to an interrogated stenosis (P_d). Since the pressure flow relationship is assumed linear at hyperaemia, the ratio of pressures P_d/P_a is proportional to the ratio of flows. Consequently, pressure can be used as a surrogate of flow. FFR is simply derived from this pressures ratio (P_d/P_a) and is defined as the ratio of maximal flow in a stenotic artery to the flow in the same artery in the theoretic absence of the stenosis. For example, an FFR of 0.65 means that the myocardium in the area of distribution of the interrogated vessel receives only 65% of the expected flow in the absence of that stenosis; or, conversely, that the stenosis causes a 35% impairment in blood supply. Since coronary pressure is transmitted without significant losses throughout the bifurcations of the coronary tree, the highest possible value of FFR is 1.0, being the latter the normal one in every patient and every vessel. FFR has a narrow ischemic threshold of 0.75-0.80, below which the potential for significant inducible ischemia is very high, and above which it is very unlikely.[13] Moreover, FFR informs about the expected gain in myocardial flow should the epicardial stenosis be relieved. This theoretical background is strongly supported by many observational studies as well as by three clinical decision-making, landmark randomised trials.[14] First, the DEFER trial (Deferral of Percutaneous Coronary Intervention) demonstrated that the annual rate of myocardial infarction and death due to epicardial stenoses with associated FFR values in the non-ischemic range (≥0.75) was very low (<1%) and not decreased by stenting.[15] Second, the FAME trial (Fractional Flow Reserve versus Angiography for Guiding PCI in Patients with Multivessel Coronary Artery Disease) showed that a tailored revascularization approach based in FFR (using 0.80 as revascularization threshold) resulted in

better clinical outcomes and reduced costs, as compared to angiographic guidance.[3] Finally, the FAME II trial (Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease) established that in patients with stable coronary artery disease and functionally significant stenoses (using also the 0.80 threshold), FFR-guided PCI plus optimal medical treatment decreased the need for urgent revascularization, as compared with lone-optimal medical treatment.[4] Altogether, this theoretical framework and the clinical evidence—including outcomes— clearly supports FFR as the index of choice for the invasive assessment of epicardial disease.[1] In the following section we now discuss available information on the physiological assessment of ISR.



$$\frac{Q_2}{Q_1} \cong \frac{P_d}{P_a} = \frac{65}{100} = FFR = 0.65$$

Figure 1 | Conceptual plot of the relationship between intracoronary pressure and flow at baseline and hyperemia in the presence and absence of a significant stenosis. Please note how at baseline (blue line) the relationship between pressure and flow is non-lineal and its characteristics vary with the metabolic status of the heart. Then, at coronary hyperemia (red line) resistance is minimised and the relation between coronary pressure and flow becomes linear. In the absence of epicardial stenosis (red line at Q1), the driving pressure (Pa) determines a normal (100%) maximal myocardial blood flow (Q1). In the presence of a stenosis responsible for a hyperaemic pressure gradient of 35 mm Hg (red line at Q2), the driving pressure will no longer be 100 mm Hg but instead will be 65 mm Hg (Pd). FFR is derived from this pressures ratio (Pd/Pa) and is defined as the ratio of maximal flow in a stenotic artery to the flow in the same artery in the theoretic absence of the stenosis. In this example, an FFR of 0.65impliesthat the stenosis causes a 35% impairment in blood supply

Table 1 | Safey of percutaneous coronary intervention deferral based on fractional flow reserve for in-stent coronary restenosis

	Year of publication	n	Stent	FFR cut-off	deferred-ISR	Follow up	Events	Event rate
Lopez-Palop et al	2004	65	NA	<0.75	41	12 months	1 TLR	2%
Kruger et al	2005	42	BMS	<0.75	22	6 months	-	-
Kobori et al	2005	155	BMS	<0.75	113	25 months	1 TVR, 3 (+) SPECTS	3.5%
Nam et al	2011	50	DES	<0.80	20	12 months	2 TVR	10%

FFR: fractional flow reserve; BMS: bare metal stents; DES: drug eluting stents; TLR: target lesion revascularisation; TVR: target vessel revascularisation; SPECT: single photon emission computed tomography.

FUNCTIONAL TREATMENT OF CORONARY RESTENOSIS

Deciding whether to further treat or not a particular ISR is a significant clinical problem, and its management remains a technical challenge.[16] This holds true, even in the drug eluting stent era, due to increasing numbers of patients undergoing PCI and the use of stents in more complex clinical and anatomic scenarios, resulting in an increase in absolute number of cases at a time with reduced relative rates of restenosis. Whilst in patients with typical anginal symptoms, proven ischemia and severe ISR, there is little discussion that an intervention is of probable benefit; it is not uncommon to find patients with recurrent angina and variable degrees of neointimal proliferation in control angiography. This leaves unanswered the pivotal question whether this hyperplasia or ISR is responsible for the symptoms and/or ischemia, and if the risk and benefit ratio of further interventions is satisfactory; since a repeat intervention in this context has a higher risk of triggering a restenotic response than in de novo coronary stenoses. Moreover, the latter decision is additionally complicated by the heterogeneous amount of functional myocardial mass being jeopardized. As the ratio of percutaneous coronary interventions (PCI) due to acute coronary syndromes over stable symptoms keeps increasing, the proportion of contemporary ISR arising from vessels supplying infarcted territories can be expected to be growing.[17] In this scenario, the functional myocardial mass supplied by the given ISR is reduced; and so will be its ischemic potential—because less flow will suffice the metabolic demands of the reduced mass.[18] In clinical practice, this implies that even severe ISR might not lead to ischemia if proven distal functional mass is significantly reduced (figure 2). In addition to these physiological considerations, several angiographic aspects may cause difficultly in the visual assessment of stenosis severity in stented and non-stented segments. Marked radiopacity of some stent designs may interfere with QCA systems and with visual assessment; and the functional relevance of diffuse neointimal proliferation, particularly in long

stents, can be also more difficult to assess than that of focal stenoses. Altogether, this highlights why visual interpretation of coronary angiograms is insufficient to depict the ischemic potential of epicardial stenoses and therefore making ISR one of the most challenging scenarios.

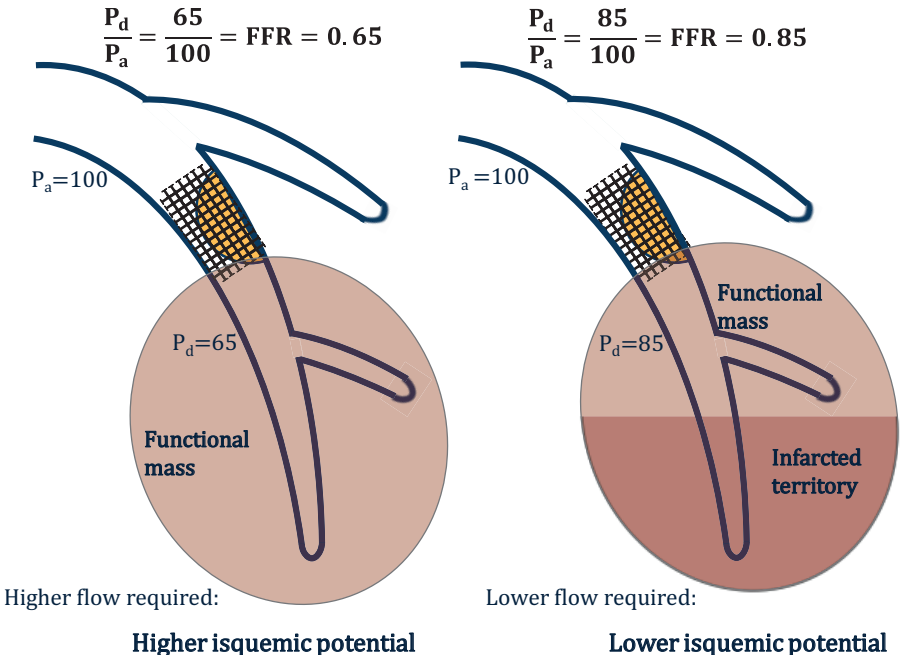


Figure 2 | This figure illustrates the influence of the functional myocardial mass on the ischemic potential of an epicardial stenosis, including ISR. In panel A,hyperaemic flow to a large normal amount of functional mass is comprised by a severe ISR.Since a large amount flow is required to cover its metabolic demands, the ischemic potential is high (FFR=0.65). Assuming that the geometry of the ISR remains identical, contrariwise, in panel B, the amount of functional myocardial mass was reduced by a chronic infarction. In this scenario, less flow will suffice the metabolic demands of the reduced functional massand thus hyperaemic gradient will decrease as well (FFR=0.85). This figure also illustrates how the mere morphology of an ISR does not necessarily reflect its functional importance.

Several non-randomised trials have investigated the clinical value of FFR to guide ISR treatment. In the bare metal stent-era, Lopez-Palop et al., studied 65 ISR of moderate severity (40 to 70% diameter stenosis (DS) by visual assessment) using FFR for further intervention guidance, with<0.75 as the threshold for treatment.[19] This study provided two key conclusions. First, that quantitative coronary angiography (QCA) is inappropriate for assessing the physiological significance of moderate ISR, since only half of stenosis with a lumen reduction>50% were hemodynamically significant; and second, that deferral based on FFR is probably safe, as no single death or myocardial infarction related to deferred-ISR developed during the one year follow-up; and only

one (2%) required further target lesion revascularization (TLR). In the same line and era, Kobori et al., investigated 155 ISR from which 113 (72.9%) were deferred based on FFR ≥ 0.75. At 25 ± 11 months, only 4 patients (3.5%) developed cardiac events: TVR in 1 and positive SPECTs in 3 patients.[20] Moreover, discordance between anatomical severity (defined as DS ≥ 50%) and functional significance (defined as FFR<0.75) was also very high (45% of the cases) underlining also the limitations of angiography to predict the functional significance of ISR. Consistent findings were additionally provided by Kruger et al., that investigated 42 patients with bare metal-ISR and compared its angiographical severity (DS) with that of 57 intermediate de novo epicardial stenosis.[21] While DS was comparable in both groups (de novo, 52 ± 11%; ISR, 52 ± 9%; p=NS), FFR was lower in the ISR group (0.77 ± 0.15 vs. 0.82 ± 0.12, p < 0.05) and more often < 0.75 (48% vs. 26%, p < 0.05). Of note, none of the 22 deferred-ISR suffered an adverse event in the 6-month period of follow-up. Finally, in the drug eluting stent era, Nam et al investigated 50 ISR lesions from 49 patients.[22] Based on FFR<0.80, 30 (60%) received additional treatment [17 (56.6%) balloon angioplasty and 13 (43.3%) repeated DES-PCI] and the remainder 20 (40%) were deferred (FFR≥0.80). This work adds to the growing evidence supporting the poor association between functional ischemia as defined by FFR and angiographic-ISR as defined by DS (%) [since a only a moderate correlation between the latter was observed (r=-0.61, p<0.01)] and further suggests that an FFR-guided strategy in patients with DES-ISR is favourable, as at 12 months of follow-up, only 2 cases (10%) of TVR developed in the deferred arm; while 7 events [one (2.3%) acute myocardial infarction and 6 (20.0%)TVR] were observed in the FFR<0.80 arm.

It is important to outline that none of the available studies have observed an acute myocardial infarction or death related to an FFR-deferred ISR. However, all applicable information on FFR-guidance in the ISR scenario comes from small, observational, non-randomized studies. Indeed, DEFER[15] excluded this entity, and although FAME I[3] and FAME II[4] allowed ISR, no accessible information on this respect has been published, thus emphasizing the need for further studies of stronger designs before definitive recommendations are made.

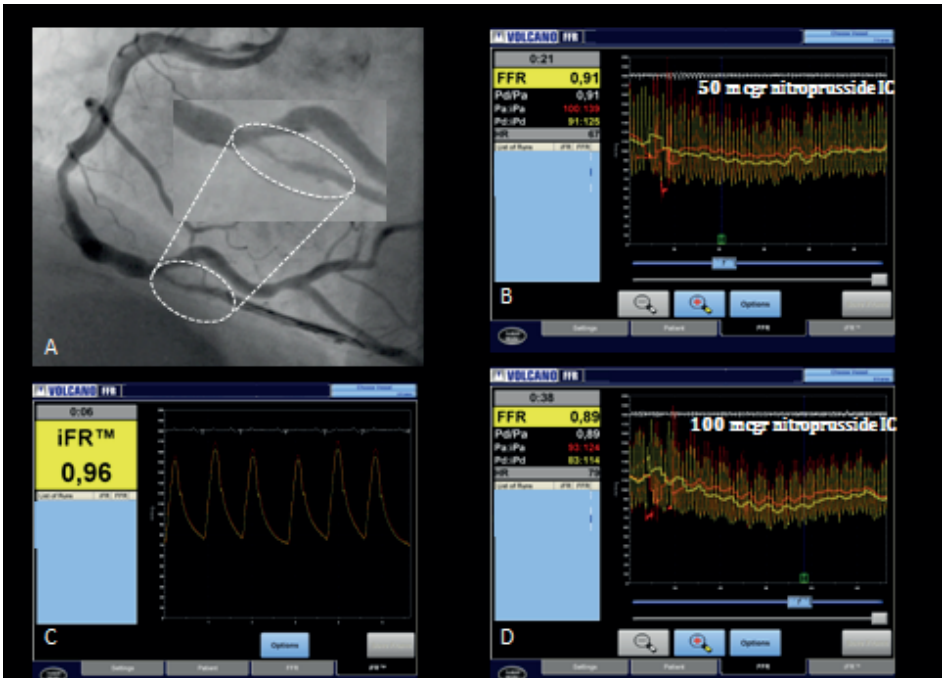


Figure 3 | A 75 year-old male patient with history of severe chronic obstructive pulmonary disease was referred for cardiac catheterization because of exertional dyspnea and atypical chest pain. Three years before, a bare metal stent was implanted in the proximal posterior descending artery. New angiograms revealed mild luminal irregularities in the left anterior descending artery and circumflex (not shown) as well as a severe, diffuse-ISR (Panel A). Functional interrogation was done first, with the instantaneous wave free ratio (iFR) (panel C) followed by FFR (panels B and D). Hyperemia was induced with sequential doses of intracoronary nitroprusside. Both iFR and FFR revealed that the restenosis was not functionally significant (values above the 0.90 and 0.80 thresholds for treatment, respectively). No further interventions were performed.

CAN PHYSIOLOGY HELP IDENTIFY PATIENTS PRONE TO DEVELOP POST-INTERVENTION ADVERSE EVENTS?

The accurate identification of patients that will develop stent failure, ISR and adverse events after successful PCI is a continuing challenge. Consequent efforts have been made, and several studies have explored the prognostic value of adjuvant intracoronary techniques to predict post-PCI events. FFR has shown to be also useful in this regard. This benefit comes from basic physiology, as normal epicardial vessels provide minimum resistance to hyperaemic flow.[9] Hence, optimal coronary stenting -that has been shown to reduce adverse events[23]- should result in the disappearance of any hyperaemic pressure drop within the respective coronary segment. This hypothesis was explored in the BMS era by Pijls et al., in a large multicenter registry (750 patients),

by relating post-stenting FFR to major adverse events.[24] At 6 months of follow-up,76 patients (10.2%) suffered at least 1 adverse event: five deaths, 19 myocardial infarctions, and 52 TVR. By multivariate analysis, post-stenting FFR was the most significant independent variable related to all types of events; and the event rate significantly increased as post-stent FFR decreased throughout the study population. As a matter of fact, the event rate rose steeply from 4.9 to 6.2 to 20.3 and finally to 29.5% as post-stent FFR decreased from >0.95, 0.90, <0.90 to <0.80, respectively. Moreover and specifically, the potential value of post-stent FFR to predict the development of ISR in both BMS and DES eras has also been explored in observational studies. Jensen et al. observed that a suboptimal post-stent FFR value was an independent predictor of binary angiographic ISR at 9 months (44.0% versus 8.1%; p<0.001) in a cohort of patients treated with BMS.[25] Similar findings in patients treated with DES were found by Nam et al., as the rate of ISR at one year was significantly higher (17.5 vs. 2.5%) in vessels with post-stent FFR ≤0.90 when compared to those that achieved a value above.[26] Whilst these studies are of limited size (< 100 patients), further evidence will soon be provided by the ongoing- PERSPECTIVE registry (Influence of FFR on the Clinical Outcome After Percutaneous Coronary Intervention) that aims to evaluate the influence of physiologic parameters on the clinical outcome after DES implantation.[27]

It is important to underscore the non-randomized design of these studies as well as the fact that whether additional intervention in the case of suboptimal FFR resulted in a decreased adverse event rate was not addressed. Put differently, whether the increase in event rates observed in cases with suboptimal post-stent FFR values was related to suboptimal PCI or to residual atherosclerotic burden within the vessel is unknown; as the post-stent FFR is also a local measurement of residual atherosclerosis; recognizing the latter entity as a systemic disease. Now, one study has evaluated prospectively the feasibility and clinical impact of targeting a post-stent FFR > 0.95, via incremental in-stent inflation pressures.[28] The FROST III investigators included 100 consecutive patients that underwent FFR measurements at baseline, after balloon predilation, and after stenting with 4 atmospheres (atm) inflation pressure increments from 8 to 20 atm. Inflations were stopped when FFR increased above 0.95, and angiographic stenosis was less than 20%. FFR > 0.95 was achieved in 81% of cases; and this FFR target was reached at 8 atm in 47% of patients, 12 atm in 16 %, 16 atm in 15%, and 20 atm in 3%. Very importantly, final FFR was significantly correlated with anginal status at 6 months. While a logical conclusion from this study is that better physiological results are obtained when stents are deployed at high pressures, caution is advised when using FFR as an endpoint for treatment. This comes from the fact that focal stenosis commonly coexist with diffuse disease, and that in many cases, longer segments of the vessel (including mild segment of stenosis) might require stenting in order to optimize post-stent FFR measurements, increasing therefore the risks associated with this de-

vices. Further studies of stronger design should rigorously address the risk and benefit ratio of including post-stent FFR as an endpoint for percutaneous treatment.

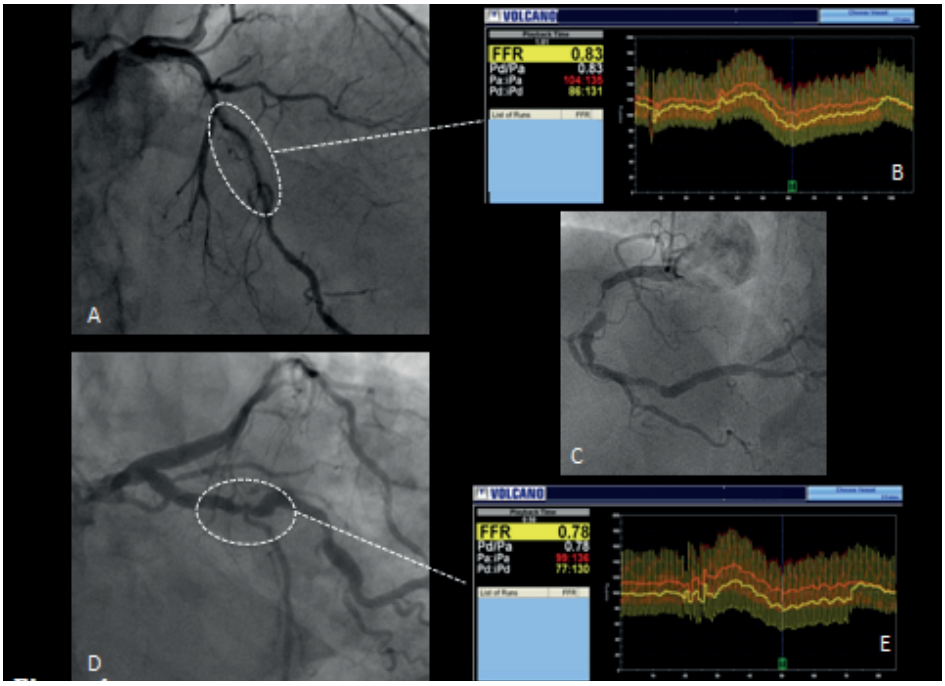


Figure 4 | A 66 year-old male patient was referred for cardiac catheterization prior to kidney transplantation. He suffered an acute anterior myocardial infarction 10 years before, treated with 2 BMS in the left anterior descending (LAD) artery at primary PCI. One year later, 1 new BMS was implanted in the LAD because of late stent thrombosis. At a staged procedure, one sirolimus eluting DES was implanted in the right coronary artery. Current angiograms revealed a critical DES-ISR in the RCA with TIMI grade 2 flow (panel C), a severe de novo stenosis in the circumflex (panel D) and a diffuse, severe BMS-ISR in the LAD. FFR was performed in the LAD (panel B) and circumflex (panel E), demonstrating that only the latter was hemodynamically significant.

CONCLUSIONS

The percutaneous treatment of ischemic heart disease is evolving, and decision-making based on physiology-guided strategies have shown to result in better patient outcomes than angiography-guided strategies. The treatment of patients with ISR remains a challenge and represents a major clinical problem. Available evidence on the advantages of physiology guided treatment of ISR is still limited. Further studies are still needed to accurately establish the potential benefit of physiology-guidance of ISR treatment.

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CHAPTER 4

Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance

Results of the ADenosine Vasodilator Independent Stenosis Evaluation II (ADVISE II Study), an international multicenter study

Escaned J, Echavarría-Pinto M, Garcia-Garcia HM, van de Hoef TP, de Vries T, Kaul P, Raveendran G, Altman J, Kurz HI, Brechtken J, Tulli M, Von Birgelen C, Schneider JE, Khashaba AA, Jeremias A, Baucum J, Moreno R, Meuwissen M, Mishkel G, van Geuns RJ, Levite H, Lopez-Palop R, Mayhew M, Serruys PW, Samady H, Piek JJ, Lerman A

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ABSTRACT

Objectives

To assess the diagnostic accuracy of the instantaneous wave-free ratio (iFR) to characterize, outside a pre-specified range of values, stenosis severity as defined by fractional flow reserve (FFR) ≤0.80, in a prospective, independent, controlled, core laboratory-based environment.

Background

Studies with methodological heterogeneity have reported some discrepancies in the classification agreement between iFR and FFR. The ADVISE II study was designed to overcome limitations of previous iFR versus FFR comparisons.

Methods

A total of 919 intermediate coronary stenoses were investigated during baseline and hyperemia. From these, 690-pressure recordings (598 patients) met core laboratory physiology criteria and included in this report.

Results

The pre-specified iFR 0.89 cut-off was the optimal for the study, and classified correctly 82.5% of the stenoses, with a sensitivity of 73.0% and specificity of 87.8% [c-statistic: 0.90 (95% CI: 0.88 to 0.92, p<0.001). The proportion of stenoses properly classified by iFR outside the pre-specified treatment (≤0.85) and deferral (≥0.94) values was 91.6% (95% CI: 88.8 to 93.9%). When combined with FFR use within these cut-offs, the percentage of stenoses properly classified by such pre-specified hybrid iFR-FFR approach was 94.2% (95% CI: 92.2 to 95.8%). The hybrid iFR-FFR approach obviated vasodilators from 65.1% (95% CI: 61.1 to 68.9%) patients and 69.1% (95% CI: 65.5 to 72.6%) stenoses.

Conclusions

The ADVISE II study supports, based on rigurous methodology, the diagnostic value of iFR in establishing the functional significance of coronary stenoses, and highlights its complementariness with FFR when used in a hybrid iFR-FFR approach.

INTRODUCTION

The instantaneous wave-free ratio (iFR) is a recently introduced pressure-derived, hyperemia-free index for the functional assessment of coronary stenosis.[1] Previous studies have investigated the classification agreement between iFR and fractional flow reserve (FFR), used as a reference standard, which in general has been good.[1-8] However, some discrepancies in their agreement have been observed, potentially related to methodological heterogeneity. While the possible benefits and limitations of non-hyperemic indices to guide coronary revascularisation still need to be determined,[9] a prospective study with rigorous methodology was deemed required to accurately establish the diagnostic value of the iFR.

Since the introduction of iFR, a hybrid iFR-FFR diagnostic strategy has been proposed, where upper and lower iFR cut-offs are used to restrict decisions based on iFR to those regions in which its agreement with FFR is very high, and FFR use is limited to the intermediate iFR range of values called "adenosine zone".[3] Hence, the ADVISE II study was designed to investigate, in a prospective, controlled, core-laboratory based environment, the diagnostic accuracy of the iFR to characterize coronary stenosis severity as determined by FFR, exploring also the usefulness and convenience of the hybrid iFR-FFR approach.

METHODS

The ADVISE II study was a prospective, international, multi-center (n=45) study, aimed to assess the diagnostic value of iFR to characterize, without concomitant administration of hyperemic agents, coronary stenosis severity as determined by the FFR (ClinicalTrials.gov. Identifier: NCT01740895). The Ethics Committees and Institutional Review Boards of each participating center approved the study, and all patients gave written informed consent.

Patient selection and pressure traces acquisition

Patients eligible for enrolment were aged 18 to 85 years, suitable for coronary angiography and percutaneous coronary intervention (PCI), and had coronary stenosis (>40% diameter stenosis by visual assessment) in one or more native major epicardial vessel or its branches. Stable angina or acute coronary syndromes (only non-culprit vessels and >48 hours from symptoms onset in case of myocardial infarction) were allowed. Complete inclusion and exclusion criteria are provided in the Appendix. Data acquisition included electrocardiographic (ECG) signal recording (required by the iFR calculation algorithm) and setting the reading of mean aortic pressure (Pa) at three

beats. After intracoronary nitrates (300 mcg) and acquisition of coronary angiograms, Pa and intracoronary distal pressure (Pd) were recorded as follows (Figure 1). Firstly, the pressure wire was zeroed and equalized, and its correct equalization (Pd/Pa ratio of 1.0±0.02) confirmed during a 10 second acquisition. Afterwards, the pressure sensor was positioned distal to the index stenosis and the guiding catheter flushed with saline. Baseline pressures were recorded for at least 20 seconds before inducing hyperemia. Adenosine administration through a large vein, at a rate of 140 µg/Kg/min., for a minimum of two minutes, and pressure wire pullback maneuver to check for pressure drift were all mandatory. In the same pressure recording, three bookmarks for core laboratory analyses were placed: when 1) adenosine infusion started, 2) pullback maneuver started and 3) when the pressure sensor reached the tip of the guiding catheter. If a Pd/Pa ratio <0.98 or >1.02 at the catheter tip was documented, the protocol mandated repeat assessment. The s5/s5i console and PrimeWire Prestige PLUS coronary pressure wire (Volcano Corporation San Diego, CA) were used in all cases.

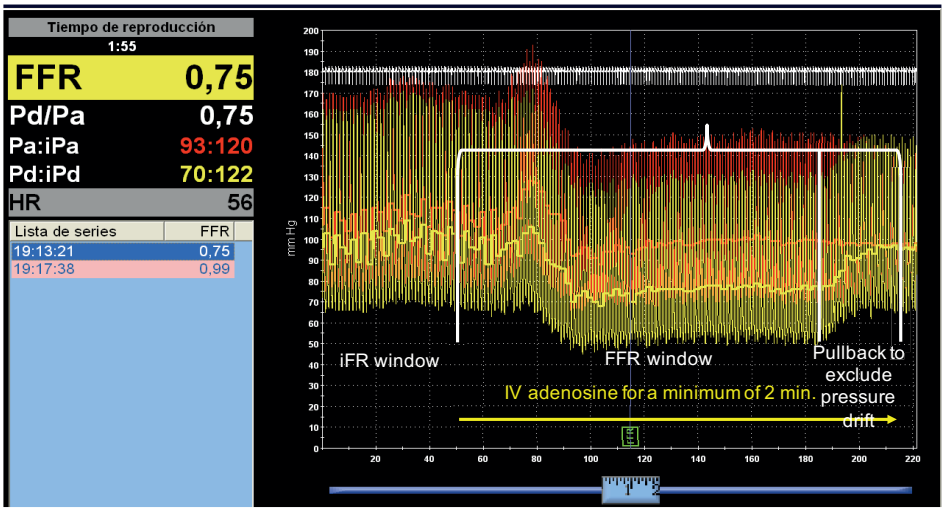

Figure 1 | Example of the methodology for pressure traces acquisition in ADVISE II. Firstly, correct normalization was recorded (in this case, FFR=0.99). Then, a single ECG and pressure recording included baseline pressures for a minimum of 20 seconds, adenosine infusion for a minimum of 2 minutes and pressure wire pullback maneuver. Three bookmarks for core laboratory analyses were placed: when 1) adenosine infusion started, 2) pullback maneuver started and 3) when the pressure sensor reached the tip of the guiding catheter. The operator was blinded to iFR, which was calculated off-line at the core lab.

iFR and FFR calculation

All pressure recordings were analyzed by an independent Core Laboratory (Cardialysis, Rotterdam, The Netherlands) using iFR calculation software (HARVEST, Volcano Corpo-

ration) fully consistent with online commercial systems. This computational algorithm performs automated analyses based on a synchronized ECG signal and determines the appropriate diastolic intervals for pressure measurements. By automatical identification of fiducial time points in the cardiac cycle, the diastolic window for pressure measurement is calculated beginning 25% into diastole and ending 5 ms before end-diastole. iFR is then calculated as the ratio of Pd to Pa during this pre-specified period of time, within mid to late diastole under non-hyperemic conditions —the wave free period— when it has been shown that intra-beat microvascular resistance is stable and minimized.[1,6,10]

FFR was experimentally and clinically validated under conditions of maximum and stable hyperemia,[11] and is automatically calculated by current computational softwares as the minimum Pd/Pa ratio found in the pressure recording. However, during intravenous adenosine infusion, the minimum hyperemic Pd/Pa ratio might develop before stabilization of hyperemia, a situation that flaws the theoretical framework of FFR, as neither driving nor distal pressures are stable.[12] Hence, conforming to its original validation,[11,13] core laboratory analyses included a thorough review of pressure recordings to corroborate that FFR was calculated 1) after initiation of adenosine infusion, 2) within stable hyperemia, and 3) before the pullback maneuver. Stable hyperemia was defined as the plateau in mean Pa after stabilization of changing hemodynamics, following the initiation of adenosine infusion and before pullback maneuver.[12] If a plateau was not clearly observed, stable hyperemia was then defined as the period of pressure recording in which no further systematic fall in Pa was observed, following the initiation of adenosine infusion but before the initiation of the pullback.[12] Within stable hyperemia, the minimum Pd/Pa ratio was then labeled as FFR.

Core laboratory analyses included an exhaustive evaluation of pressure waveforms to confirm that none of the following exclusion criteria were present: inappropriate normalization of the pressure wire (Pd/Pa ratio <0.98 or >1.02), ECG artifacts or significant arrhythmias in the first 20 seconds of the recording ("iFR calculation window"), loss of Pa or Pd signals at any point during the recording, automatic calculation pitfalls (identification of FFR during ectopic beats, Pa or Pd noise, wire whipping artifacts, etc.), dampening of Pa or Pd waveforms, pressure drift higher than <0.98 or >1.02, and absence of ECG or pressure-pullback recording.

Hybrid iFR-FFR approach

This hybrid iFR-FFR diagnostic strategy was designed to increase adoption of physiology-guided PCI, by decreasing the need for vasodilators whilst maintaining a very high classification agreement with a lone-FFR strategy.[3] Two independent iFR values with very high negative predictive and positive predictive values to exclude (defer-iFR value) and identify (treatment-iFR value) FFR-significant stenoses were investigated,

whilst it was assumed that only those stenoses with iFR values in-between would require vasodilator drugs for standard FFR classification. On the grounds of retrospectively acquired data, it was found that a treatment iFR value of ≤0.85, a deferral iFR value of ≥0.94, and the use of FFR within the 0.86 and 0.93 iFR values ("adenosine zone") resulted in an overall 95% classification agreement with an lone-FFR strategy, while obviated the need for vasodilators in 57% of patients.

Endpoints

The primary endpoint of the study was the percentage of stenoses properly classified by the iFR values ≤0.85 and ≥0.94, as proposed by the hybrid iFR-FFR approach. Hemodynamic severity was defined as FFR≤0.80. Pre-specified secondary endpoints were 1) the diagnostic performance of the iFR 0.89 cut-off; 2) the optimal iFR cut-off against FFR≤0.80 derived from receiver operating characteristic curve (ROC) analyses; 3) the minimum iFR exclusion ranges around the iFR 0.89 cut-off in which the iFR and FFR agreement was equal to or greater than 80%, 90% and 95%; 4) the correlation coefficient between iFR and FFR; and, 5) the proportion of stenosis and patients free from vasodilator drugs expected from the above-mentioned pre-specified hybrid iFR-FFR approach.

Role of the sponsor

The sponsor of the study (Volcano Corporation) had no role in the study design, data acquisition, data analysis or writing of the manuscript. All analyses were independently performed by the core laboratory (Cardialysis). The corresponding author had full access to all data and had the final responsibility for the decision to submit for publication.

Statistical analyses

For quantitative variables, data are expressed as mean ± SD. Non-normal data are reported as the median with first and third quartiles (Q1, Q3). For categorical data, counts and percentages are provided. The 95% confidence intervals of the means of continuous variables and percentages of categorical variables were calculated with t-tests and Clopper-Pearson (Exact) approaches, respectively. ROC curve analyses were performed to determine the optimal iFR cut-off against FFR ≤0.80, defined as the value that maximized correct classification. Pearson´s correlation coefficient (r) between iFR and FFR was computed, and Fisher´s Z transformation was used to provide its 95% confidence intervals. Linear regression was used to further characterize the iFR and FFR relationship, and being a multicenter study, between–center variability was assessed by adding center as random effect. However, for none of the centers a significant effect parameter was found, and the total effect of adding such center effect to the analysis was non significant (p=0.165). We therefore concluded that the center effect could be

ignored. The SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and STATA 12.1 (StataCorp, College Station, Texas) statistical softwares packages were used. Applicable tests were two-tailed and differences were considered significant at $P<0.05$.

RESULTS

Study population

Between January 9th and June 28th 2013, 919 stenoses from 797 patients were investigated and included in the study. Of these stenoses, 229 (24.9%) met at least 1 of the pre-defined core laboratory exclusion criteria, leaving 690 stenoses from 598 patients for final analyses. A STARD-type (14) flow chart depicting this process is provided in Figure 2. Clinical and angiographic characteristics of the study population are shown in Table 1 and 2. Overall, mean age was 63.6 ± 10.8 years and 68.9% were male. The most common clinical presentation was chronic stable angina (53.5%), followed by unstable angina (25.3%), and the left anterior descending artery was the most commonly interrogated vessel (54.5%). Figure 3 shows the distribution of the FFR values in the study. In general, the study population was composed of stenoses of intermediate angiographic (diameter stenosis: 60 ± 13% by visual assessment) and physiological severity [FFR; mean ± SD: 0.83 ± 0.11; median (Q1, Q3): 0.84 (0.77, 0.90)]. Finally, 248 (35.9%) vessels had FFR≤0.80.

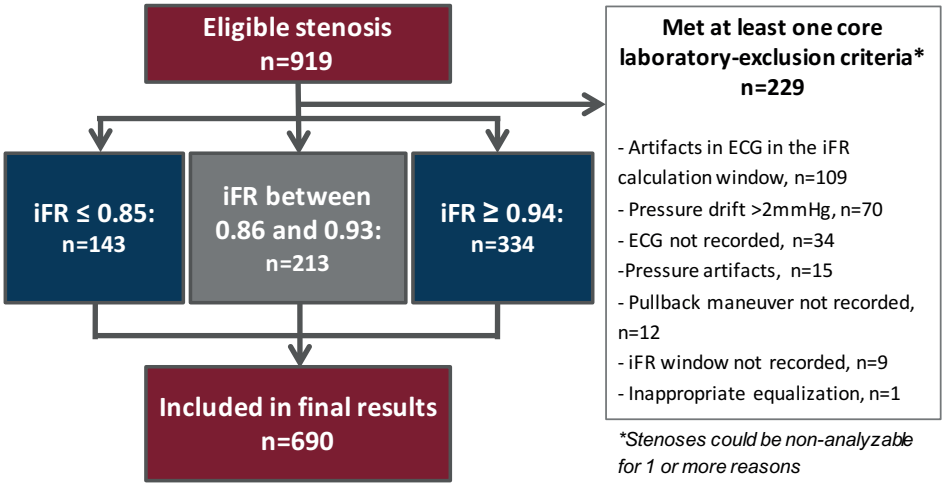

Figure 2 | STARD-type flow diagram showing the process followed by eligible stenosis from inclusion to final results.

Table 1 | General characteristics of study population n= 598

		95% CI*
Baseline Demographics		
Age (years)	63.6±10.8	[62.7–64.5]
Gender (Male)	68.9	[65.0%, 72.6%]
Medical History		
Prior Myocardial infarction	35.2	[31.3%-39.2%]
Prior PCI	49.1	[45.0%, 53.2%]
Prior CABG	4.7	[3.2%, 6.7%]
Congestive Heart Failure	8.4	[6.3%, 11.0%]
Hypertension	78.8	[75.3%, 82.1%]
Diabetes	35.0	[31.1%, 39.0%]
Current Smoker (<=6 Month)	22.6	[19.3%, 26.3%]
History of other vascular disease	17.4	[14.4%, 20.8%]
Renal Dysfunction (serum creatinine >2.0)	2.9	[1.7%, 4.6%]
Pulmonary Disease	12.0	[9.5%, 14.9%]
Clinical presentation		
Stable Angina	53.5	[49.4%, 57.6%]
Unstable angina	25.3	[21.8%, 28.9%]
Silent ischemia	13.1	[10.5%, 16.1%]
NSTEMI (>48 hrs before enrollment)	5.6	[3.9%, 7.7%]
STEMI (>48 hrs before enrollment)	2.5	[1.4%, 4.1%]

Numbers are percentages or mean ± standard deviation
*95% confidence intervals of the mean

Table 2 | General characteristics of epicardial stenosis included in study n=690

		95% CI*
Vessel		
Left anterior descending artery	54.5	[50.7%, 58.3%]
Left Circumflex	25.7	[22.4%, 29.1%]
Right coronary artery	19.9	[16.9%, 23.0%]
Stenosis characteristics		
Lesion Length (mm)	14.00±7.92	[13.40–14.59]
Reference Vessel Diameter (mm)	2.97±0.54	[2.93–3.01]
Percentage of Diameter Stenosis	59.7±13.2	[58.7–60.7]
Lesion Type (AHA)		
A	34.9	[31.3%, 38.6%]
B1/B2	52.2	[48.4%, 56.0%]
C	12.9	[10.4%, 15.6%]
Current in-stent restenosis	7.1	[5.3%, 9.3%]

Numbers are percentages or mean ± standard deviation
*95% confidence intervals of the mean

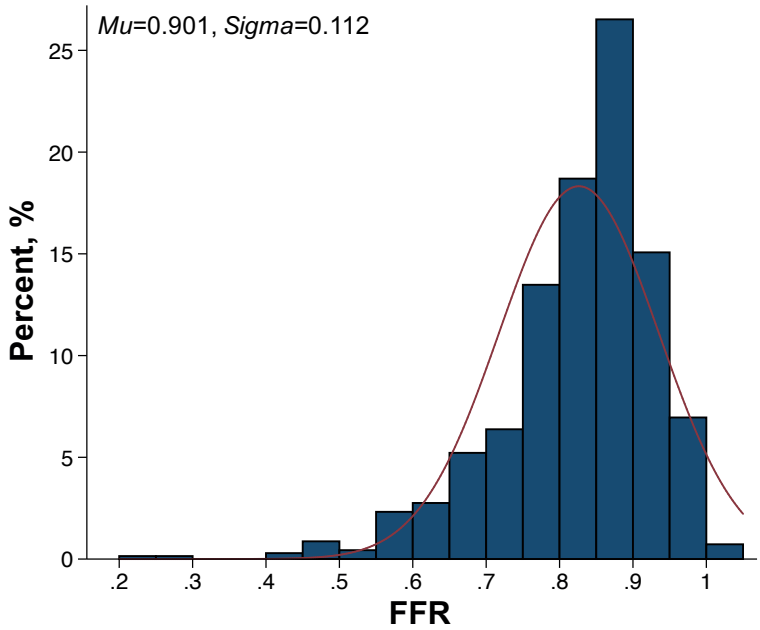

Figure 3 | Frequency histogram with superimposed normal distribution of the FFR values in study population. Please note the unimodal FFR distribution as well as data clustering around the FFR 0.80 cut-off point.

Diagnostic accuracy of iFR against FFR

Figure 4 (panel A) shows the scatterplot of the relationship between iFR and FFR. There was a strong linear correlation between both indices (r= 0.81, 95% CI: 0.78 to 0.83, p<0.001). ROC analyses identified 0.89 as the optimal iFR cut-off, with an area under the ROC curve (c- statistic) of 0.90 (95% CI: 0.88 to 0.92, p<0.001) (Figure 4, panel B). Notably, the optimal iFR cut-off observed in the study matched the pre-specified one. This 0.89 iFR cut-off classified correctly 82.5% of total stenoses, with a sensitivity of 73.0% and specificity of 87.8%. For the study prevalence (FFR ≤0.80, 35.9%), the positive predictive and negative predictive values of this cut-off were 77.0% and 85.3%, respectively.

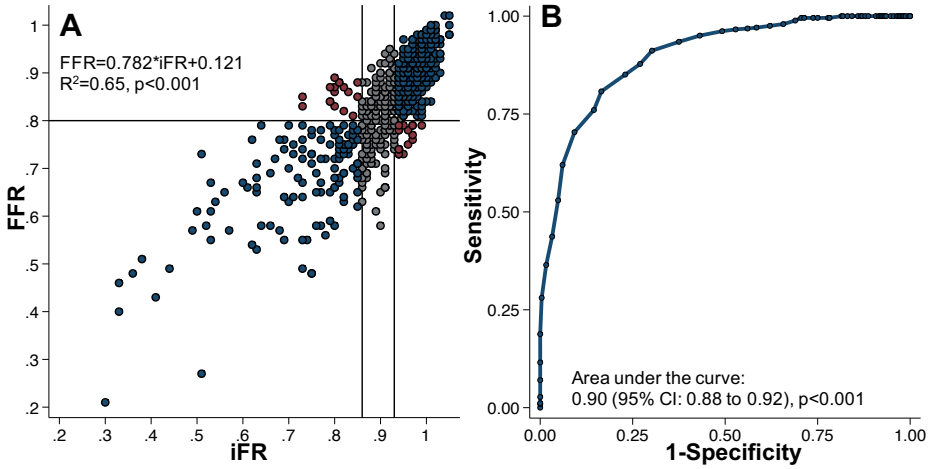

Figure 4 | Panel A: Scatterplot of the relationship between iFR and FFR. Vertical lines are placed at the boundaries of the "adenosine zone" (iFR values of 0.86 and 0.93). The horizontal line is placed at the clinically adopted 0.80 cut-off value of FFR. Panel B: ROC curve of iFR against FFR≤0.80. The optimal iFR cut-off identified in ADVISE II was 0.89.

Study endpoints

The iFR treatment (≤ 0.85) and deferral (≥ 0.94) values classified correctly 88.1% (95% CI: 81.6 to 92.9%) and 93.1% (95% CI: 89.8 to 95.6%) of the stenoses, respectively. Thus, the overall proportion of stenoses properly classified by iFR outside such pre-specified iFR treatment (≤ 0.85) and deferral (≥ 0.94) values was 91.6% (95% CI: 88.8 to 93.9) (Figure 5). The best iFR exclusion range around the pre-specified 0.89 cut-off to achieve ≥80% diagnostic accuracy was this cut-off itself, since it classified correctly 82.5% of total stenoses. To achieve 90% and 95% classification agreement with FFR, the minimum iFR exclusion ranges around the optimal 0.89 cut-off were ≤0.86 (to predict FFR ≤0.80) and ≥0.94 (to predict FFR >0.80), which provided a percentage agreement of 91.0%; and ≤0.78 (to predict FFR ≤0.80) and ≥0.95 (to predict FFR >0.80), which provided a percentage agreement of 95.3%. Finally, Figure 6 demonstrates how most of the classification disagreement between iFR and FFR was located within the FFR "grey zone" (FFR values between 0.75 and 0.80) where the ischemic potential of the stenosis is known to be less certain.[15]

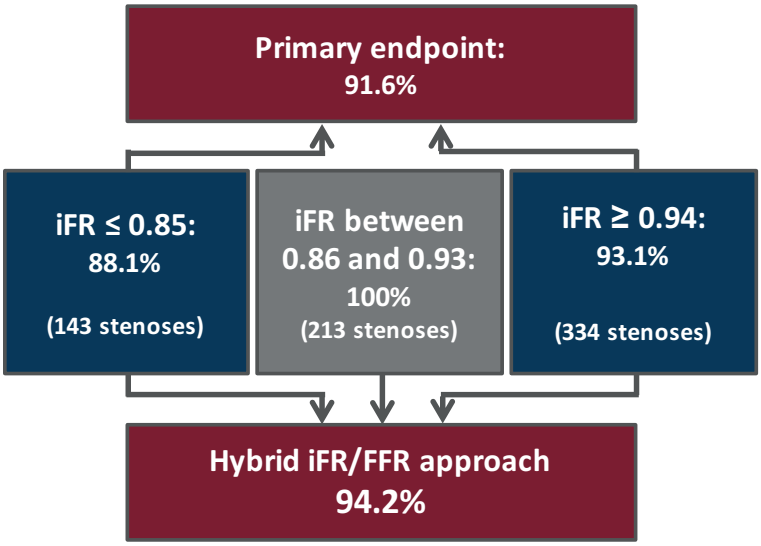

Figure 5 | Primary endpoint of the study and hybrid iFR-FFR approach. The iFR treatment (≤0.85) and deferral (≥0.94) values classified correctly 88.1% and 93.1% of investigated stenoses, respectively. The overall proportion of stenoses properly classified by iFR outside the pre-specified iFR values was 91.6%. This value increased to 94.2% after including standard classification with FFR in-between (Hybrid iFR-FFR approach).

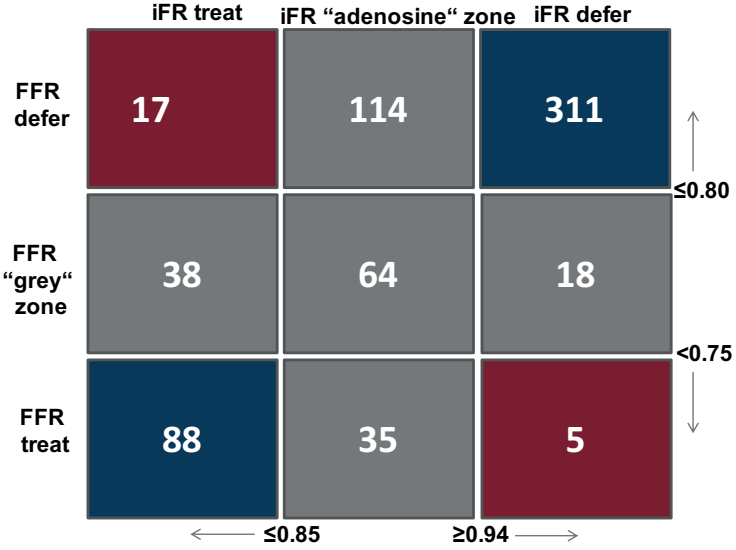

Figure 6 | Absolute counts of stenoses across categories of iFR and FFR. Please note how most of the between-indices disagreement was located within the FFR "grey zone" (FFR values between 0.75 and 0.80) where the ischemic potential of the interrogated stenosis is known to be less certain.

Hybrid iFR-FFR approach

The percentage of stenoses properly classified by the pre-specified hybrid iFR-FFR approach was 94.2% (95% CI: 92.2 to 95.8%), and had an associated sensitivity, specificity, positive predictive and negative predictive values of 90.7%, 96.2%, 93.0% and 94.9%, respectively (Figure 5). By doing so, the estimated proportion of patients and stenoses free from vasodilator agents by such pre-specified hybrid iFR-FFR approach amounted to 65.1% (95% CI: 61.1 to 68.9%) and 69.1% (95% CI: 65.5 to 72.6%), respectively.

DISCUSSION

The results of the ADVISE II study support the diagnostic value of iFR in establishing the hemodynamic severity of coronary stenoses, and highlight its complementariness with FFR when used in a hybrid iFR-FFR approach.

iFR as an alternative for physiological assessment of coronary stenosis

Although decision-making based on intracoronary physiology was initiated 20 years ago with Doppler-tipped guide wires,[15] the demonstration that intracoronary physiology is not only safe but results in better patient outcomes, came from studies comparing FFR with coronary angiography.[16,17] This clinical evidence has made FFR the technique of choice for physiological assessment of coronary stenosis.[18] Hence, the introduction of iFR took place at time in which FFR constituted the paradigm (and for many the synonym) of intracoronary physiology, which was concomitantly facilitated by many common aspects between the two techniques. iFR is derived from the same theoretical framework as FFR (i.e., the relationship between the translesional pressure ratio and the impairment in myocardial blood supply caused by the interrogated stenosis), and is obtained with conventional pressure wires and appropriate software.[1,11] Without doubt, the main attractiveness of iFR is the avoidance of vasodilator drugs, identified as a cumbersome requirement for FFR interrogation.[19] Thus, iFR appeared to many as a potential step ahead towards the simplification of physiological stenosis assessment introduced by FFR many years ago.

The publication of the first study on iFR generated significant interest among interventional cardiologists.[1-8] The RESOLVE study,[8] a recent pooled-retrospective analysis, provides an excellent perspective of published and unpublished iFR vs FFR comparisons performed within the first year after the publication of the ADVISE study.[1] In RESOLVE, data from individual studies was re-analyzed after standardization and application of inclusion and exclusion criteria, and iFR recalculated using the original iFR calculation algorithm. There was relatively little variation in the diagnostic accuracy

of iFR among the 6 independent research groups (n=1,593), and it was proposed that these differences resulted probably from inconsistencies in data collection and analysis inherently linked to the retrospective design; including non-uniform patient and lesions characteristics, varying acquisition equipment and protocols, absence of ECG and final pressure wire pullback to exclude pressure drift, among others, as highlighted by the investigators.

ADVISE II was designed to address the limitations of retrospective studies like RESOLVE, through a prospective multicenter design, with rigorous, standardized methodology and independent analysis at a core laboratory. Key differential aspects included FFR technique standardization, corroboration of appropriate pre-measurement equalization, and the acquisition of a single ECG and pressure recording encompassing baseline, induction and achievement of hyperemia, pressure wire pullback and persistence of calibration at the catheter tip. This rigorous methodology becomes highlighted by the high exclusion rate (nearly 25% of tracings) in ADVISE II, superior to that reported in RESOLVE (17%), which is probably explained by the fact that in RESOLVE exclusions due to ECG were not considered. In our study, nearly half (48%) of the excluded traces resulted from ECG pitfalls, probably mirroring lack of awareness of catheterization laboratory personnel on the relevance of ECG for accurate iFR calculation indicating an important methodological difference with RESOLVE. Importantly, in consonance with FFR theoretical framework,[11] ADVISE II mandated FFR calculation as the minimal Pd/Pa ratio during the steady-state hyperemic plateau. Finally, a higher c-statistic (0.90) in ADVISE II than in RESOLVE (0.81) was documented, whilst a very similar optimal iFR cut-off value was found (0.89 in ADVISE II, 0.90 in RESOLVE). This provides further evidence on the appropriateness of the use of this cut-off value in future studies.

Finally, RESOLVE also reported a good diagnostic performance of the largely neglected baseline Pd/Pa ratio. As the interest in the diagnostic performance of baseline Pd/Pa emerged when ADVISE II was already initiated, baseline Pd/Pa analyses were not included as pre-specified endpoints of the study. Yet, to investigate the value of this non-hyperemic index, a post-hoc analysis of ADVISE II data with the same methodology applied to the iFR versus FFR comparison reported in this paper has been performed, and is discussed in detail elsewhere.[20]

Use of the hybrid iFR - FFR approach

The simplest way of assessing the diagnostic accuracy of iFR is to use FFR dichotomized at 0.80 as reference standard. However, this approach is fraught by the limitations of dichotomizations in biological continuous systems.[2,3,21] This makes comparisons sensitive to the characteristics of coronary stenosis populations, where a lower inter and intra-technique agreements are by definition expected when used in unimodal distributions peaking around cut-offs, as compared with broader distributions where

more very severe and minimal stenoses are present.[21] In this regard, it is important to acknowledge that the distribution of FFR values in ADVISE II was intermediate (diameter stenosis: 60± 13%; FFR: 0.83±0.1) (Figure 3) which is the most challenging for the purpose of establishing the diagnostic accuracy of iFR, as data clustering near the FFR cut-off helps small differences lead to classification disagreement.[2,3,21]

To overcome these limitations, a hybrid iFR-FFR approach has been proposed as a way to translate to practice the potential value of iFR as a diagnostic tool. ADVISE II supports the diagnostic value of this hybrid iFR-FFR diagnostic approach, as it properly classified 94.2% of total stenosis, with values of specificity, sensitivity, positive predictive and negative predictive values above 90%. With this strategy, adenosine would not be required in 69% of the stenoses, and in 65% of patients adenosine would not be needed at all. These figures support the potential of iFR to ease catheterization laboratory workflow and to reduce costs associated with ischemia-driven revascularization.

Implications of ADVISE II results for clinical practice

ADVISE II probably constitutes the definitive direct comparison between iFR and FFR. Since the low adoption of FFR[22] is clearly the first obstacle for translating the benefits of ischemia-driven revascularization to patients, the results of ADVISE II may contribute to increase its implementation, particularly when used synergistically with FFR. This is an urgent task, since recent studies like RIPCORD have demonstrated that revascularization decisions based on angiography and available clinical information are modified in >30% of cases when physiological interrogation is performed.[23] At a time that FFR is used in a minority of cases and, therefore, similar rates of misdiagnosis should be expected in non-FFR practices, a huge net benefit would be expected if a hybrid iFR-FFR approach is adopted, even if 5.8% stenoses would not be properly classified according to FFR.[24]

A second obstacle to translate available evidence on the benefit of FFR to patients is the restriction of physiological interrogation to intermediate stenosis, and not to all potential revascularization targets, irrespective of their angiographic appearance. It is important to note that in randomized studies FFR has been measured in all stenoses regardless of their angiographic severity.[16,17,25] However and as highlighted by observational studies including ADVISE II, most interventional cardiologists do not measure FFR in stenoses judged as clearly severe or non-severe, on the grounds that it interferes with catheterization laboratory workflow and increases costs. Whilst the cost-effectiveness analysis of FAME has clearly demonstrated that the latter perception is wrong,[25] the sharp decrease in the need for adenosine found in ADVISE II constitutes a potential solution for the former obstacle. Indeed, the forthcoming multicentre SYNTAX II trial (ClinicalTrials.gov. Identifier: NCT02015832) that applies ischemia driven

revascularization to patients with triple vessel disease treated with PCI has opted for a hybrid iFR-FFR approach to reduce procedural time in this type of complex procedures.

LIMITATIONS

ADVISE II is the first prospective, core laboratory-based intracoronary physiology study. Therefore, being a validation analysis, stringent core-laboratory criteria were applied. Whilst this approach reduces the potential for bias and threats to statistical internal validity, it might also limit the generalization of the findings to different populations. However, the fact that the diagnostic accuracy of iFR observed in clinical retrospective registries shows very little variations from that observed in this meticulous prospective study is reassuring.

What's known?

Studies with methodological heterogeneity have reported some discrepancies in the classification agreement between iFR and FFR.

What's new?

With a rigorous methodology, ADVISE II identified that the pre-specified hybrid iFR-FFR approach properly classified 94.2% of the stenoses while obviated vasodilators need in 69.1% (95% CI: 65.5 to 72.6%).

What's next?

Baseline indices can reliably identify ischaemia generating stenosis in selected subsets. Future studies should focus now on their role in clinical decision-making.

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CHAPTER 5

Diagnostic Accuracy of Baseline Distal-to-Aortic Pressure Ratio to Assess Coronary Stenosis Severity: A Post-Hoc Analysis of the ADVISE II Study

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RESEARCH LETTER

The demonstration that coronary revascularization based on functional rather than anatomic stenosis assessment results in better patient outcomes has stimulated the interest in fractional flow reserve (FFR) and other physiological indices.[1] The instantaneous wave free ratio (iFR), introduced in late 2011, was developed to facilitate the functional assessment of coronary stenoses by obviating the need for vasodilator drugs.[2] The baseline Pd/Pa ratio (calculated as the mean non-hyperemic trans-stenotic pressure ratio across the whole cardiac cycle) has also been proposed as a simpler index than FFR to estimate stenosis severity,[3] and a renewed interest in baseline Pd/Pa´s diagnostic value has been generated by the concept of iFR and studies like RESOLVE.[1] The ADVISE II study (ADenosine Vasodilator Independent Stenosis Evaluation II) was a large, prospective, multicenter, core laboratory-based international study, designed to determine the extent to which iFR accurately reflects FFR.[4] Since the RESOLVE study was launched further to the design and approval by ethical review boards of ADVISE II, baseline Pd/Pa analyses were not included as pre-specified endpoints of the study. Despite this, the ADVISE II investigators believe that the meticulously collected and analyzed data provides an opportunity to investigate the diagnostic performance of baseline Pd/Pa relative to FFR. Accordingly, in this post-hoc analysis of the ADVISE II study, we report the diagnostic accuracy of baseline Pd/Pa against FFR, using the same methodology as for the iFR versus FFR comparison.

The methodology and results of the ADVISE II study, as well as the list of participating investigators and centers, have been reported elsewhere.[4] Baseline Pd/Pa was calculated as the mean trans-stenotic pressure ratio during baseline, and was derived from the same cardiac beats used for iFR computation. Both indices were obtained from pressure recordings (minimum of 20 seconds) obtained after crossing the stenosis and before starting the infusion of adenosine. FFR was defined as the Pd/Pa ratio during stable hyperaemia, induced by intravenous infusion of adenosine at a rate of 140/mcg/kg.[4] A total of 919 intermediate coronary stenoses were investigated during baseline and hyperemia. From these, 690-pressure recordings (598 patients) met core laboratory physiology criteria and included in this analysis. Median FFR was 0.84 (quartile 1 and 3: 0.77, 0.90). The scatterplot of the baseline Pd/Pa and FFR relationship is shown in the Figure (panel A). Both indices were strongly correlated (r= 0.84, 95% CI: 0.82 to 0.86, p<0.001). Using FFR≤0.80 as cut-off to define significant stenoses, receiver operating characteristic (ROC) analysis identified 0.91 as the optimal baseline Pd/Pa cut-off, with an area under the ROC curve (c-statistic) of 0.90 (95% CI: 0.86 to 0.93, p<0.001). This 0.91 baseline Pd/Pa cut-off classified correctly 83.2% of total stenoses, with a sensitivity of 66.5% and specificity of 92.5%. Panel B of the Figure shows the ROC curves of iFR and baseline Pd/Pa against FFR≤0.80. No significant difference between

the areas under the ROC iFR and baseline Pd/Pa curves was documented [difference in c-statistics -0.00 (95% CI: -0.01 to 0.00), p=0.350]. To achieve 90% classification agreement with FFR, the minimum baseline Pd/Pa exclusion ranges around the optimal 0.91 cut-off were ≤0.89 (to predict FFR≤0.80) and ≥0.94 (to predict FFR>0.80), and provided a percentage agreement of 90.4%. To achieve 95% classification agreement with FFR, the minimum baseline Pd/Pa exclusion ranges around the same 0.91 cut-off were ≤0.88 (to predict FFR≤0.80) and ≥0.97 (to predict FFR>0.80), and provided a percentage agreement of 95.5%. The proportion of patients and stenoses free from adenosine by these hybrid baseline Pd/Pa-FFR strategies amounted to 75.6% (95% CI: 71.9 to 79.0%) and 78.4% (95% CI: 75.1 to 81.4%), for a 90% classification agreement; and to 47.0% (95% CI: 42.9 to 51.1%) and 51.4% (95% CI: 47.6 to 55.2%), for a 95% classification agreement. Finally, even in the most conservative scenario (100% agreement), 14% of stenosis with baseline Pd/Pa<0.81 would not require hyperemic stress for correct classification.

The design of ADVISE II study offers several methodological advantages over previous iFR versus FFR comparisons that reduces the potential for bias and threats to statistical validity. These include 1) dedicated and prospectively defined data collection 2) better data control, 3) additional checks for data integrity and consistency, and 4) a level of clinical detail appropriate to address the research question. Therefore, ADVISE II allows to draw of several strong conclusions. First, both baseline Pd/Pa and iFR are strongly correlated with FFR. Second, at the extremes of the distribution of values of both these indices, the probability of significant stenosis (FFR≤0.80, in the low tail) and non-significant stenosis (FFR>0.80, in the high tail) is very high. Indeed, both indices could reach a 100% classification agreement in the low tail (iFR<0.73, baseline Pd/Pa<0.81) whilst only iFR reached a 100% classification match in the high tail (value of 1.0). These findings confirm that, when FFR is used as a reference, a proportion of stenoses can be classified correctly without hyperaemic stress, existing a trade-off between higher diagnostic accuracy and adenosine spare. In this interpretation, however, it has to be kept in mind that 1) iFR, baseline Pd/Pa and FFR are intrinsically correlated —because all rely on pressure as surrogate of myocardial flow impairment; 2) baseline Pd/Pa and FFR have a greater intrinsic association, as they both assess pressure throughout the cardiac cycle and not over a finite period of time in diastole; and 3) FFR is used as the standard of reference. In this regard, two recent head-to-head comparisons of the diagnostic accuracy of iFR, baseline Pd/Pa and FFR that used as reference standard non-pressure derived tests of myocardial flow impairment [coronary flow reserve and single-photon emission computed tomography— both with wealth of supportive outcome data[5,6]] observed a similar discrimination power for both resting (baseline Pd/Pa, iFR) and hypereamic (FFR) indices. Further studies should address if differences between resting and hyperaemic indices in terms of the identification of revascularize-

tion targets are clinically relevant. Finally, the calculation of baseline Pd/Pa in ADVISE II slightly differs from that used in clinical practice, since baseline Pd/Pa was derived from optimal beats selected by the iFR calculation algorithm. These, in addition to the demanding methodology in the catheterization laboratory and analyses mandated in ADVISE II, might help explain why, contrastingly, RESOLVE could not find an upper boundary of baseline Pd/Pa which predicted with ≥90% accuracy a negative FFR value. Further clinical studies should address if the larger spread of possible iFR values and its more balanced sensitivity and specificity[4,7] confers to this index a pragmatic value above baseline Pd/Pa.

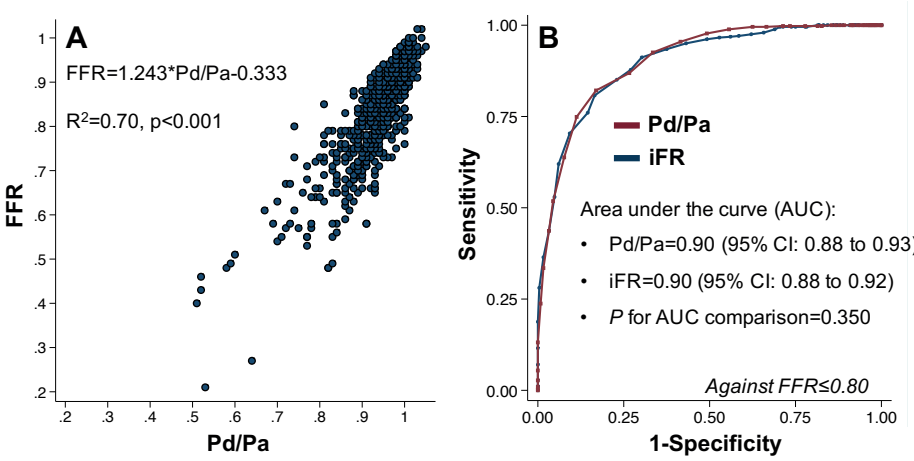

Figure 1 | Panel A: Scatterplot of the baseline Pd/Pa and FFR relationship. Panel B: ROC curves of iFR and baseline Pd/Pa against FFR≤0.80.

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CHAPTER 6

Combining baseline distal-to-aortic pressure ratio and fractional flow reserve in the assessment of coronary stenosis severity

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ABSTRACT

Objective

We sought to understand 1) the physiological basis of baseline distal-to-aortic pressure ratio (Pd/Pa) and fractional flow reserve (FFR) agreement and discordance, using coronary flow reserve (CFR), stenosis resistance (SR) and microcirculatory resistance (MR) measurements; and form there, 2) to investigate the potential value of combining Pd/Pa with FFR in the diagnostic rationale.

Background

Pd/Pa is always available before FFR assessment, and emerging data supports the notion that baseline indices can determine the ischemic potential of coronary stenosis in selected subsets.

Methods: 467 stenosed vessels from 363 patients were investigated with pressure and flow sensors during baseline and hyperemia: 168 vessels (135 patients) with thermodilution-derived flow, and 299 vessels (228 patients) with Doppler-derived flow.

Results

Pd/Pa correlated more strongly with CFR than FFR (ρ difference=0.129; p for ρ comparison<0.001). Although Pd/Pa and FFR were closely correlated (ρ=0.798; 95% CI: 0.767 to 0.828), categorical discordance was observed in 19.3% of total vessels. Such discordance was associated with the patients´ clinical profile, and characterized by contrastive changes in SR, MR and the underlying CFR. Notably, all stenosis with Pd/Pa≤0.83 (n=74, 15.8%) progressed to FFR≤0.80, and although no Pd/Pa cut-off was able to exclude the development of FFR≤0.80 in the high end of values, only 15 (10.1%) vessels with Pd/Pa≥0.96 (n=149, 31.9%) developed FFR≤0.80, from which none had definite ischaemia, as defined by CFR≤1.74.

Conclusions

Combining baseline Pd/Pa with FFR seems to provide a more comprehensive physiological examination of stenosed coronary arteries, and a closer pressure-based appraisal of the flow reserve of the downstream myocardial bed.

INTRODUCTION

Fractional flow reserve (FFR) has become the standard method to assess coronary stenosis severity in the catheterization laboratory following the demonstration that physiological rather than anatomical selection of stenosis candidates for revascularization results in better patient outcomes.[1] This positive evidence has stimulated the interest in FFR and other physiology indices, and a desire for simplification has specifically boosted the attention to non-hyperemic indices.[2] The baseline distal-to-aortic pressure ratio (Pd/Pa) is always available before FFR assessment, and several studies have shown that a Pd/Pa value close to 0.90 provides the best classification match with the clinically adopted 0.80 FFR cut-off, which is approximately 80%.[3,4] This implies that most stenoses that will develop FFR≤0.80 have already relatively low Pd/Pa values, and conversely, that most stenoses that will develop a final FFR>0.80 arise from high values of Pd/Pa. This also denotes, however, that in approximately 20% of the cases, Pd/Pa will not match dichotomously with FFR, because in some vessels an FFR≤0.80 value will emerge from a near-normal Pd/Pa ratio, whilst in others, an FFR>0.80 will be preceded by an already-fairly low Pd/Pa. Although this disagreement is used to stress the importance of standardizing measurements at hyperemia, its physiological basis is poorly described.

In this study we investigated stenosed coronary arteries with combined intracoronary pressure and flow sensors, since this allows selective interrogation of the epicardial stenosis resistance (SR), microcirculatory resistance (MR) and the coronary flow reserve (CFR) of the downstream vascular bed.[5] We aimed firstly to explore the physiological basis of the agreement and discordance between baseline Pd/Pa and FFR, and secondly to test if adding baseline Pd/Pa to the diagnostic rationale conveys important information able to expand the physiological lone-FFR assessment.

METHODS

Study population

Patients with a clinical indication for FFR interrogation of ≥1 intermediate coronary stenosis [40% to 70% diameter stenosis (DS)], investigated at Hospital Clinico San Carlos, Madrid, Spain, and the Academic Medical Centre, Amsterdam, the Netherlands, were prospectively studied. Patients with myocardial infarction <5 days, contraindications to adenosine, left ventricle ejection fraction <30%, left main disease or significant valvular pathology were excluded, as well as vessels supplying previously known infarcted territories, with serial stenoses, marked diffuse narrowings or with patent

surgical grafts. All patients gave informed consent and approval from the Institutional Review Boards was obtained according to local regulations.

Cardiac catheterization and hemodynamic measurements

Cardiac catheterization was performed according to standard practice. Angiographic views were obtained following intracoronary nitrates (0.2 mg) in a manner suitable for quantitative coronary angiography (QCA) analysis. After diagnostic angiography, sensor-equipped guidewires were used to measure intracoronary pressure and flow according to described methodologies.[6,7] Briefly, in Hospital Clinico San Carlos, coronary flow was assessed with the coronary thermodilution method.[8] Resting and hyperemic thermodilution curves were obtained in triplicate, and CFR calculated as the ratio of average baseline mean transit time (Tmn) to hyperemic Tmn. The inverse of baseline Tmn and hyperemic Tmn was computed, and labeled as baseline and hyperemic flow, respectively.[8] In the Academical Medical Centre, coronary flow velocity was assessed using Doppler sensors as described elsewhere.[7] Baseline and hyperemic average peak flow velocities were recorded, and coronary flow velocity reserve calculated as the ratio of hyperemic to baseline flow velocity. Since coronary flow velocity reserve and thermodilution-derived CFR are unitless and very strongly correlated,[9] the term CFR was used and datasets merged. Indices of flow, SR and MR were calculated as depicted in Table 1. Hyperemia was induced with adenosine, either by intravenous infusion through a central vein (140µg/kg/min) at Hospital Clinico San Carlos, or intracoronary boluses (20-40µg) at the Academical Medical Centre. Finally, FFR ≤0.80 and CFR <2 were used as cut-offs.[1,7]

Table 1 | Physiology indices used in study

CFR= hyperemic flow/ baseline flow	
Pd/Pa = mean Pd /mean Pa (baseline)	**Thermodilution-derrived flow:**
FFR = mean Pd /mean Pa (hyperemia)	**1/ mean transit time, sec**
SR= (mean Pa - mean Pd)/ flow*	**Doppler-derived flow:**
MR= mean Pd/ flow*	**Average peak flow velocity, cm/sec**

CFR: coronary flow reserve; Pd: distal coronary pressure; Pa: aortic pressure; FFR: fractional flow reserve, SR: stenosis resistance, MR: microcirculatory resistance.
*SR and MR were calculated at baseline and hyperemia.

Statistical analysis

Data was analyzed on per-patient basis for clinical characteristics, and on per-vessel basis for the rest of calculations. For patient-level analyses, Center was added as covariate to linear and logistic regression models in order to account for potential differences between the populations. Additionally, Huber-White robust standard errors were used to adjust for additional variability of arteries from the same subject. From these models, adjusted means and prevalences with 95% confidence intervals

(CI) are presented. For vessel-level analyses, we believed it was better to document the consistencies and the differences between the Centers and their techniques to measure flow. Therefore, individual Doppler and thermodilution findings are also provided in Tables and in the Supplement. Finally and since Pd/Pa, FFR and CFR are vessel-specific indices that link upstream epicardial disease with the functionality and extension of the downstream microcirculatory bed, independence was assumed for vessel-level analyses. Continuous variables are presented as mean±SD or median [quartile 1 and 3 (Q1-3)] and categorical variables as counts and percentages. Normality and homogeneity of the variances were tested using Shapiro-Wilk and Levene tests, respectively. Continuous variables were compared with t tests or Mann-Whitney U tests, and categorical variables with Chi square or Fisher´s exact tests, as appropriate. Correlation coefficients (Pearson´s r, Spearman´s ρ) between physiology indices were calculated. For Pd/Pa dichotomization, receiver-operating characteristic (ROC) analyses were used to determine its optimal cut-off against FFR≤0.80, defined as that maximizing correct classification. Overall differences across Pd/Pa and FFR categories were compared with one-way analysis of variance (ANOVA), Kruskal-Wallis, Chi square or Fisher´s exact tests, followed by post-hoc t tests, Mann-Whitney U or Fisher´s exact tests with Bonferroni-adjusted significance level. In scatterplots, spherical controlled noise ("jitter") was used to prevent overprinting of dots. Differences were considered significant at $p<0.05$ (two-sided), and the STATA 12.1 (StataCorp, College Station, Texas) software was used for all calculations.

RESULTS

Baseline characteristics

Clinical, angiographic, and physiological characteristics of the study population are shown in Tables 2 and 3. In total, 467 stenosed vessels from 363 patients were investigated: 168 vessels (135 patients) with thermodilution-derived flow (Thermo) and 299 vessels (228 patients) with Doppler-derived flow (Doppler). Mean age was 62±11 years and the majority of patients (n=305, 84.0%) underwent catheterization because of stable symptoms. Overall, coronary stenoses were of intermediate severity, both angiographically (DS: 52.7 ± 11.4%) and physiologically [median FFR=0.81 (Q1-3, 0.72-0.88)].

Table 2 | General characteristics of studied patients

		Both-abnormal (A)	Only-FFR-abnormal (B)	Only Pd/Pa-abnormal (C)	Both-normal (D)	
	Total	Pd/Pa≤0.91, FFR≤0.80	Pd/Pa>0.91, FFR≤0.80	Pd/Pa≤0.91, FFR>0.80	Pd/Pa>0.91, FFR>0.80	P
	n=363					
Age*	61.7 (59.5 to 63.9)	60.7 (58.6 to 62.8)	58.6 (55.8 to 61.4)	64.5 (60.7 to 68.2)	62.9 (60.9 to 64.8)	<0.001
Male	75.6 (65.4 to 83.6)	80.0 (71.2 to 86.7)	72.4 (58.3 to 83.1)	62.9 (44.0 to 78.5)	75.1 (66.3 to 82.1)	0.130
Cardiovascular risk factors						
Hypertension	49.3 (39.6 to 58.9)	45.8 (36.8 to 54.9)	41.2 (29.6 to 54.0)	71.4 (55.4 to 83.7)	50.7 (42.1 to 59.1)	<0.001
Diabetes	20.2 (12.9 to 29.9)	18.1 (11.8 to 26.6)	29.3 (18.6 to 42.5)[d]	31.4 (17.6 to 49.7)	17.4 (11.4 to 25.6)[b]	0.002
Dyslipidemia	61.4 (50.8 to 71.0)	65.1 (55.4 to 73.6)	58.6 (44.8 to 71.2)	51.4 (34.0 to 68.5)	60.9 (51.7 to 69.3)	0.487
Smoker	29.0 (20.5 to 39.4)	30.7 (22.4 to 40.4)	37.9 (25.8 to 51.8)	17.1 (7.6 to 34.2)	27.1 (19.7 to 35.9)	0.279
Previous myocardial infarction	43.0 (33.3 to 53.5)	41.6 (32.5 to 51.1)	29.3 (18.6 to 42.7)	37.1 (22.3 to 54.9)	49.1 (40.0 to 58.1)	0.016
Multivessel disease	68.7 (58.5 to 77.2)	65.1 (55.6 to 73.4)	71.1 (57.8 to 81.7)	77.1 (59.6 to 88.5)	69.6 (60.8 to 77.1)	0.537
Unadjusted patient n, (%)**	291 (100%)	102 (35.1%)	42 (14.4%)	24 (8.2%)	123 (42.3%)	<0.001

All analysis are $_{adj}$means* with 95% CI and $_{adj}$prevalences with 95% CI with the exception of the unadjusted patient n, (%)**

**Patients with more than one interrogated vessels were excluded

Table 3 | General characteristics of studied vessels

		Both-abnormal (A)	Only-FFR-abnormal (B)	Only Pd/Pa-abnormal (C)	Both-normal (D)	
	Total	Pd/Pa≤0.91, FFR≤0.80	Pd/Pa>0.91, FFR≤0.80	Pd/Pa≤0.91, FFR>0.80	Pd/Pa>0.91, FFR>0.80	P
	n=467	n=166	n=59	n=35	n=207	
Stenosis location						0.008
LAD	226 (48.4)	98 (59.0)	32 (54.2)	16 (41.9)	80 (38.7)	
LCx	110 (23.6)	28 (16.9)	12 (20.3)	8 (22.9)	62 (30.0)	
RCA	131 (28.1)	40 (24.1)	15 (25.4)	11 (31.4)	65 (31.4)	
Quantitative coronary angiography						
RD, mm	2.84 (2.41 to 3.29)	2.84 (2.38 to 3.33)	2.72 (2.35 to 3.26)	2.68 (2.29 to 3.05)	2.90 (2.50 to 3.37)	0.231
MLD, mm	1.24 (1.03 to 1.59)	1.11 (0.88 to 1.33)[d]	1.19 (1.03 to 1.56)[d]	1.26 (1.07 to 1.54)	1.44 (1.14 to 1.71)[a,b]	<0.001
DS, %	53±11	58±12[c,d]	54±10[d]	49±9[a]	49±10[a,b]	<0.001
Physiology parameters						
Pd/Pa	0.93 (0.88 to 0.96)	0.85 (0.70 to 0.89)	0.94 (0.93 to 0.96)	0.90 (0.89 to 0.91)	0.96 (0.94 to 0.98)	-
FFR	0.81 (0.72 to 0.88)	0.69 (0.55 to 0.75)	0.76 (0.73 to 0.79)	0.85 (0.82 to 0.87)	0.89 (0.86 to 0.93)	-
Pd/Pa- FFR	0.10 (0.06 to 0.16)	0.13 (0.09 to 0.19)[b,c,d]	0.19 (0.16 to 0.22)[a,c,d]	0.05 (0.03 to 0.07)[a,b,d]	0.07 (0.04 to 0.10)[a,b,c]	<0.001
Measurements of flow						
CFR, all*	2.16 (1.54 to 2.70)	1.60 (1.27 to 2.20)[b,c,d]	2.40 (1.89 to 2.91)[a,c]	2.01 (1.44 to 2.50)[a,b,d]	2.43 (1.95 to 3.00)[a,c]	<0.001
CFVR (Doppler)	2.21 (1.70 to 2.76)	1.60 (1.30 to 2.17)[c,d]	2.40 (1.92 to 2.91)[c,]	2.17 (1.88 to 2.84) [a]	2.50 (2.15 to 3.00) [a]	<0.001
CFR (thermo)	1.90 (1.39 to 2.7)	1.60 (1.10 to 2.35)[d]	2.22 (1.50 to 3.1)	1.81 (1.40 to 2.42)	2.18 (1.51 to 3.09)[a]	0.019
APV, baseline	16 (12 to 21)	14 (10 to 20)	17 (12 to 23)	16 (15 to 23)	17 (13 to 20)	0.059
APV, hyperemia	36 (26 to 49)	26 (16 to 39)[b,c,d]	38 (30 to 51)[a]	45 (30 to 54)[a]	41 (32 to 54)[a]	<0.001
Tmn, baseline	0.59 (0.33 to 0.91)	0.56 (0.30 to 0.84)	0.72 (0.48 to 1.33)	0.50 (0.33 to 0.73)	0.71 (0.38 to 1.17)	0.181
Tmn, hyperemia	0.29 (0.20 to 0.44)	0.30 (0.22 to 0.42)	0.32 (0.22 to 0.51)	0.25 (0.17 to 0.33)	0.31 (0.19 to 0.44)	0.577

Table 3 | General characteristics of studied vessels (continued)

		Both-abnormal (A)	Only-FFR-abnormal (B)	Only Pd/Pa-abnormal (C)	Both-normal (D)	
Measurements of stenosis resistance						
BSR (Doppler)	0.40 (0.17 to 0.82)	1.06 (0.74 to 2.55)[b,c,d]	0.33 (0.20 to 0.47)[a,c,d]	0.57 (0.45 to 0.71)[a,b,d]	0.17 (0.11 to 0.30)[a,b,c]	<0.001
HSR (Doppler)	0.50 (0.26 to 0.87)	1.13 (0.76 to 2.86)[b,c,d]	0.61 (0.38 to 0.79)[a,c,d]	0.32 (0.48 to 0.65)[a,b,d]	0.25 (0.14 to 0.36)[a,b,c]	<0.001
BSR (thermo)	3.60 (1.77 to 6.84)	6.72 (3.91 to 12.15)[b,c,d]	3.36 (0.87 to 9.31)[a,d]	4.59 (3.3 to 5.8)[a,d]	1.79 (0.98 to 3.52)[a,b,c]	<0.001
HSR (thermo)	3.71 (2.10 to 5.97)	5.94 (3.90 to 8.99)[c,d]	4.59 (3.36 to 8.40)[c,d]	2.82 (2.10 to 3.90)[a,b,]	2.34 (2.10 to 5.97)[a,b]	<0.001
Measurements of microcirculatory resistance						
BMR (Doppler)	5.44 (4.15 to 7.08)	5.13 (3.81 to 7.00) [d]	5.54 (4.04 to 708)	5.00 (4.13 to 6.07)	5.80 (4.90 to 7.38) [a]	0.041
HMR (Doppler)	2.07 (1.56 to 2.75)	2.20 (1.58 to 2.95)	1.87 (1.32 to 2.37)	1.91 (1.50 to 2.30)	2.08 (1.61 to 2.67)	0.058
BMR (thermo)	45.4 (26.5 to 77.3)	32.8 (21.7 to 71.2)[d]	51.1 (41.0 to 123.7)	35.9 (30.7 to 48.4)[d]	55.2 (34.5 to 92.7)[a,c]	0.005
HMR (thermo)	17.5 (12.2 to 25.9)	16.2 (10.3 to 21.6)	12.1 (11.3 to 23.2)	17.09 (10.5 to 22.4)	19.4 (14.4 to 30.1)	0.039

Values are mean±S.D., median (25^{th}-75^{th}) or n (%)

LAD: left anterior descending artery; LCx: circumflex; RCA: rigth coronary artery; RD: reference diameter; MLD: minimum lumen diameter; DS: diameter stenosis; CFR: coronary flow reserve; CFVR: coronary flow velocity reserve; APV: average peak flow velocity; Tmn: mean transit time; BSR: baseline stenosis resistance; HSR: hyperemic stenosis resistance; BMR: baseline microcirculatory resistance; HMR: hyperemic microcirculatory resistance.

*Doppler and thermodilution vessels

[a]p<0.05 compared to A

[b]p<0.05 compared to B

[c]p<0.05 compared to C

[d]p<0.05 compared to D

Relationship between Pd/Pa and FFR

Figure 1 shows the scatterplot of the Pd/Pa and FFR relationship. A moderate-to-strong correlation between Pd/Pa and FFR was observed in the overall population (ρ =0.798; 95% CI: 0.767 to 0.828), which was similar between technologies (Supplemental Figure): Thermo-vessels ρ=0.789 (95% CI: 0.724 to 0.839); Doppler-vessels ρ=0.821 (95% CI: 0.781 to 0.855); p for ρ comparison= 0.337. Using FFR≤0.80 to define significant stenosis, ROC analyses identified 0.91 as the optimal Pd/Pa cut-off, with an area under the curve of 0.882 (95% CI: 0.851 to 0.913) (Figure 1, panel B). This 0.91 Pd/Pa cut-off classified correctly 80.7% of total stenoses, with a sensitivity of 68.9% and specificity of 91.7%. Consequently, Pd/Pa≤0.91 [n=201 (43.0%)] and FFR≤0.80 [n=225 (48.2%)] were used for further categorizations: (A) both-abnormal [Pd/Pa≤0.91 and FFR≤0.80, n=166 (35.6%)]; (B) only-FFR-abnormal [Pd/Pa>0.91 and FFR≤0.80, n=59 (12.6%)]; (C) only-Pd/Pa-abnormal [Pd/Pa≤0.91 and FFR>0.80, n=35 (7.5%)] and (D) both-normal [Pd/Pa>0.91 and FFR>0.80, n=207 (44.3%)]; being (B) and (C) discordant-vessels.

Finally and aiming to explore a perfect classification agreement between Pd/Pa and FFR on individual basis, no Pd/Pa cut-off was able to exclude the development of a FFR≤0.80 in the high end of values, whilst, conversely, all stenosis with Pd/Pa≤0.83 (n=74, 15.8%) developed FFR≤0.80.

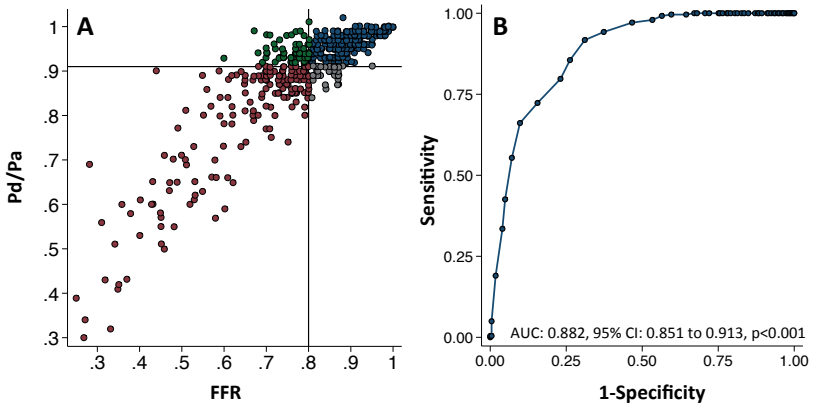

Figure 1 | Baseline Pd/Pa and FFR relationship. Panel A: Scatterplot of the Pd/Pa and FFR relationship. The horizontal and vertical lines are placed at the Pd/Pa (0.91) and FFR (0.80) cut-offs, respectively. Panel B: ROC curve of Pd/Pa against FFR≤0.80.

Clinical characteristics across the Pd/Pa and FFR categories

Table 2 depicts the clinical characteristics of the study population. Some were different across the Pd/Pa and FFR categories. The more significant were age and the prevalence of hypertension: B-vessels were more frequently observed in younger patients, whilst C-vessels were more prevalent in elderly and hypertensive patients.

Relationship of Pd/Pa and FFR with measurements of flow

Pd/Pa (ρ=0.474; 95% CI: 0.401 to 0.542, p<0.001) and FFR (ρ=0.344; 95% CI: 0.261 to 0.442, p<0.001) were both significantly correlated with CFR (Figure 2), although Pd/Pa correlated more strongly (ρ difference=0.129; 95% CI: 0.066 to 0.243, p for ρ comparison<0.001). Overall, coronary flow increased with hyperemia a median +116% (Q1-3, +54 to +172%). However, the increase in flow (Table 3 and 4 and Figure 3) was significantly different across Pd/Pa and FFR categories (p for overall comparison<0.001). The smallest and largest increases in flow were observed in A- [+60% (Q1-3, +25 to +120%)] and D-vessels [+140% (Q1-3, +91 to +192%)], respectively. C-vessels exhibited moderate increases of flow [+97% (Q1-3, +45 to +154%)], whilst—notably—the increase in flow of B-vessels was high [+144% (Q1-3, +95 to +201%)], and did not statistically differ (p=0.977) from that observed in the most normal D-vessels. Similar trends were observed when the percentage of vessels with exhausted flow reserve (CFR<2) was investigated across Pd/Pa and FFR categories (Figure 2, panel B). If baseline Pd/Pa was >0.91 (n=266, 57%), the prevalence of exhausted CFR was low (n=82, 30.8%), and did not statistically differ (p=0.425) if final FFR was ≤0.80 (B-vessels, n=32, 35.6%) or >0.80 (D-vessels, n=61, 29.5%). Conversely, if Pd/Pa was ≤0.91 (n=201, 43%), the prevalence of exhausted CFR was high (n=201, 63.7%), and only marginally statistically differ (p=0.053) if final FFR was ≤0.80 (A-vessels, n=111, 66.9%) or >0.80 (C-vessels, n=17, 48.6%).

Stenosis resistance across Pd/Pa and FFR categories

Baseline and hyperemic SR values were significantly different across the Pd/Pa and FFR categories (Table 2). The highest SR were observed in A-vessels, the lowest in D-vessels, and discordant vessels exhibited intermediate SR values. Hyperemia increased SR a median of +11% (Q1-3, -21 to +62%) in the total vessel population. However, the modification in SR induced by hyperemia was very different across Pd/Pa and FFR categories. As shown in Table 3 and Figure 3, in concordantly abnormal and normal vessels, SR was only slightly modified by hyperemia, as it only increased +6% (Q1-3, -15 to +23%) in A vessels and +17% (Q1-3, -22 to +79%) in D-vessels. In discordant vessels, however, the modification in SR with hyperemia was more substantial, as it increased +72% (Q1-3, +25 to +160%) in B-vessels, whilst it decreased -33% (Q1-3, -46 to -16%) in C-vessels. Consistency in this finding was observed in both Thermo and Doppler-vessels (Table 4 and Figure 3).

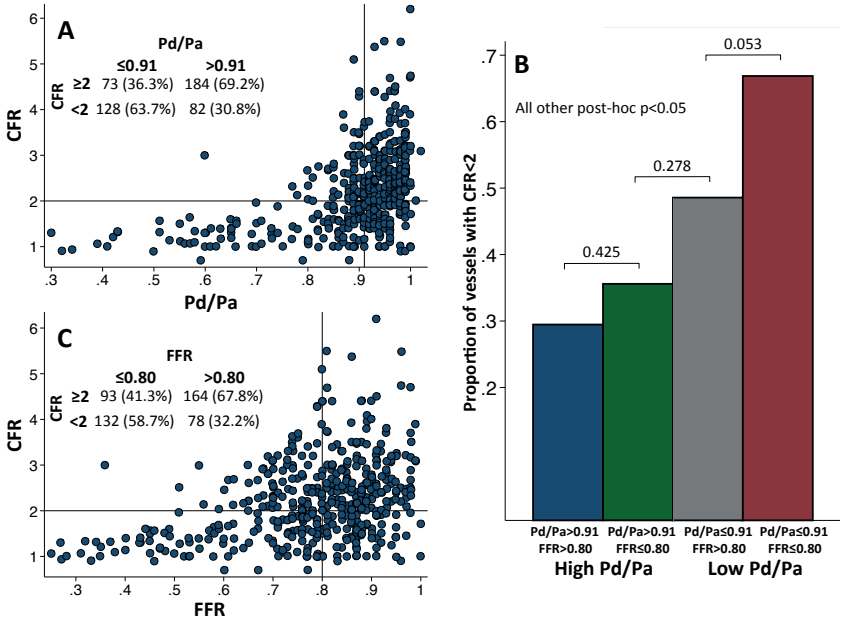

Figure 2 | Relationship of CFR with baseline Pd/Pa and FFR. Scatterplots showing the Pd/Pa (Panel A) and FFR (Panel C) relationships with CFR. Vertical lines are placed at Pd/Pa (0.91) and FFR (0.80) cut-offs, respectively, and horizontal lines at the CFR (2) cut-off. Panel B shows the proportion of vessels with exhausted flow reserve (CFR<2) across Pd/Pa and FFR categories.

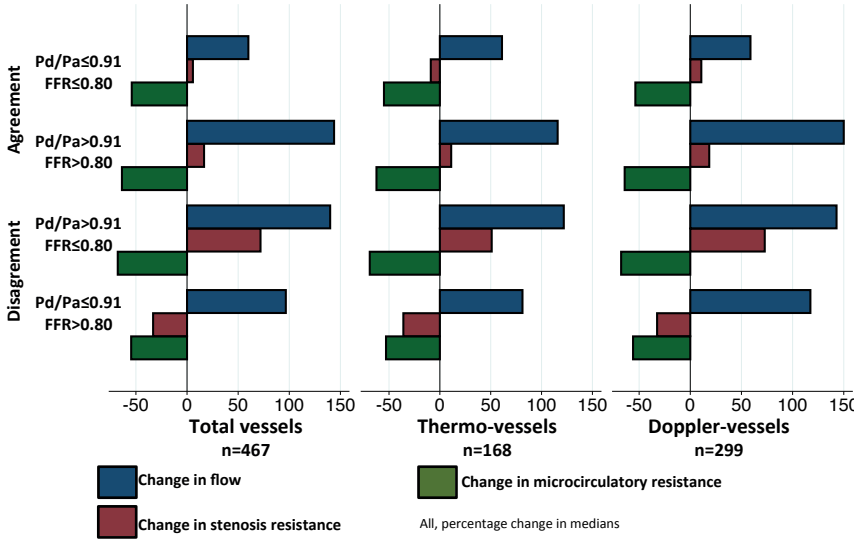

Figure 3 | Hyperemic modification in flow, stenosis resistance and microcirculatory resistance across Pd/Pa and FFR categories. Bar plots of median percentage-change from baseline to hyperemia, in flow, SR and MR across Pd/Pa and FFR categories. Overall and individual Thermo and Doppler findings are provided. Please not that this plot shows median percentage-change, and not baseline nor hyperaemic values. Such values are provided in Table 3.

Table 4 | Change in flow, stenosis resistance and microcirculatory resistance measurements across Pd/Pa and FFR categories

	Total	Both-abnormal (A)	Only-FFR-abnormal (B)	Only Pd/Pa-abnormal (C)	Both-normal (D)	P
		Pd/Pa≤0.91, FFR≤0.80	Pd/Pa>0.91, FFR≤0.80	Pd/Pa≤0.91, FFR>0.80	Pd/Pa>0.91, FFR>0.80	
	n=467	n=166	n=59	n=35	n=207	
Change in flow, %						
Overall	116 (54 to 172)	60 (25 to 120) [b,c,d]	140 (91 to 192) [a,,c]	97 (45 to 154) [a,b,d]	144 (95 to 201) [a,c]	<0.001
Doppler-vessels	122 (68 to 176)	59 (30 to 114) [b,c,d]	143 (97 to 192) [a]	117 (88 to 184) [a]	150 (115 to 200) [a]	<0.001
Thermodilution-vessels	88 (39 to 167)	61 (12 to 135)	121 (49 to 213)	81 (43 to 141)	115 (51 to 208)	0.018
Change in stenosis resistance, %						
Overall	11 (-21 to 62)	6 (-15 to 23)[a,b,c]	72 (25 to 160) [a,c,d]	-33 (-46 to-16) [a,b,d]	17 (-22 to 79)[a,b,c]	<0.001
Doppler-vessels	16 (-15 to 71)	11 (-9 to 25)[b,c]	723 (25 to 150) [a,c,d]	-33 (-45 to -13) [a,b,d]	19 (-22 to 83)[b,c]	<0.001
Thermodilution-vessels	-3 (-31 to 36)	-9 (-26 to 20)[a,b,c]	51 (28 to 200) [a,c,d]	-36 (-46 to -25) [a,b,d]	11 (-21 to 67) [a,b,c]	<0.001
Change in microcirculatory resistance, %						
Overall	-61 (-70 to 50)	-54 (-65 to -38)[b,d]	-68 (-77 to -59)[a,c,d]	-54 (-70 to -43)[b,d]	-64 (-71 to -54)[a,b,c]	<0.001
Doppler-vessels	-62 (-69 to 52)	-54 (-64 to -41)[b,d]	-68 (-75 to -59)[a,c]	-55 (-70 to -51)[b]	-64 (-70 to -58)[a]	<0.001
Thermodilution-vessels	-59 (-72 to -41)	-55 (-71 to -35)	-69 (-77 to -59)	-53 (-69 to -37)	-62 (-73 to -45)	0.166

Values are median (25th to 75th) percentage-change from baseline to hyperemia
[a]p<0.05 compared to A
[b]p<0.05 compared to B
[c]p<0.05 compared to C
[d]p<0.05 compared to D

Microcirculatory resistance across Pd/Pa and FFR categories

In the total population, hyperemia decreased MR a median of -61% (Q1-3, -70 to -50%) (Table 3). The reduction in MR was largest in B-vessels [-68% (Q1-3, -77 to -59%)] and smallest in A- [-54% (Q1-3, -65 to -38%)] and C-vessels [-54% (Q1-3, -70 to -43%)]. In Doppler-vessels, the minimum MR was not statistically different across the Pd/Pa and FFR categories, whilst in Thermo-vessels, an overall significant difference was observed, being lower and higher in B- and D-vessels, respectively (Table 2 and Figure 3).

DISCUSSION

Notwithstanding the limitations of considering a "true" baseline[8] and a "true" maximal hyperemic state,[10] in this work we explored the possibility of expanding with simplicity the physiological assessment of coronary stenosis by combining Pd/Pa with the standard FFR. This is important at a time where 1) randomized trials have moved optimal guidance of coronary revascularization from angiography to physiology,[1] and 2) emerging data supports the notion that hyperemia-free indices can accurately determine the ischemic potential of coronary stenosis in selected subsets.[2-4]

We observed that a baseline Pd/Pa value of 0.91 classified correctly the majority (80.7%) of the stenosis against that clinically adopted 0.80 FFR cut-off. Furthermore, we observed that Pd/Pa was more closely correlated with CFR than FFR, and that the Pd/Pa and FFR discordance was associated with the patients´ clinical profile, and characterized by contrastive changes in SR, MR and the underlying CFR. The combination of baseline Pd/Pa with FFR seems hence to provide a more comprehensive physiological examination of stenosed coronary arteries, and a closer pressure-based appraisal of the flow reserve of the downstream myocardial bed.

Combining baseline Pd/Pa with FFR in the assessment of coronary stenosis severity

From a broad perspective, intracoronary physiology has pursued standardized hyperemic stress to assess coronary stenosis severity, largely neglecting the information readily available during the baseline state. This rationale contrasts with that of all the other non-invasive tests aimed to detect electrical, contractile or perfusional manifestations of ischemia, in which hyperemic findings are always weighted against those observed during baseline. Nevertheless, interventionalists are accustomed to witness modifications of variable magnitude in the Pd/Pa ratio, from the time they cross the stenosis during baseline to the moment of achievement of hyperemia. For example, an FFR value of 0.70 may develop from a near-normal baseline Pd/Pa of 0.99, or from a frankly

abnormal Pd/Pa of 0.80. This Pd/Pa value, however, is conventionally not considered worthwhile —even though it is always readily accessible— and therefore all stenoses reaching the same FFR value are currently pondered alike. Our findings suggest that the physiological assessment of epicardial stenosis severity with the standard FFR is augmented by the simple incorporation of the baseline Pd/Pa, since the CFR underlying a low (≤0.80) or a high (>0.80) FFR value was largely dependent on the initial Pd/Pa value (Figure 4). We documented that most vessels with near-normal (>0.91) Pd/Pa values exhibited concomitant non-ischemic CFR values, even if a final FFR≤0.80 was achieved (Figure 5, panel A). Conversely, a significant percentage of vessels with abnormal (≤0.91) Pd/Pa exhibited moderately-to-highly exhausted CFR values, even if a final FFR>0.80 was only achieved (Figure 5, panel A). Therefore, the combination of baseline Pd/Pa with FFR seems physiologically incremental and practically appealing. In the same line,

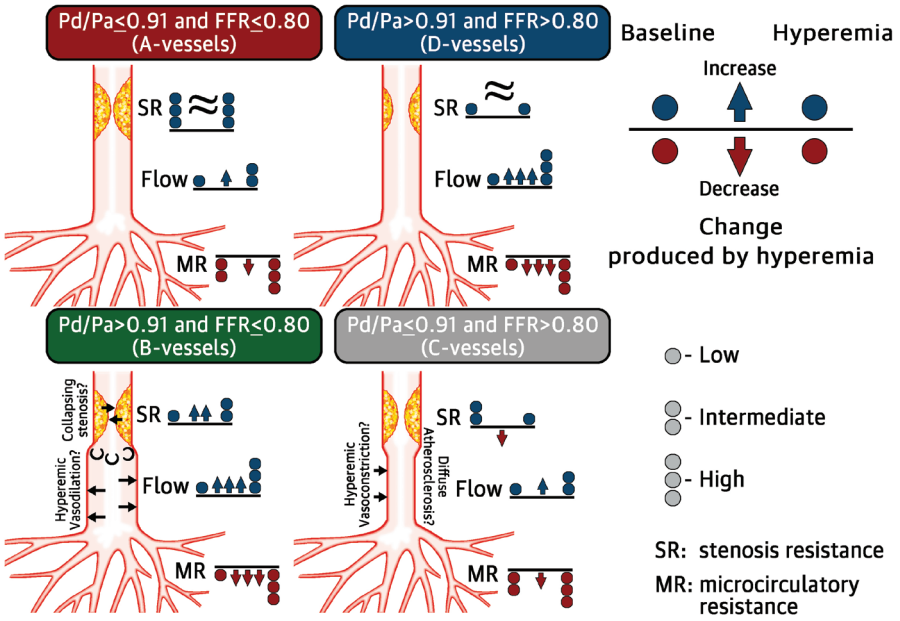

Figure 4 | Schematic representation of hemodynamic patterns derived from the Pd/Pa and FFR relationship. This figure summarizes the observed values of SR, the increase in flow and the drop in MR during baseline and hyperemia across the Pd/Pa and FFR categories. The red panel show vessels with Pd/Pa≤0.91 and FFR<0.80 (A-vessels). The increase in flow was lowest; SR highest, and the drop in MR relatively low. SR was only slightly modified by hyperemia. The blue panel shows vessels with Pd/Pa>0.91 and FFR>0.80 (D-vessels). Herein, the rise in flow was highest; SR lowest, and the drop in MR high. SR was only slightly modified by hyperemia. The green panel shows vessels with Pd/Pa>0.91 and FFR≤0.80 (B-vessels). Here, the increase in flow was very high; SR low, and the drop in MR the highest. SR was significantly modified, increasing from low to intermediate values. Finally, the gray panel shows vessels with Pd/Pa≤0.91 and FFR>0.80 (C-vessels). Herein, the increase in flow was only moderate; SR intermediate at baseline, and the decrease in MR low. SR was significantly modified, decreasing from intermediate to low hyperemic values.

our findings substantiate the observed better correlation of the underlying CFR with baseline rather than hyperemic pressure-indices,[11] which provides further support to the clinical use of the baseline state. Finally and comparable to previous studies,[3,4] we observed that Pd/Pa and FFR dichotomously disagreed in approximately 20% of vessels. In the following paragraphs, these haemodynamic patterns are discussed in detail.

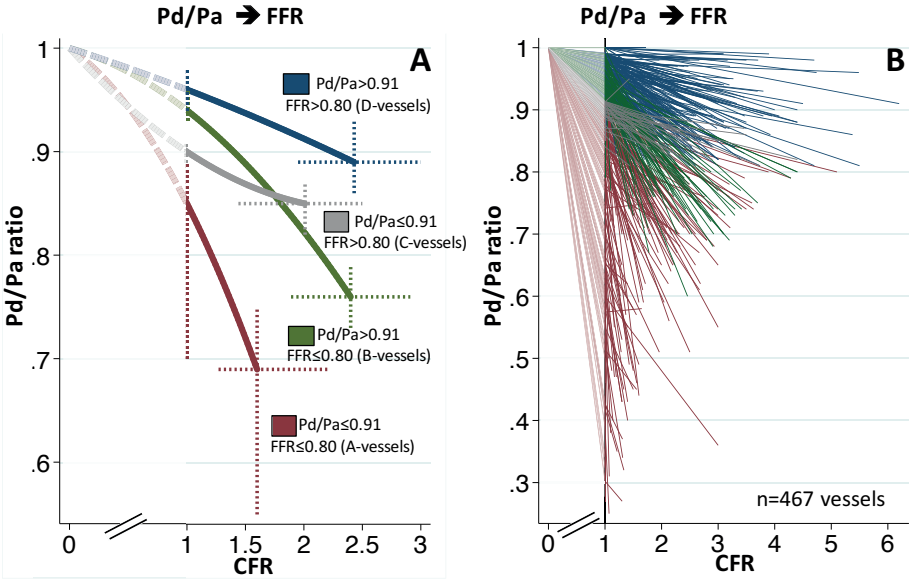

Figure 5 | Relationship of CFR with baseline Pd/Pa and FFR. These plots link individual Pd/Pa and FFR values with their underlying CFR. In panel B all vessels are shown. Colors are those of the Pd/Pa and FFR categories shown in the legend. Please note this is only a schematic representation, as the transition from Pd/Pa to FFR is not linear. Panel A is a summary. Solid lines were fitted using a linear + quadratic fit through the median values of Pd/Pa and the median values of FFR observed in each category. Distance in x-axis is median CFR of each category. All dashed lines represent interquartiles ranges.

Vessels with baseline Pd/Pa>0.91 and FFR≤0.80

Stenosed coronary arteries exhibiting mild pressure drops at baseline (Pd/Pa>0.91) that significantly worsened (FFR≤0.80) during hyperemia represented 12.6% of the total population and most (62.8%) of the Pd/Pa and FFR disagreement. Physiologically, this pattern was characterized by low baseline SR that significantly increased during hyperemia (+73%) achieving final intermediate magnitudes, large increases in flow (+140%) and the largest drops (-68%) in MR. Since pressure loss due to friction predominates during baseline and pressure loss due to separation predominates during hyperemia,[12] it seems reasonable to speculate that in this type of vessels, friction energy losses are small whilst separation energy losses are more substantial. Although

the mechanisms leading to the observed large hyperemic rise in SR in this vessels´ subgroup are unclear, it seems plausible to suggest that this stenosis are prone to separation losses, either do to their fixed anatomical component or to hyperemic changes in their functional geometry,[13] such as its partial collapsing as described by Brown[13] and Siebes[14] ("dynamic stenosis") or hyperemic vasodilation at the exit throat ("D" losses) as proposed by Gould.[12] Importantly and in spite of achieving final FFR values ≤0.80, the increase in flow in these vessels was high, and did not statistically differed from that observed in the most normal (Pd/Pa>0.91 and FFR>0.80) D-vessels. This could be explained by the fact that SR only reached intermediate levels at hyperemia. Finally, the sizable drop in MR possibly indicates preserved autoregulation and microcirculatory function. Altogether, these findings help to justify why these hemodynamic pattern was more likely observed in younger subjects and in patients where hypertension was less likely, since hypertension[15] and increasing age[16] have been associated with a decrease in the hyperemic response. From a clinical point of view, our data suggests that the underlying CFR of most vessels with FFR≤0.80 values arising from near-normal Pd/Pa values will not be exhausted by the stenosis. Figure 6 shows in-depth analyses of this assumption, where B-vessels (Pd/Pa>0.91 and FFR≤0.80) were further examined according to more clinically meaningful CFR ischaemia thresholds.[1,17,18] Notably the same Figure illustrates how amongst all vessels with Pd/Pa≥0.96 (n=149, 31.9%), only 15 (10.1%) developed FFR≤0.80 (Figure 6), from which none had definite ischaemia, as defined by CFR≤1.74, and only 5 (3.4%) mild to moderate ischaemia, as defined by CFR>1.74 to <2.0.[1,17,18] Since substantial data supports the notion that the risk of future adverse events is low when the CFR is preserved[1,17,18] it seems reasonable to question if the small proportion of FFR≤0.80 vessels arising from Pd/Pa values ≥0.96 will receive significant benefit from revascularization.

Vessels with baseline Pd/Pa≤0.91 and FFR>0.80

Vessels exhibiting fairly important pressure drops at baseline (Pd/Pa≤0.91) that did not significantly worsened during hyperemia (FFR>0.80) were the scarcest (7.5%). Herein, the increase in flow was moderate (+97%), and the drop (-54%) in MR low. Since most of the energy loss during baseline is explained by viscous friction,[12] it can be hypothesized that in these vessels, the fairly important pressure loss at baseline and the absence of a significant worsening (FFR≤0.80) during hyperemia could suggest meaningful friction but small separation energy losses, findings compatible with predominant diffuse atherosclerosis.[1,12] The concomitantly small drop in MR could alternatively suggest microcirculatory dysfunction as cause of the moderately exhausted CFR.[19] Interestingly, in this hemodynamic pattern, SR was intermediate at baseline and was significantly reduced (-33%) to low levels in hyperemia. The reduction in SR from baseline to hyperemia is a poorly described phenomenon, suggested by Brown[13]

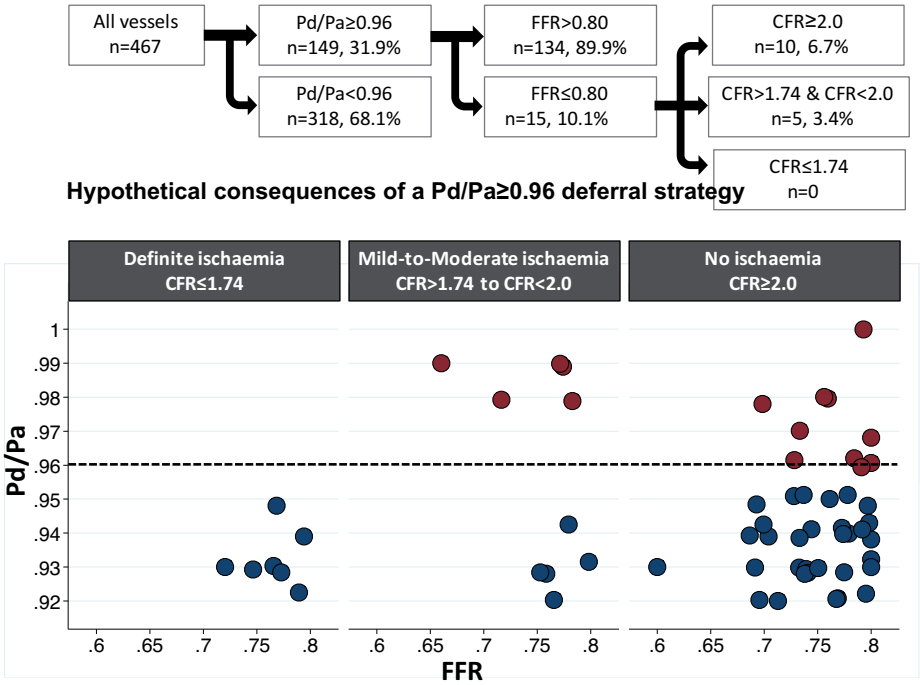

Figure 6 | Hypothetical consequences of a Pd/Pa≥0.96 deferral strategy. This figure shows B-vessels (stenosis with Pd/Pa>0.91 and FFR≤0.80) across more meaningful ranges of CFR impairment. Amongst all stenosis with Pd/Pa>0.91 that are candidates for revascularization according to FFR≤0.80, no stenosis with Pd/Pa≥0.96 (highlighted in red and above the horizontal dotted line) had CFR≤1.74, highly suggestive of definite ischaemia. Moreover, only 5 (3.4%) of the stenosis with FFR≤0.80 parting from Pd/Pa≥0.96 had a CFR suggestive of mild to moderate ischaemia (>1.74 and CFR<2.0). This high Pd/Pa values were not anecdotical, since across the whole study population (n=467), a significant proportion of vessels (n=149, 31.9%) had Pd/Pa≥0.96.

and appraised invasively in humans by Sambuceti and colleagues.[20] Although the mechanisms underlying this hyperemic decrease in SR are unclear, it seems plausible to suggest that diffuse atherosclerosis or less likely paradoxical hyperemic epicardial vasoconstriction (by modifying the functional geometry of the stenosis and decreasing separation losses at the exit throat) could lead to this condition.[21,22] Finally, almost half of these vessels (48.6%) presented an exhausted CFR. Since a diminished CFR conveys a significant risk for future adverse events,[1,18] it seems reasonable to question if this sub-group of vessels might carry a worse prognosis in spite of an FFR value above 0.80.

LIMITATIONS

This study has several limitations. Firstly, Pd/Pa and FFR were used in a dichotomous fashion. Whilst this approach oversimplifies the continuum of risk, it also increases clinical applicability, and is currently advocated for FFR use. Secondly, different hyperemic routes and doses of adenosine were used, as well as methodologies to measure intracoronary flow. However, consistency in individual findings was noted between Doppler and Thermo vessels, which we believe strengthens the external validity and implications of our observations. Third, investigated stenoses were of intermediate angiographic severity, so the generalization of our findings to other ranges of disease is unclear. Fourth and most importantly, clinical inference remains speculative, particularly in the light of the well-documented clinical benefit of FFR guidance of coronary revascularization as compared to angiography. Finally and even if initial invasive data is encouraging,[7] it should be acknowledged that most of CFR prognostic information comes from non-invasive studies.[1,18] Hence, caution should be urged when translating the powerful risk stratification of CFR to the invasive sphere. The DEFINE-FLOW study (Combined Pressure and Flow Measurements to Guide Treatment of Coronary Stenoses) (Clinical trials identifier: NCT02328820) is currently evaluating the safety of PCI deferral in vessels with low-FFR but preserved CFR, and will shed further lights on the topic.

CONCLUSIONS

In this work we sough to understand the physiological basis of baseline Pd/Pa and FFR agreement and discordance with combined pressure and flow measurements. Although Pd/Pa and FFR were closely correlated, discordance was observed in 19.3% of vessels. Such discordance was associated with the patient´s clinical profile and characterized by contrastive changes in SR, MR and the underlying CFR. All stenosis with Pd/Pa≤0.83 (n=74, 15.8%) progressed to FFR≤0.80, and although no Pd/Pa cut-off was able to exclude the development of an FFR≤0.80 in the high end of values, only 15 (10.1%) vessels with Pd/Pa≥0.96 (n=149, 31.9%) developed FFR≤0.80, from which none had definite ischaemia, as defined by CFR≤1.74. Combining baseline Pd/Pa with FFR seems thus to provide a more comprehensive physiological examination of stenosed coronary arteries.

What's known?

Baseline Pd/Pa is always accessible before FFR assessment, and emerging data supports the notion that baseline indices can determine the ischemic potential of coronary stenosis in selected subsets.

What's new?

Discordance between baseline Pd/Pa and FFR is associated with the patients´ clinical profile, and characterized by contrastive changes in stenosis resistance, microcirculatory resistance and the coronary flow reserve (CFR). The CFR underlying a low or a high FFR is largely dependent on the initial Pd/Pa value. Combining baseline Pd/Pa with FFR seems hence to provide a more comprehensive physiological examination of stenosed coronary arteries.

What's next?

Future studies should focus now on the role of baseline physiology indices in the clinical decision-making process.

SUPPLEMENTAL MATERIAL

In this study, different hyperemic routes and doses of adenosine were used, as well as methodologies to measure intracoronary flow. Individual Thermodilution and Doppler findings are provided in Tables 3 and 4 of the main manuscript and in Figure 3. This Supplemental figure illustrates the Pd/Pa and FFR relationship observed individually in Thermodilution and Doppler vessels, and provides statistical comparisons.

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The Pd/Pa and FFR relationship was similar between Thermodilution and Doppler-vessels:

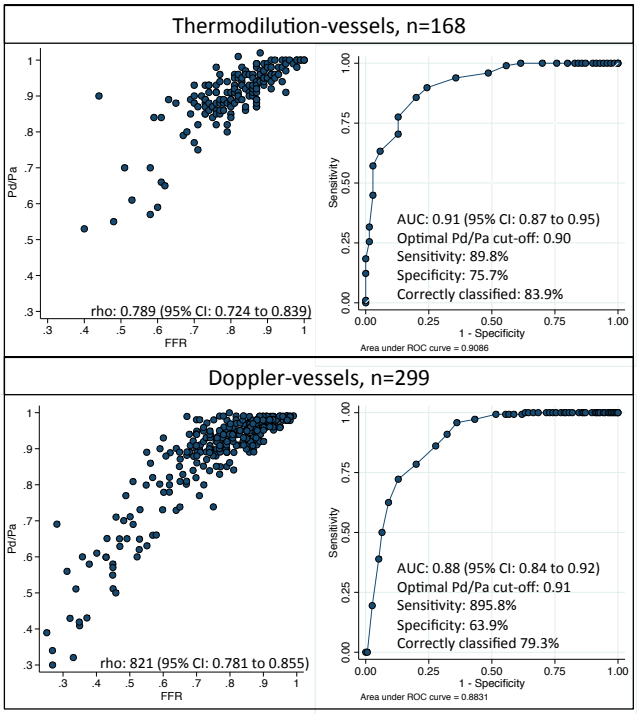
Difference between:

- Spearman (rho) correlations:

  0.033 (95% CI: -0.097 to 0.276)
  p=0.337

- Area under the receiver operating curves:

  0.02 (95% CI: -0.01 to 0.02)
  p=0.389



Supplemental Figure | Pd/Pa and FFR relationship observed individually in Thermodilution and Doppler vessels.

CHAPTER 7

Appropriateness of intermediate left main stenosis revascularization deferral based on fractional flow reserve and intravascular ultrasound: a systematic review and meta-regression including 908 deferred left main stenosis from 12 studies

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Submitted

ABSTRACT

Background

Assessment of stenosis severity in the left main (LM) location is frequently performed using either FFR and IVUS with some advantages and limitations pertinent to each technique. Even though current guidelines recommend IVUS and FFR as decisions making tools in case of ambiguous stenosis, only studies with small populations have been performed. Thus, we conducted a comprehensive systematic review and meta-regression to critically appraise, separately, the long-term safety and efficacy of FFR and IVUS guided strategy in deferring intermediate LM stenosis

Material

MEDLINE/PubMed was systematically screened for studies reporting on deferred treatment of an angiographically ambiguous LM based upon FFR or IVUS evaluation. Baseline, angiographic and outcome data exclusively from were appraised and pooled separately for each strategy (FFR or IVUS) according to random-effect models with inverse-variance weighting.

Results

A total of 908 LM stenosis from 12 studies in which revascularization was deferred on the grounds of FFR (8) or IVUS (5) were included. Median follow-up was 29.0 months 29.0 months (Q1-3, 25.1-32.0) for FFR studies and 31.5 months (Q1-3, 24.0-40.8) for IVUS studies. Adjusted per year follow-up occurrence of death, myocardial infarction, LM revascularization and composite MACE in the FFR deferred group (n=345) were 2.6% [0.7 – 4.5], 1.5% [-1.2 – 4.1], 2.0% [0.6 – 3.5] and 8.2% [5.3 – 11.0] respectively, while in the IVUS group (n= 563) the same endpoints were reached in 3.0% [1.6 – 4.4], 0.5% [-0.6 – 1.6], 2.2% [0.2 – 4.2] and 6.4% [3.1 – 9.7; all 95% confidence intervals] respectively. Meta-regression analysis suggests the influence of a distal LM stenosis on MACE in FFR group (β =0.06 [0.01 -0.11] p=0.01) and age in IVUS group (β =0.4 (0.15 – 0.66) p=0.001,). Multiple regression analysis in individual studies identified that diabetes mellitus (OR 4.40, 95% CI 1.17 - 16.42; p = 0.023) and the use of lower doses of intracoronary adenosine (OR 1.39 [1.02 -1.89]; 95% CI, p = 0.041) were independent predictors of MACE in FFR-deferred studies, while plaque burden at the MLA site (OR 1.34, 95% CI 1.03 – 1.73; p=0.025), number of other diseased vessels (OR 1.39 95% CI 1.01–1.90 p= 0.044), age (OR 1.05 95% CI 1.02–1.09 P=0.004), smoking habit (OR 2.42 95% CI 1.13–5.14 p =0.022), any untreated vessel with a stenosis more than 50% (OR 3.80; 95% CI 1.08–13.34 p =0.037) and diabetes mellitus (OR 6.32, 95% CI 1.82-22.04; p= 0.004) were independent predictors of MACE in IVUS-deferred studies.

Conclusions

Both strategy of deferring LM intermediate stenosis on the basis of FFR or IVUS showed an acceptable risk of Target Lesion Revascularization and MACE in a mid-term follow-up. However, data suggested specific effects of both anatomical and physiological variables to predict events.

INTRODUCTION

Adequate characterization of the haemodynamic relevance of stenoses located in the left main coronary artery (LM) is of critical prognostic importance. Without myocardial revascularization, the presence of significant LM stenosis is associated with high mortality rates.[1] Conversely, revascularization of a non-significant LM stenosis implies patient exposure to unnecessary risks.

The angiographic evaluation of LM stenosis severity is frequently difficult due to the anatomical location prone to vessel foreshortening and overlapping. To overcome these limitations, adjunctive invasive diagnostic tools such as intravascular ultrasound (IVUS) and fractional flow reserve (FFR) have shown to reliably expand angiographic appraisal. Notably, the last Expert Consensus statement of the Society of Cardiovascular Angiography and Interventions[1] clearly indicate as reasonable and feasible the use of both FFR and IVUS to access the severity of a LM intermediate stenosis establishing whenever or not proceed to the revascularization. Besides, current 2014 European guidelines on revascularization[2] indicates a class 1A for FFR in stable ischemic heart disease although without a specific recommendation in LM diseases patients. However, up to now no study has sought to compare the safety of revascularization deferral based on the grounds of these two techniques.

Therefore, our purpose was to perform a comprehensive systematic review and meta-regression of available studies in which FFR and IVUS were used to decide upon LM disease treatment deferral, to critically appraise, separately, their long-term safety and efficacy.

METHODS

The present research was elaborated according to current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment and recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE).[3,4] English language restriction was applied. Search strategy and protocol were published and available on web.[5]

Search strategy and study selection.

Pertinent articles were searched in Medline, Cochrane Library, Biomed Central and Google Scholar in keeping with established methods,[6] with Mesh strategy and with terms related to patients that underwent assessment of an angiographically ambiguous LM, using FFR or IVUS to determine the need for revascularization and in which revascularization deferral was decided on the technique: ((fractional AND flow AND reserve) OR (FFR) OR (pressure AND wire) OR pressure wire) OR ((IVUS) OR (Intravascular AND ultrasound) OR (ultrasound)) AND (left AND (stem OR main) OR (left main)) AND ((myocardial AND infarction) OR (revascularization OR bypass OR angioplasty) OR (death)) NOT (review[pt] OR editorial[pt] OR letter[pt]). Two independent reviewers (E.C. M.EP) first screened retrieved citations at the title and/or abstract level, with divergences resolved after consensus. If potentially pertinent, they were then appraised as complete reports according to the following explicit selection criteria. Inclusion criteria were: (i) an intermediate/ambiguous stenosis of the LM (ii) performing standard FFR or IVUS measurement (iii) revascularization deferral decision based on these techniques and (iv) long-term follow up results reported (iv) long term outcomes reported as death, myocardial infarction (MI), left main revascularization, any revascularization and the composite of Major Adverse Cardiac Events (MACE) defined as Death, MI and any revascularization. Exclusion criteria were (i) duplicate reporting (in which case the manuscript reporting the largest sample of patients was selected); (ii) studies reporting only single case reports or (iv) studies non-reporting follow-up of patients or (v) not reporting outcomes of interest. From pertinent studies, only data about patients in which revascularization was deferred on the grounds of FFR or IVUS were finally included in the analysis.

Data extraction

Two unblinded independent reviewers (E.C, FDA) abstracted the following data on pre-specified forms: authors, journal, and year of publication, location of the study group, baseline features, angiographic features, FFR and IVUS features, clinical presentation. End-points of interest were death, myocardial infarction (MI), target vessel revascularization of the LM.

Internal validity and quality appraisal

Unblinded independent reviewers (E.C FDA) evaluated quality of included studies on pre-specified forms. Modifying the MOOSE items to take into account the specific features of included studies, we separately abstracted and appraised study design, setting, data source, statistical methods for multivariable analysis as well as risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the

underlying risk of bias). Moreover we awarded overall credibility of studies included, to summarized previous features. Zero points were assigned for retrospective design and one center study, 1 for prospective arrangement and for a multicenter setting. Moreover 2 points were ascribed for low risk of bias, 1 for moderate risk and zero for high risk or unclear. If the sum of these scores was 10 a very high credibility was granted, if it was between 7 and 9 high, 4 and 6 moderate, 1 and 3 low, 0 very low.

Data analysis and synthesis

Continuous variables are reported as median and quartile 1 and 3 (Q1-3). Categorical variables are expressed as n/N (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals. Small study bias was appraised by graphical inspection of funnel plots. Standard hypothesis testing was set at the two-tailed 0.05 level. Independent predictors of MACE at the multivariate analysis were appraised separately from each study and reported as Odd Ratio (OR) and 95% confidence intervals (CI). ORs from studies reporting the same predictor were pooled together according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95%. Pooled analyses were made using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Meta-regression analyses were performed for baseline and peri-procedural features to appraise effect on MACE at follow-up using Comprehensive Meta-Analysis software (Biostat Software, New York, USA).

RESULTS

A total of 92 citations were first screened and appraised at abstract level. From these, 25 articles were selected, among which 13 were discarded, because they did not meet inclusion / exclusion criteria.[7-9] Finally, seven studies about FFR[20=26] and five about IVUS[27-31] were included in our review (Figure 1).

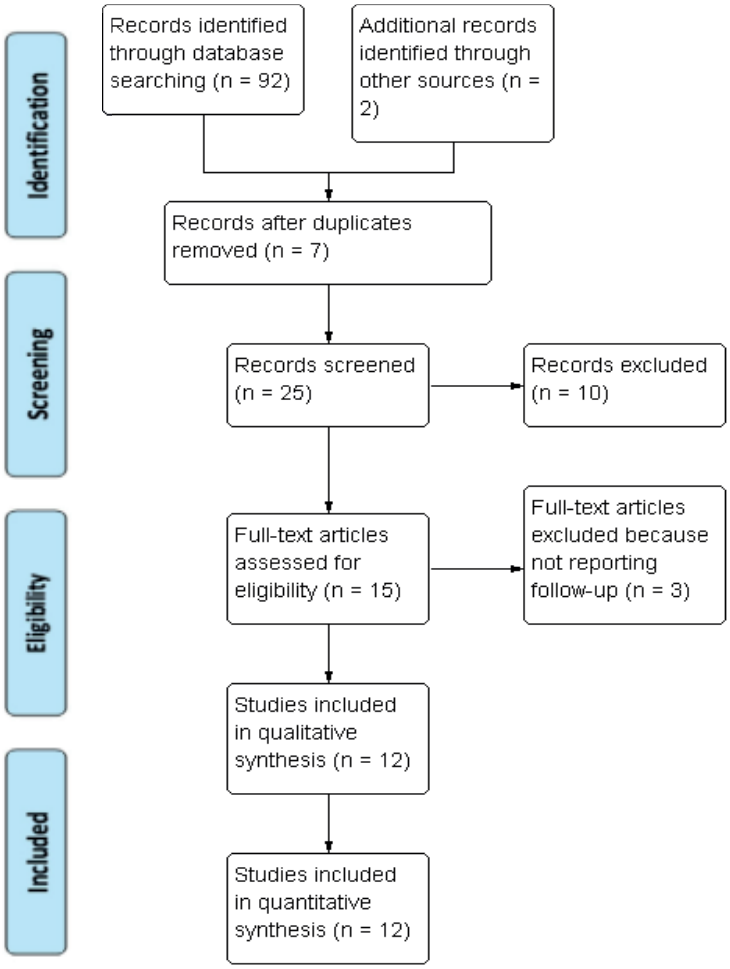


Figure 1 | Search strategy according to PRISMA criteria

The methodological and quality assessment was reported in the Supplementary Figure A (see Supplementary Appendix), showing an overall average quality of the selected studies. All were performed in Europe or North America, the most are prospective, single center, with acceptable risk of analyzed bias. For each study, definitions of the FFR and IVUS cut-offs used for deferral were recalled (Table 1 and 2). Overall, patient status was recorded at outpatient clinic examination or by telephone interview. Detailed information about outcomes and follow-up definition are reported un the Supplementary Table. In all studies follow-up angiography was performed only in case of recurrent of complaints. FFR cut-off was 0.75 in four of seven studies and 0.80 in the others three. Five out of seven studies used intravenous administration of adenosine (140 μg/kg per min for more than 2 min) though a femoral vein. Three IVUS studies[28-30] pre-specified the minimum lumen

Table 1 | Information about selected studies with FFR-deferred strategy. STEMI: ST-elevation myocardial Infarction; VD: Vessel Disease; AMI: Acute myocardial Infarction; CCS Canadian Cardiovascular Society grading scale for angina; LAD: Left Anterior Descending; LCA: Left Coronary Artery

First Author, year of publication	Journal	FFR-Deferred lesions included (n=345)	Design / Region	FFR cut-off	Adenosine administration	Clinical presentation	Follow-up modality	Follow-up duration (months ± SD)
Bech, 2001	Haart	24	Prospective, two centers / Europe	0.75	Femoral vein, infusion rate of 140 μg/kg per min for 2-4 min.	Allcomers to angiography	Clinical visits at least once a year. Angiographic follow in case of recurrent complaints or coronary events.	29±15
Courtis, 2009	Am J Cardiol	82	Prospective, single center / North America	<0.75 and >0.80	Intracoronary administration of adenosine at a dose ≥30 μg	Allcomers excluding: STEMI within 24h and other VD	clinical visits and/or phone contact.	14±12
Hamilos, 2009	Circulation	138	Prospective single center / Europe	0.8	Femoral vein, infusion rate of 140 μg/kg per min for more than 2 min.	Stable CCS I-IV	Clinical visits. Angiographic follow in case of recurrent complaints or coronary events.	35±25
Jasti, 2004	Circulation	37	Prospective, single center / North America	0.75	Intracoronary infusion of adenosine (42 to 56 μg),	Allcomers excluding: Recent AMI, 3VD, unstable angina	Serial telephone interview every 6 months and office visit every year. Angiographic follow clinically driven	38
Jimenez-Navarro, 2004	Invasive Cardiology	20	Prospective, single center / Europe	0.75	Femoral vein, infusion rate of 140 μg/kg per min for more during 2 min.	Allcomers excluding: AMI within 4 days, cardiogenic shock, 3VD	Clinical visits or telephone interviews	26±12
Legutko, 2005	Kardiol Pol	20	Prospective, single center / Europe	0.75	Femoral vein, infusion rate of 140 μg/kg per min over 5 min	Stable setting excluding: other severe VD in LCA.	Clinical visits	24
Lindstaedt,2006	Am Heart J	24	Prospective, single center / Europe	<0.75 and >0.80	Femoral vein, infusion rate of 140 μg/kg per min for more during 1.5 min.	Allcomers excluding: AMI within 10 days, Severe VD both in LAD and Cx.	Telephone interviews	29±14

Table 2 | Information about selected studies with IVUS-deferred strategy

First Author, year of publication	Journal	IVUS-Deferred lesions included (n=563)	Design / Region	IVUS area cut-off (mm^2)	Clinical presentation	Follow-up duration (months ± SD)
De La Torre (LITRO), 2011	JACC	179	Multicenter, prospective / Europe	6	Allcomers to angiography (47% ACS, excluding LM ulceration, dissection or thrombus)	24
De la Torre, 2007	Rev Esp Cardiol	48	Single-center, prospective / Europe	6	Allcomers to angiography (64% ACS, excluding ulceration, dissection, or thrombus)	40±17
Fassa, 2005	JACC	114	Retrospective / North America	7.5	Allcomers to angiography (25% ACS)	43.2
Okabe, 2008	J. invasive cardiol	100	Single center, prospective (only deferred lesion) / North America	Clinicians decision	Allcomers to angiography	31.5±17
Abizaid, 1999	JACC	122	Single center, prospective / North America	Clinicians decision	Allcomers to angiography (46% ACS)	11.7

area cut-off to defer the treatment (6 mm2 in two studies, 7.5mm2 in one) whilst in the remaining two the decision was taken by the operator. In these 2 studies, mean MLA in the treatment deferred group was 10.4 mm2[31] and 9.3 mm2.[27] Notably, almost all FFR studies excluded patients with acute coronary syndrome at presentation while IVUS studies allowed unstable patients (ranging from 25% to 64% of cases) although presence of LM ulceration, dissection or thrombus were an exclusion criteria in half of the included works.

A total of 908 LM stenosis in which revascularization was deferred on the grounds of FFR (345 patients) or IVUS (563 patients) were included. Baseline and peri-procedural characteristics are reported in table 3. Median age was similar (63.8 years [60.8 – 64.8] in FFR and 63.4 [63.0 – 64.5] in IVUS studies) and most patients were male. Prevalence of diabetics was similar (median 22.5% [20.0 – 25.8] vs. 24.5% [22.5 – 28.5] in FFR and IVUS group respectively) while smokers were more prevalent in FFR group (median 44.0% [32.5 – 48.8] vs 24.0% [21.2 – 24.6] in IVUS group) and familiar history for coronary artery disease was almost 2-fold in IVUS group (median 17.0% [13.0 – 28.5] vs. 30.8% [22.4 – 39.2]). Notably, the angiographic characteristics of the included LM stenoses were similar between both groups (Diameter of Stenosis = 45.0% [37.2 – 44.8] in IVUS vs.42.5% [44.1 – 46.5] in FFR) as well as distal LM involvement (51.0% [50.0 – 66.0]) vs. 51.0% [34.8 – 56.3] respectively). Concomitant presence of at least another vessel with stenosis (> 50%) was reported in about 60% of cases.

Table 3 | Baselines, angiographic and peri-procedural features.

	LM LESION FFR-DEFERRED (n=343, 7 studies)	**LM LESION IVUS-DEFERRED (n=563, 5 studies)**
Age (years)	63.8 (60.8 – 64.8)	63.4 (63.0 – 64.5)
Male gender	76.5 (75.0 – 79.5)	67.0 (62.0 – 86.6)
Hypertension	42.5 (33.7 – 51.5)	58.0 (50.9 – 60.0)
Smoker (former or current)	44.0 (32.5 – 48.8)	24.0 (21.2 – 24.6)
Diabetes Mellitus	22.5 (20.0 – 25.8)	24.5 (22.5 – 28.5)
Dislipidemia	53.9 (37.7 – 69.5)	48.3 (48.0 – 65.9)
Familiarity for CAD	17.0 (13.0 – 28.5)	30.8 (22.4 – 39.2)
Ejection Fraction	58.9 (58.2– 59.8)	53.0 (50.0– 56.6)
- MLD (mm)	2.24 (2.23 – 2.28)	1.92 (1.83 – 1.88)
- Stenosis (%)	42.0 (36.4 – 43.5)	45.0 (44.1 – 46.5)
IVUS MLA	-	9.3 (9.3 – 10.4)
FFR	0.88 (0.87 – 0.90)	-
Distal LM stenosis	51.0 (50.0 – 66.0)	51.0 (34.8 – 56.3)
Other than LM diseased vessels:		
-1 vessel disease	38.0 (32.0– 41.0)	37.0 (35.5– 52.1)
-2 vessels disease	24.0 (22.8– 28.1)	24.0 (18.0– 37.0)
-3 vessels disease	0 (0 – 8)	0 (0 – 11)

*values are median of percentages with 25th and 75th percentiles

The overall median follow-up was 29.0 months (Q1-3, 25.1 - 32.0) for FFR studies and 31.5 months (Q1-3 24.0 40.8) for IVUS studies. The per year of follow-up adjusted-occurrence of overall MACE were 8.2% [5.3 – 11.0] in the FFR group and 6.4% [3.1 – 9.7; all 95% confidence intervals] in the IVUS group. Death, myocardial infarction and LM revascularization were respectively 2.6% [0.7 – 4.5], 1.5% [-1.2 – 4.1], 2.0% [0.6 – 3.5] in the FFR group, and 3.0% [1.6 – 4.4], 0.5% [-0.6 – 1.6] and 2.2% [0.2 – 4.2]; all 95% confidence intervals] in the IVUS group (Figure 2 and 3). The crude events occurrence is reported in Table 4. Meta-regression analysis suggests the influence of a distal LM stenosis on MACE in FFR group (β =0.06 [0.01 -0.11] p=0.01) and of age in IVUS group (β =0.4 (0.15 – 0.66) p=0.001, Supplementary Figure B). No other cofactors influenced the outcomes Table 5. Multiple regression analysis in individual studies identified that diabetes type 2 (OR 4.40, 95% CI 1.17 - 16.42; p = 0.023) and the use of lower doses of intracoronary adenosine (OR 1.39 [1.02 -1.89]; 95% CI, p = 0.041) as independent predictors of MACE in FFR-deferred studies while plaque burden at the MLA site (OR 1.34, 95% CI 1.03 – 1.73; p=0.025), number of other vessels diseased excluding LM (OR 1.39 95% CI 1.01–1.90 p= 0.044), age (OR 1.05 95% CI 1.02–1.09 P=0.004), smoking habit (OR 2.42 95% CI 1.13–5.14 p =0.022), any untreated vessel with a stenosis more than 50% (OR 3.80; 95% CI 1.08–13.34 p =0.037) and diabetes mellitus (OR 6.32, 95% CI 1.82-22.04; p= 0.004) as independent predictors of MACE in IVUS-deferred studies (Figure 4).

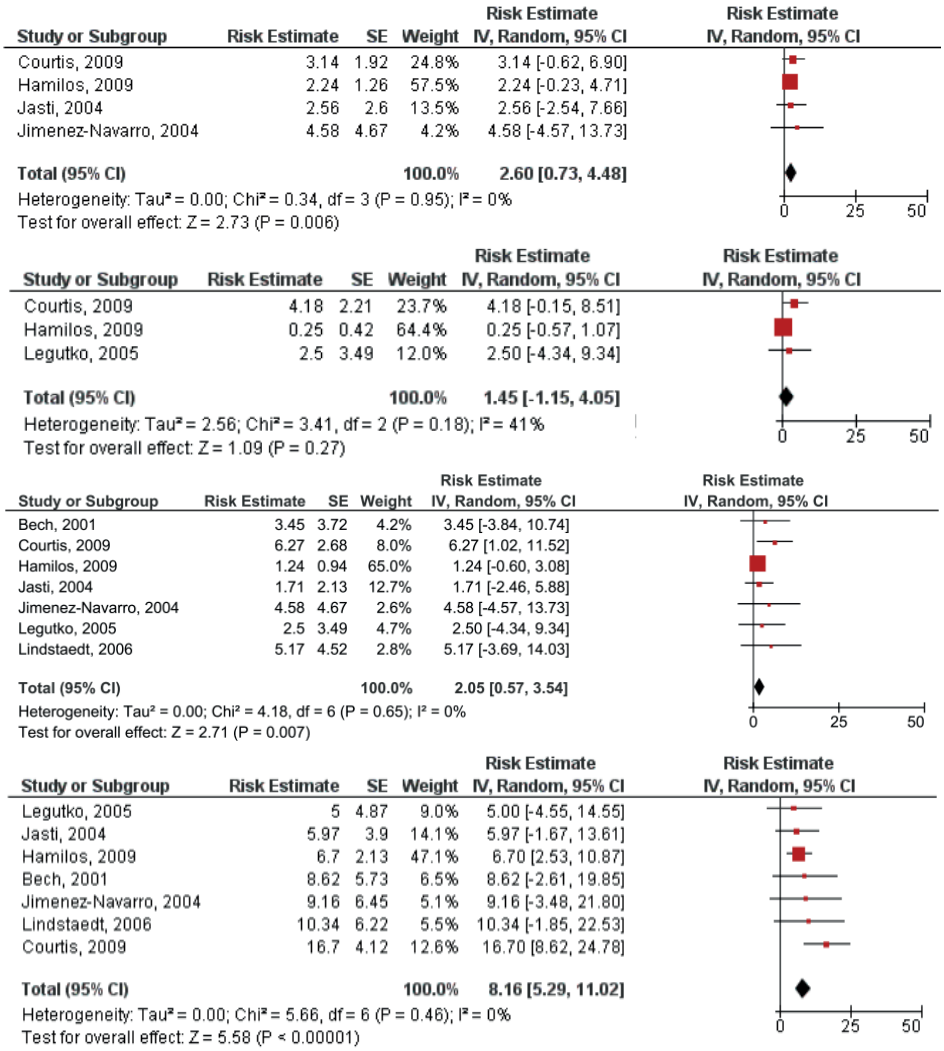


Figure 2 | FFR-deferred left main studies. Pooling of adjusted-per year events. A: Pooling of adjusted per year follow-up occurrence of death. B: Pooling of adjusted per year follow-up occurrence of Acute Myocardial Infarction. C: Pooling of adjusted per year follow-up occurrence of Target Lesion Revascularization. D: Pooling of adjusted per year follow-up occurrence of MACEs.

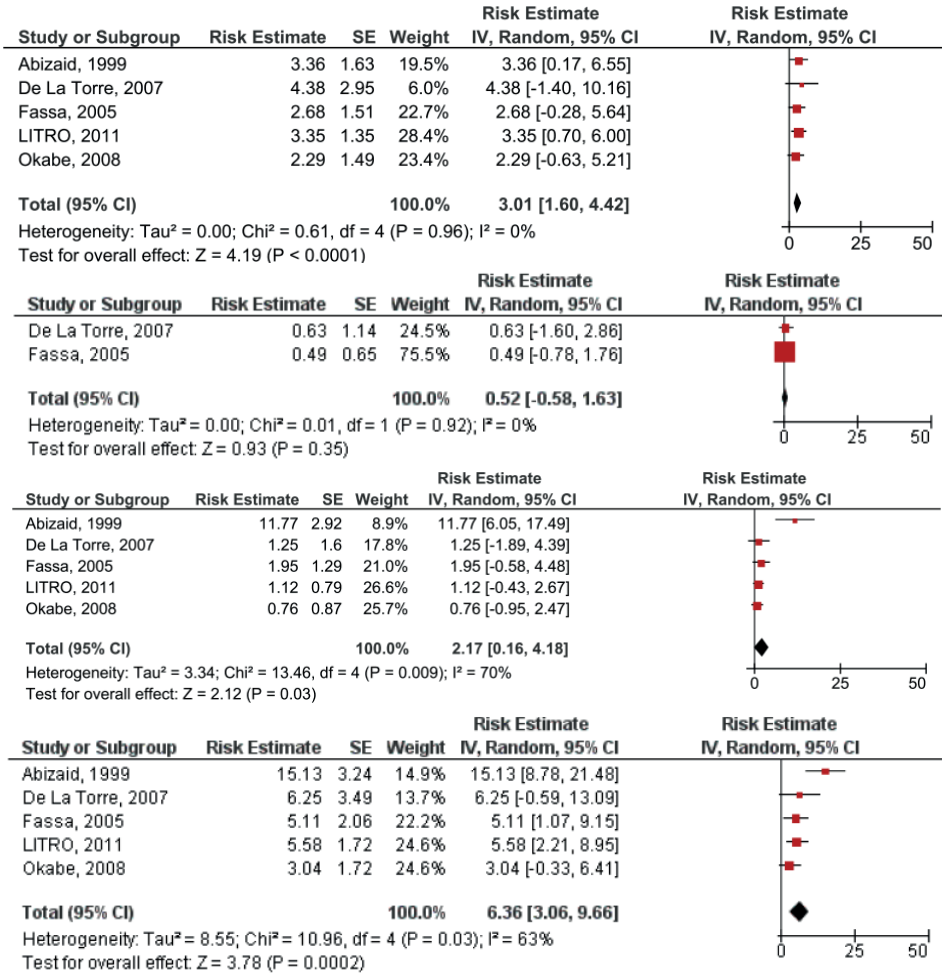


Figure 3 | IVUS-deferred left main studies. Pooling of adjusted-per year events. A: Pooling of adjusted per year follow-up occurrence of death. B: Pooling of adjusted per year follow-up occurrence of Acute Myocardial Infarction. C: Pooling of adjusted per year follow-up occurrence of target lesion revascularization. D: Pooling of adjusted per year follow-up occurrence of MACEs.

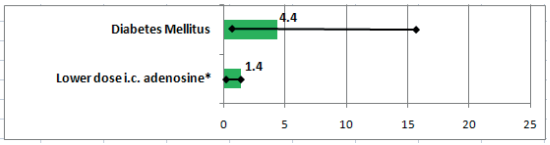
Table 4 | Crude events occurrences.

	LM LESION FFR-DEFERRED (n=345; 7 studies)	LM LESION IVUS-DEFERRED (n=563; 5 studies)
MACEs (Death, MI, any revascularization)	67 (19.4)	77 (13.6)
All-cause-death - Cardiac death	17 (4.9) 2 (0.6) – reported in 1 of 7 studies	40 (7.1) 12 (2.1) – reported in 3 of 5 studies
MI	6 (1.7)	3 (0.5)
LM Revascularization	21 (6.1)	30 (5.3)

*values are number and percentages MI: Myocardial Infarction

Table 5 | Metaregression (unrestricted maximum likelihood) between selected variables and overall MACEs in IVUS and FFR LM deferred-studies. Beta (β) is meta-regression coefficent, and p value (p) for interaction.

Moderator	IVUS studies		FFR studies	
	Slope(β)	p-value for interaction	Slope(β)	p-value for interaction
age	0.4	0.001	-0.10	0.22
Female sex	-0.007	0.75	-0.07	0.33
hypertension	0.01	0.59	-0.04	0.06
smoke habit	-0.06	0.48	0.01	0.61
dyslipidemia	0.0005	0.87	-0.04	0.13
diabete mellitus	-0.05	0.31	-0.01	0.54
MLD QCA	0.23	0.90	0.007	0.99
MLA IVUS	-0.35	0.15	-	-
multivessel disease	0.05	0.10	-0.004	0.79
Distal LM lesion	0.02	0.28	0.06	0.01



* for each decrease in 30 µg of intracoronary adenosine.

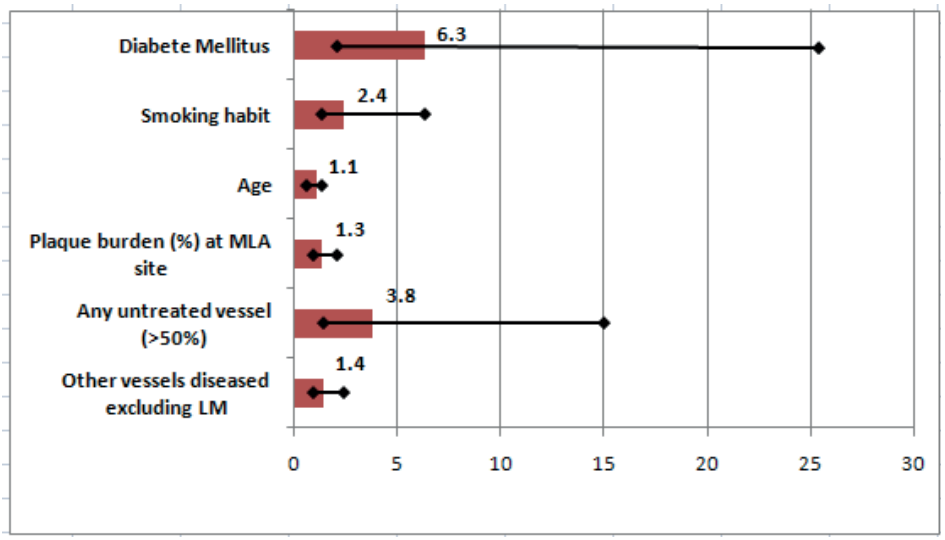


Figure 4 | Independent predictors of MACEs in FFR-guided (Panel A) and in IVUS-guided (Panel B) studies.

DISCUSSION

In this work, we performed a systematic review on the value of IVUS and FFR as decision making tool in LM intermediate stenosis. Up to now no direct data allows a full statistical comparison between these two techniques. Hereby, we aimed to lead the reader's attention to the best available evidence coming up from published studies.

The main finding is that deferral of LM treatment based on both intravascular techniques seem to be associated with a similar risk of MACE and LM revascularization at medium term follow up, although numerically, the rate of MACE for FFR deferral was higher than for IVUS deferral.

On the grounds of the different principles used by physiological (FFR) and anatomical (IVUS) interrogation, it can be expected that each technique will have both advantages and limitations.

Advantages and limitations of ambiguous LM disease deferral based on FFR

FFR relies in the assessment of the stenosis during maximal hyperaemia. This can be hampered by inadequate intracoronary administration of adenosine, particularly in ostial LM stenosis. As a matter of fact, one of the studies included[21] in our analysis identified low dosage of intracoronary adenosine as a determinant of long-term events, suggesting that perhaps false negative results regarding LM stenosis severity were obtained. This might constitute a warning for operators and an argument supporting the use of intravenous administration of adenosine for LM stenosis interrogation. This is the preferred route of administration of hyperemic agent because it allows time to pull the guide catheter out of the ostium. Additionally, another potential source of error is the engagement of the stenosis in the diseased LM as a consequence of suction caused by increased hyperaemic flow.

Interestingly, we reported at the meta-regression analysis a significant interaction between presence stenosis involving the distal segment of LM and events in FFR group. This angiographic feature as well as the presence of stenoses in the Left Anterior Descending (LAD) and Left Circumflex (LCX) has to be taken into account because may impact on the haemodynamic relevance of LM stenosis. It is interesting that four of seven FFR studies[20-22-24] included patients with LAD/LCX stenoses, reflecting real life in clinical practice. The influence of a distal stenosis on the FFR depends on the extent to which hyperemic flow across the LM stenosis will be decreased by the distal lesion.[32] To overcome this limitation it will be advisable to confirm pressure gradient across LM by checking FFR in both the LAD and LCX performing a pullback of the wire. Conversely, the implementation of this maneuver was not clearly defined in the selected studies. Nevertheless, in such scenario, many operators feel more reassured by using IVUS. The fact that the percentage of distal disease to the LM was similar in the FFR and IVUS study groups has to be kept in mind regarding the lower number of MACE in the IVUS group, meaning that distal disease might have led to more false negatives in the FFR group regarding LM stenosis relevance.

An obvious limitation of the present analysis is that the IVUS and FFR criteria used varied between some studies. It might be argued that the use of a 0.80 FFR cut-off might lead to a safer identification of non-significant LM stenosis (higher negative predictive value than the 0.75 FFR cut-off). Yet, event rate in the study by Hamilos et al.[22] (in which a 0.80 FFR cut-off was used) was not substantially different even pooling separately studies using 0.75 as FFR cut-off. (6.7% [2.5 – 10.9] vs 9.5% [5.5 – 13.4]; all 95% C.I.).

Advantages and limitations of ambiguous LM disease deferral based on IVUS

IVUS interrogation allows quantification of atheromatous plaque burden. It is important to remember that long-term outcome in patients with coronary atherosclerosis is influ-

enced by both ischemic burden and extent of atherosclerotic disease.[33,34] As a matter of fact in one of the studies included in the analysis IVUS-derived plaque burden at the LM stenosis was identified as a predictor of events in the long term. Additionally, presence of untreated vessel and diabetes mellitus were reported[27] as strong determinants of MACE. Of note, in this case MACE were largely driven by revascularization rates, undertaken at the discretion of the interventionist.

Interestingly, according to different MLA criteria used in the IVUS guided group, differences in cardiac events rate adjusted per year were not apparently registered (5.6% and 6.3% for MLA = 6 mm2 vs. 5.1% for MLA = 7.5 mm2). Previous studies tried to offer a conjunctive analysis of the relationship between anatomy of a diseased LM and physiology. Park et al.[16] investigated 112 patients with isolated LM stenoses (30% to 80% diameter stenosis severity) that underwent both IVUS and FFR before revascularization. LM MLA recorded by IVUS was an independent predictor of an FFR >0.80 (adjusted OR: 0.37, $p < 0.001$) and the optimal IVUS MLA cut-off for an FFR of ≤0.80 was 4.5 mm2 (77% sensitivity, 82% specificity). Similarly, lesion length on angiography was also found to be significantly in relation with FFR.[15] As such, the dynamic relationship between lesion length, MLA (by IVUS), and FFR remains still under investigation. It is likely that longer, diffuse lesions with larger IVUS-derived MLA might be ultimately found to harbor greater physiological significance than short, focal lesions with lesser MLAs.[36] The clinical implication of this relationship is still uncertain but suggest again a combined anatomical and physiological approach to provide a more extensive evaluation of an intermediate LM stenosis. Nevertheless, LM-MLA cut-off value seems to be population dependent and ethnicity related as we can suspect looking how different is the average LM-MLA in the study of Fassa et al.[30] performed in North America (7.6 mm2), compared to the study from Parj et al[16] performed in Korea (4.8 mm2) advocating extreme caution in the optimal cut-off value definition.[35]

LIMITATIONS

Our study has several limitations. Firstly, we are attempting to compare two different techniques and since that FFR and IVUS are such distinct, a direct comparison does not seem feasible. To overcome these limitations, we pooled separately data from IVUS and FFR studies. making indirect comparison in terms of crude event rate and adjusted per year event rate. The heterogeneity of the studies in terms of population and deferral criteria represents as well a source of bias limiting the applicability of our findings to all the population. Even if the methodology could be arguable, up to date we do not have definitive data coming from randomized trials. As the matter of fact, in the latest European Guidelines on myocardial revascularization IVUS indication for

the assessment of severity in LM stenosis received a poor grade of recommendation while FFR a class 1 indication in stable ischemic heart disease with lack of specific recommendation in LM diseases patients.

CONCLUSIONS

Both strategy of deferring LM intermediate stenosis on the basis of FFR or IVUS showed an acceptable risk of Target Lesion Revascularization and MACE in a mid-term follow-up. However, data suggested specific effects of both anatomical and physiological variables to predict events.

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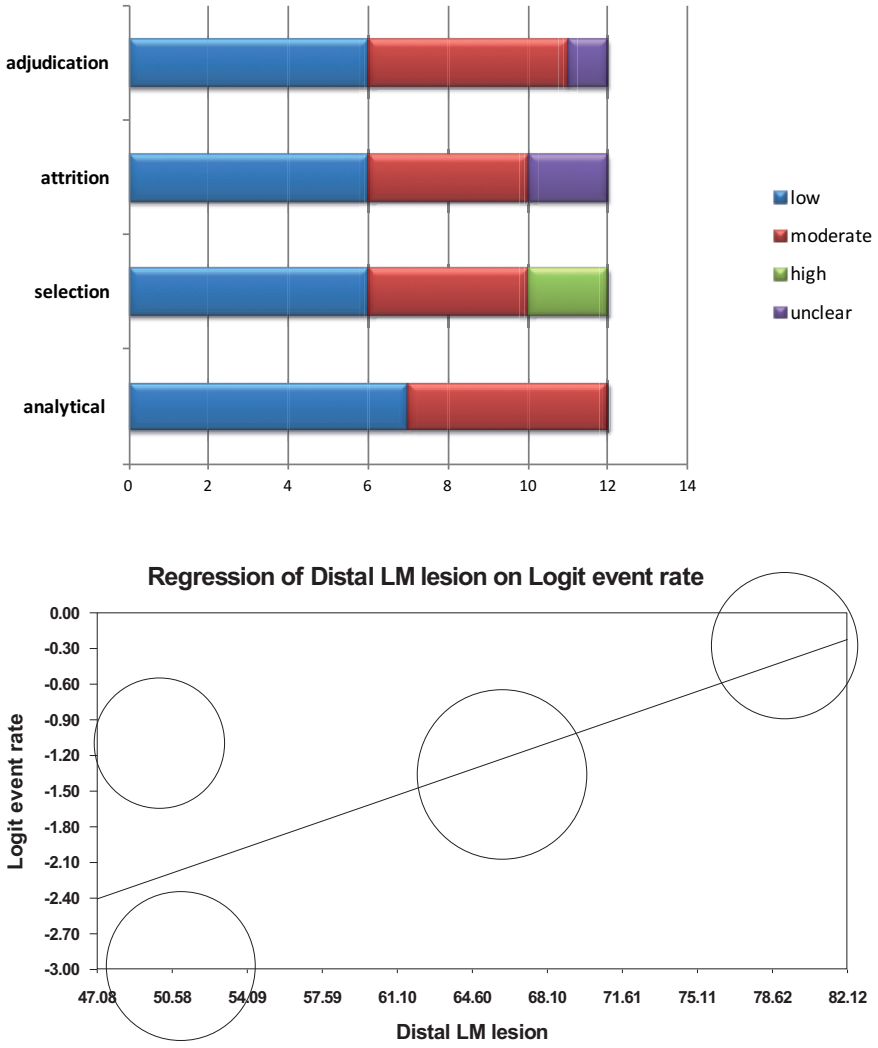

Supplementary Figure | Panel A: Methodological and quality assessment of included studies. Panel B: Meta-regression (unrestricted maximum likelihood) between LM distal stenosis and overall MACEs in FFR-deferred studies.

Supplementary Table | Addictional informations about study primary outcome and follow-up. MI: Myocardial Infarction; TVR: Target Vessel Revascularization; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery By-pass graft

First Author, year of publication	Modality	Study Outcomes	Follow-up modality	Completeness of Follow-up (%)
Bech, 2001	FFR	Death, MI, any revascularization, LM revascularization	Clinical visits at least once a year. Angiographic follow in case of recurrent complaints or coronary events.	100
Courtis, 2009	FFR	Death, MI, any revascularization, LM revascularization	clinical visits and/or phone contact.	100
Hamilos, 2009	FFR	Death, MI, any revascularization, LM revascularization	Clinical visits. Angiographic follow in case of recurrent complaints or coronary events.	98
Jasti, 2004	FFR	Death, MI, any revascularization, LM revascularization	Serial telephone interview every 6 months and office visit every year. Angiographic follow clinically driven	100
Jimenez-Navarro, 2004	FFR	Death, Cardiac Death, MI, any revascularization, LM revascularization	Clinical visits or telephone interviews	100
Legutko, 2005	FFR	Death, MI, any revascularization, LM revascularization	Clinical visits	100
Lindstaedt,2006	FFR	Death, MI, any revascularization, LM revascularization	Telephone interviews	100
De La Torre (LITRO), 2011	IVUS	Death, Cardiac Death MI, any revascularization, LM revascularization	Two and five-years follow-up were planned reviewing clinical reports or by telephone interview	100
De la Torre, 2007	IVUS	Death, Cardiac Death,MI, any revascularization, LM revascularization	planned reviewing clinical reports or by telephone interview	100
Fassa, 2005	IVUS	Death, MI and TVR (defined as a PCI of the LM or CABG to the left coronary system due to progression of the LM disease),	Hospital records	86.4
Okabe, 2008	IVUS	Death, MI, any revascularization, LM revascularization	Telephone contact	100
Abizaid, 1999	IVUS	Death, Cardia Death MI, any revascularization, LM revascularization	Serial telephone interviews 1, 3, 6 and 12 months from baseline	98

Part B

Systemic effects of adenosine and its impact on the physiological assessment of coronary stenosis

CHAPTER 8

Low coronary microcirculatory resistance associated with profound hypotension during intravenous adenosine infusion: implications for the functional assessment of coronary stenoses

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Circ Cardiovasc Interv. 2014 Feb;7(1):35-42

ABSTRACT

Background

Intravenous adenosine infusion (IV-adenosine) produces coronary and systemic vasodilatation generally leading to systemic hypotension. However, adenosine-induced hypotension during stable hyperemia is heterogeneous, and its relevance for coronary stenoses assessment with fractional flow reserve (FFR) remains largely unknown.

Methods and results

FFR, coronary flow reserve (CFR) and microcirculatory resistance (IMR) were measured in 93 stenosed arteries (79 patients). Clinical and intracoronary measurements were analyzed among tertiles of the percentage degree of adenosine-induced hypotension, defined as: %ΔPa= -[100 - (hyperemic aortic pressure x 100 /baseline aortic pressure)]. Overall, %ΔPa was -13.6 ± 12.0%. Body mass index was associated with %ΔPa (r=0.258, p=0.025) and obesity an independent predictor of profound adenosine-induced hypotension (tertile 3 of %ΔPa) [OR 3.95 (95% CI: 1.48, 10.54), p=0.006]. %ΔPa was associated with IMR (ρ = 0.311, p=0.002), CFR (r= -0.246, p=0.017) and marginally with FFR (r= 0.203, p=0.051). However, IMR (beta=0.003, p<0.001) and not %ΔPa (beta=-0.001, p=0.564) was a predictor of FFR. When compared with tertiles 1 and 2 of %ΔPa [n=62 (66.6%)], stenoses assessed during profound adenosine-induced hypotension [n=31 (33.3%)] had lower IMR [12.4 (8.6-22.7) vs 20 (15.8-35.5); p=0.001] and FFR values (0.77 ± 0.13 vs 0.83 ± 0.12, p=0.021) as well as a non-significant increase in CFR (2.5 ± 1.1 vs 2.2 ± 0.87, p=0.170).

Conclusions

The modification of systemic blood pressure during IV-adenosine infusion is related to the hyperemic microcirculatory resistance in the heart. Profound adenosine-induced hypotension is associated with obesity, lower coronary microcirculatory resistance, and lower FFR values.

INTRODUCTION

Central intravenous (IV) administration of adenosine at a constant rate is the recommended method to induce coronary hyperemia for fractional flow reserve (FFR) assessment because it enables a steady hyperemic state.[1] IV-adenosine produces vasodilatation in coronary and non-coronary vascular beds, which typically decreases mean blood pressure (BP) a -10% to -15% during stable hyperemia.[2] Nevertheless, observational[3, 4] and experimental studies[5-7] have observed a large inter-patient variability in the BP response to IV-adenosine, with most patients developing mild hypotension, while in others, BP profoundly decreases during stable hyperemia. The possible relevance of these varying BP responses to IV-adenosine for stenosis assessment with FFR, however, has been barely addressed in the literature. Accordingly, in the present study, we investigated the relationship between adenosine-induced hypotension and clinical and intracoronary physiological measurements, in an unselected series of patients with epicardial stenoses suitable for physiological interrogation, in which FFR, coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) were measured during their clinical evaluation in the catheterization laboratory.

METHODS

Study population

Patients with a clinical indication for FFR interrogation of 1 or more vessels showing an intermediate stenoses [40% to 70% diameter stenosis by quantitative coronary angiography (QCA)], investigated at Hospital Clinico San Carlos, Madrid, Spain, were prospectively studied. Culprit vessels of acute coronary syndromes, serial stenoses, marked diffuse narrowings, left main stenosis, surgical grafts, contraindications to adenosine and severe vessel tortuosity or calcification were excluded. Very distal narrowings, not amenable for revascularisation (vessel diameter <1 mm), were allowed. All patients gave informed consent, and Institutional Review Board approval was obtained according to current regulations.

Angiographic analysis

Angiographic views were obtained after administration of intracoronary nitrates (0.2 mg). Offline QCA analysis was performed in optimal projections using validated QCA software (CASS II, Pie Medical, Maastricht, the Netherlands). The filmed guide catheter filled with contrast medium was used as a calibrating device. Minimum lumen diameter, percent diameter stenosis, lesion length and reference lumen diameter were measured. Data were collected by two experienced reviewers blinded to physiological data.

Intracoronary physiological indices

Coronary guidewires equipped with sensors of pressure and temperature (St. Jude Medical, St. Paul, Minnesota) were used according to described methodologies.[8-11] FFR was calculated as the ratio of distal coronary pressure (Pd) to proximal coronary pressure (Pa) at stable hyperemia induced by IV-adenosine (140µg/kg/min through a central vein). Persistence of calibration was checked. CFR was measured simultaneously with FFR using the thermodilution method.[12] Resting and hyperemic thermodilution curves (in triplicate) were obtained, and CFR calculated as the ratio of mean transit time (Tmn_{bas}) divided by mean hyperemic transit time (Tmn_{hyp}). Because of its pressure dependency, CFR was corrected for changes in BP as described elsewhere.[13] IMR was calculated as the product of mean distal coronary pressure during stable hyperemia and $Tmn_{hyp.}$[10] In arteries with FFR<0.75, IMR was corrected for coronary wedge pressure using a proposed method.[14] Uncorrected IMR values are also provided. A meticulous technique was followed to avoid potential pitfalls affecting these indices.

Variations in mean aortic blood pressure produced by adenosine

Mean aortic (P_a) and distal (P_d) pressures were measured with the guiding catheter and the coronary guidewire at rest ($P_{a\text{-}bas}$ and $P_{d\text{-}bas}$) and during stable hyperemia ($P_{a\text{-}hyp}$ and $P_{d\text{-}hyp}$). The adenosine-induced absolute (ΔP_a) and percentage BP change ($\%\Delta P_a$) were calculated as: $\Delta Pa = -[P_{a\text{-}bas} - P_{a\text{-}hyp}]$ and $\%\Delta P_a = -[100 - (P_{a\text{-}hyp} \times 100 / P_{a\text{-}bas})]$.

Cut-offs values

FFR ≤0.80 (low-FFR) and CFR <2 (low-CFR) were used as threshold values.[1] The adenosine-induced hypotension was analyzed across tertiles of %ΔPa, and labeled as: mild-, moderate- and profound-hypotensive responses (1th, 2nd and 3th tertile, respectively). Based on the reported variability of IMR in patients with and without CAD, values of IMR ≥30 u were assumed abnormal (high-IMR).[15]

Statistical analysis

All continuous variables are presented as mean ± SD or median (interquartile range), according to their normal or non normal distribution. Categorical variables are presented as counts and percentages. Normality and homogeneity of the variances were tested using the Kolmogorov-Smirnov and Levene tests. Data were analyzed on a per-patient basis for clinical characteristics, and on a per-vessel basis for the rest of calculations. Patients with discrepancies in $\%\Delta P_a$ tertiles among interrogated vessels were excluded from per-patient analyses. For the purposes of analysis, vessels within the same patient were assumed to be independent. Continuous variables were compared with (independent or paired) t tests or Mann-Whitney U tests, as appropriate. Categorical variables were compared by the Fisher´s exact test. Differences in variables across decreasing

tertiles of $\%\Delta P_a$ were compared with one-way analysis of variance (ANOVA), Kruskal-Wallis or Fisher´s exact tests, followed by Tukey´s, Games-Howell or Fisher´s post hoc tests, as appropriate. After the inspection of the data, the combination of tertiles 1 and 2 was considered, as the 3rd tertile $\%\Delta P_a$ showed differences with respect to the others in terms of IMR and FFR values. Therefore, the former tertile was also compared with tertile 1 and 2 using t tests, Mann-Whitney U or Fisher´s exact tests, as appropriate. Tests of linear trend across decreasing tertiles of $\%\Delta P_a$ (polynomial contrasts for continuous and Mantel-Haenszel tests for categorical variables) were conducted. Correlation coefficients (Pearson´s r or Spearman´s ρ) between quantitative variables were also calculated. Multivariable linear regression analyses, including $\%\Delta P_a$ and microcirculatory resistance, were used to determine predictors of FFR. Binary logistic regression analysis in both, uni and multivariable models were used to identify clinical predictors of adenosine-induced hypotension. Models were constructed using the backward selection algorithm considering as the set of possible coviarates all variables with a p value <0.10. Differences were considered significant at $p<0.05$ (two-sided). The SPSS 20.0 (IBM Corp, Armonk, New York) statistical software package was used for all calculations.

RESULTS

Baseline characteristics

Clinical characteristics of the study population (93 arteries studied in 79 patients) are shown in Table 1. Overall, $P_{a\text{-}bas}$ was 90 ± 18 mmHg and fell to 78 ± 20 mmHg ($P_{a\text{-}hyp}$) during stable hyperemia ($p<0.001$). Thus, adenosine produced a decrease in BP (ΔP_a) of -12 ± 11 mmHg (min - max, +13 to -48 mmHg) that corresponded to a percentage fall ($\%\Delta P_a$) of -13.6 ± 12% (min - max, +13.3% to -45.7%) (figure 1). A tertile analysis according to $\%\Delta P_a$ is also shown in Table 1. Values of -6.7% and -17.2% defined the $\%\Delta P_a$ tertiles. Body mass index (BMI) was associated with $\%\Delta P_a$ ($r=-0.236$; $p=0.037$), and a statistical trend towards higher drops in BP ($\%\Delta P_a$) was observed in patients with obesity (BMI≥30 kg/m^2) (-16.9 ± 12.1% vs -11.4 ± 12%, $p=0.056$). When compared with tertiles 1 and 2 of $\%\Delta P_a$ (n=49), patients experiencing profound-hypotensive responses (tertile 3 of $\%\Delta P_a$) (n=25) were more likely to be diabetic (44% vs 18.4%, $p=0.021$) and obese (60% vs 28.6%, $p=0.009$). FInally and even though diabetes and dyslipidemia were statistically associated with profound-hypotensive responses in univariate analyses, obesity remained as its only independent predictor [OR 3.95 (95% CI: 1.48, 10.54), $p=0.006$]. Of note, the used adenosine dosage was not statistically associated with $\%\Delta P_a$ ($r=0.173$, $p=0.128$)

Table 1 | General characteristics of study population

Tertile analysis according to adenosine induced hypotensive responses (H)*					
	Total population n=79	Tertile 1 Mild-H %ΔPa >(-6.7%) n=24	Tertile 2 Moderate-H %ΔP= -6.7 to -17.2% n=24	Tertile 3 Profound-H %ΔPa <(-17.2%) n=25	p value (overall)
Age	65 ± 10	63 ± 11	64 ± 11	67 ± 10	0,421
Male	65 (82.3)	20 (83.3)	21 (87.5)	20 (80.0)	0,922
Body surface area, m^2	1.95 ± 0.18	1.94 ± 0.21	1.95 ± 0.13	1.99 ± 0.18	0,574
Body mass index, kg/m^2	28.9 ± 4.3	28.0 ± 3.6	28.9 ± 5.0	30.4 ± 4.2	0,151
Adenosine dose, mg/min	11.28 ± 1.72	11.05 ± 1.87	11.08 ± 1.44	11.65 ± 1.79	0,387
Cardiovascular risk factors.					
Hypertension	59 (74.7)	16 (66.7)	19 (79.2)	18 (72.0)	0,645
Diabetes	20 (25.3)	5 (20.8)	4 (16.7)	11 (44.0)	0,084[l]
Dyslipidemia	54 (68.4)	19 (79.2)	12 (50.0)	19 (76.0)	0,073
Obesity (BMI≥30 kg/m^2)	30 (38.0)	8 (33.3)	6 (25.0)	15 (60.0)[a]	0,033[l]
Smoker	22 (27.8)	9 (37.5)	8 (33.3)	5 (20.0)	0,411
Previous myocardial infarction	44 (55.7)	14 (58.3)	14 (58.3)	13 (52.0)	0,874
Multivessel disease	39 (49.4)	11 (45.8)	11 (45.8)	13 (52.0)	0,876
Clinical presentation.					
Stable angina	40 (50.6)	12 (50.0)	11 (45.8)	13 (52.0)	0,626
Post-myocardial infarction	25 (31.6)	6 (25.0)	11 (45.8)	7 (28.0)	
Unstable angina II B	11 (13.9)	4 (16.7)	2 (8.3)	4 (16.0)	
Unstable angina IIIB	3 (3.8)	2 (8.3)	-	1 (4.0)	

Values are mean ± S.D, median (25^{th}-75^{th}) or n (%).

*Six patients with discordant BP responses between vessels across tertiles of $\%\Delta P_a$ were excluded

II B: primary angina, at rest, within past month but not within preceding 48 hr; III B: primary angina, at rest, within preceding 48 hr.

[a] P<0.05 compared to tertile 1

[l] P<0.05 for linear trend

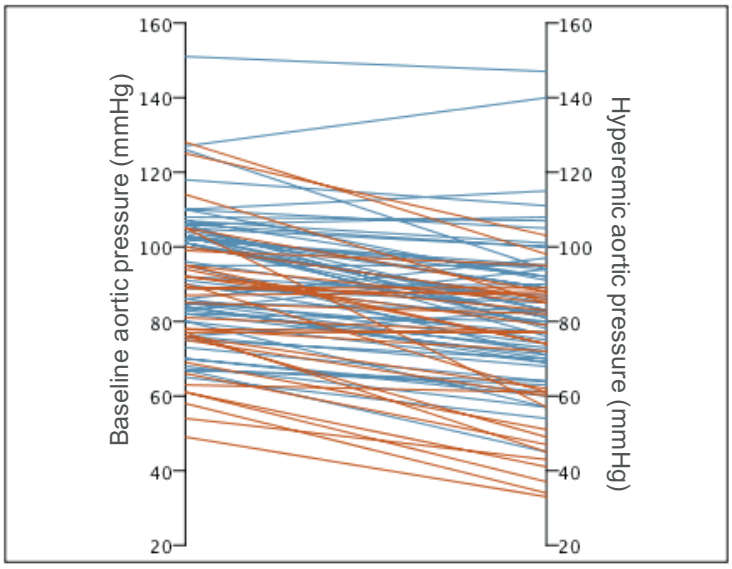

Figure 1 | Plot of mean aortic pressure at baseline and during stable hyperemia. Cases in red are those that developed the lowest tertile (<15 u) of IMR values.

Relationship between adenosine-induced hypotension and fractional flow reserve

Angiographic and physiological characteristics of studied vessels are found in Table 2. Neither QCA analyses, baseline pressures nor the hyperemic trans-stenotic pressure gradient ($P_{a\text{-}hyp}$-$P_{d\text{-}hyp}$) (r=0.086, p=0.412) were associated with $\%\Delta P_a$. Moreover, FFR was not statistically associated with $P_{a\text{-}bas}$ (r=-0.077, p=0.461) or $P_{a\text{-}hyp}$ (r=-0.159, p=0.127). However, a trend towards a significant association between FFR and $\%\Delta P_a$ (r= 0.203, p=0.051) was observed, suggesting a relationship between the degree of adenosine-induced hypotension and hyperemic-coronary hemodynamics. This association became stronger when stenoses assessed during profound-hypotensive responses (n=31) were compared with those in tertiles 1 and 2 of $\%\Delta P_a$ (n=62), since during the former, FFR values were significantly lower (0.77 ± 0.13 vs 0.83 ±0.12, p=0.021) and more likely to be below the ≤0.80 cut-off (61.3% vs 32.3%, p=0.008) (figure 2, panel A). Moreover, a trend in the prevalence of FFR values ≤0.80 across decreasing tertiles of $\%\Delta P_a$ was observed (p for trend=0.041), changing from 35.5% (OR=1) to 29.0% (OR=0.744 95% CI: 0.255 to 2.166) and 61.3% (OR 2.879, 95% CI: 1.026 to 8.074) from the first, to the second and third tertiles of $\%\Delta P_a$ respectively, without a significant deviation from linearity (p= 0.073) (Table 2). Finally, the $\%\Delta P_a$ observed during the assessment of stenoses with FFR ≤0.80 (n=39) was significantly higher than in those with FFR>0.80 (n=54) (-17.1 ± 11.9% vs -11.0 ± 11.6%, p=0.014).

Table 2 | General characteristics of epicardial stenoses included in study according to adenosine-induced hypotensive effect Tertile analysis according to adenosine induced hypotensive responses (H)*

	Total vessels **n=93**	**Tertile 1 Mild-H %ΔPa >(-6.7%) n=31**	**Tertile 2 Moderate-H %ΔP= -6.7 to -17.2% n=31**	**Tertile 3 Profound-H %ΔPa <(-17.2%) n=31**	**•p value (overall)**
Stenosis location.					
Left anterior descending artery	40 (43.0)	14 (45.2)	13 (41.9)	13 (41.9)	0,947
Circumflex	21 (22.6)	8 (25.8)	6 (19.4)	7 (22.6)	
Right coronary artery	32 (34.4)	9 (29)	12 (38.7)	11 (35.5)	
Quantitative coronary angiography.					
Reference diameter, mm	3.06 ± 0.64	3.05 ± 0.75	2.91 ± 0.59	2.80 ± 0.70	0,380
Minimal lumen diameter, mm	1.30 ± 0.43	1.26 ± 0.52	1.33 ± 0.35	1.30 ± 0.42	0,857
Diameter stenosis, %	48 ± 13	50 ± 13	47 ± 10	48 ± 12	0,693
Lesion length, mm	8.0 ± 3.7	8.1 ± 4.4	7.8 ± 2.9	7.1 ± 3.2	0,593
Physiological parameters.					
%ΔP, %	-13.6 ± 12.0	-0.9 ± 5.5[b]	-13.1 ± 2.8	-26.7 ± 7.8[a,b]	<0,001[l]
ΔP, mmHg	-12 ± 11	-1 ± 5[b]	-12 ± 3	-23 ± 7[a,b]	<0,001[l]
$P_{a\text{-}bas}$, mmHg	90 ± 18	93 ± 19	88 ± 13	89 ± 22	0,552
$P_{d\text{-}bas}$, mmHg	81 ± 18	84 ± 21	80 ± 13	78 ± 21	0,386
$P_{d\text{-}bas}/P_{a\text{-}bas}$, mmHg	0.91 (0.88-0.95)	0.93 (0.89-0.96)	0.91 (0.90-0.96)	0.90 (0.86-0.94)	0,350
$P_{a\text{-}hyp}$, mmHg	78 ± 20	92 ± 20[b]	77 ± 12	66 ± 20[a,b]	<0,001[l]
$P_{d\text{-}hyp}$, mmHg	64 ± 21	76 ± 22[b]	64 ± 12	51 ± 18[a,b]	<0,001[l]
$P_{a\text{-}hyp}$-$P_{d\text{-}hyp}$, mmHg	15 ± 10	16 ± 11	13 ± 9	15 ± 10	0,388
FFR	0.81 ± 0.12	0.82 ± 0.13	0.84 ± 0.10	0.77 ± 0.13	0,058
FFR ≤ 0.80	39 (41.9)	11 (35.5)	9 (29.0)	19 (61.3)[b]	0,033[l]
FFR < 0.75	22 (23.7)	6 (19.4)	3 (9.7)	13 (41.9)[b]	0,011[l]

Table 2 | General characteristics of epicardial stenoses included in study according to adenosine-induced hypotensive effect Tertile analysis according to adenosine induced hypotensive responses (H)* (continued)

	Total vessels **n=93**	**Tertile 1** **Mild-H** **%ΔPa >(-6.7%)** **n=31**	**Tertile 2** **Moderate-H** **%ΔP= -6.7 to -17.2%** **n=31**	**Tertile 3** **Profound-H** **%ΔPa <(-17.2%)** **n=31**	**•p value** **(overall)**
CFR	2 ± 0.80	2 ± 0.7	2.4 ± 1	2.5 ± 1.2	0,132
CFR < 2	42 (45.2)	16 (51.6)	14 (45.2)	12 (38.7)	0,635
Corrected IMR, U	18.0 (12.1-28.3)	19.0 (12.1-40.8)	20.4 (16.8-29.1)	12.7 (8.7-22.7) [a,b]	0,003
Uncorrected IMR , U	19.5 (12.7-30.3)	22.0 (16.0-42.0)	22.0 (16.0-29.0)	12.8 (10.0-23.0) [a,b]	0,002
Corrected IMR ≥ 30 u	21 (22.6)	12 (38.7)	7 (22.6)	2 (6.5)[a]	0,010[l]
Uncorrected IMR ≥ 30 u	23 (24.7)	12 (38.7)	7 (22.6)	4 (9.7)[a]	0,019[l]
Tmn_{bas}, seg	0.73 ± 0.49	0.76 ± 0.49	0.82 ± 0.52	0.60 ± 0.44	0,184
Tmn_{hyp}, seg	0.37 ± 0.21	0.38 ± 0.21	0.41 ± 0.26	0.32 ± 0.13	0,192

Values are mean ± S.D, median (25^{th}-75^{th}) or n(%).

$P_{a\text{-}bas}$: aortic pressure (baseline); $P_{a\text{-}hyp}$: aortic pressure (hyperemia); $P_{d\text{-}bas}$: distal pressure (baseline); $P_{d\text{-}hyp}$: distal pressure (hyperemia); FFR: fractional flow reserve; CFR: coronary flow reserve; IMR: index of microcirculatory resistance; Tmn_{bas}: basal mean transit time; Tmn_{hyp}: hyperemic mean transit time.

[a] P<0.05 compared to tertile 1

[b] P<0.05 compared to tertile 2

[l] P<0.05 for linear trend

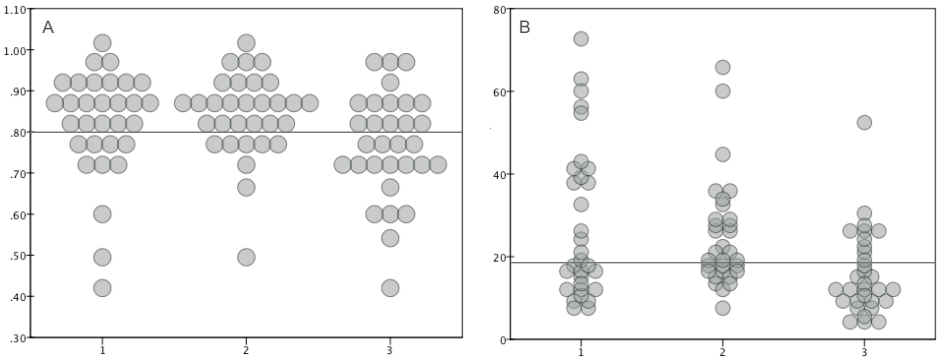

Figure 2 | Visual distribution of fractional flow reserve and microcirculatory resistance values across the tertiles of adenosine-induced hypotension.In Panel A, FFR values are explored across the tertiles of %ΔPa. It can be observed that during profound-hypotensive responses to IV-adenosine (tertile 3 of %ΔPa) FFR values tend to be lower. The horizontal line is placed at the cut-off value of 0.80. Panel B shows IMR values among tertiles of %ΔPa. It can be also observed that during profound-hypotensive responses to IV-adenosine (tertile 3 of %ΔPa) IMR values tend to be lower. The horizontal line is placed at the median value of IMR (18 U).

Relationship between adenosine-induced hypotension, microcirculatory resistance and coronary flow reserve

A significant association between IMR and $\%\Delta P_a$ (ρ= 0.311, p=0.002) was observed, suggesting a proportionality between the change in systemic arterial resistance and minimun microcirculatory resistance produced by adenosine infusion (figure 3). Moreover, stenoses assessed during profound-hypotensive responses, (n=31) (figure 2, panel B) had significantly lower IMR values than those assessed in tertiles 1 and 2 of $\%\Delta P_a$ (n=62) [12.7 (8.7-22.7) vs 20 (15.8-35.5); p=0.001]. A decreasing trend in the prevalence of high-IMR values (≥30 U) across tertiles of $\%\Delta P_a$ was also observed (p for trend=0.0025), decreasing from 38.7% (OR=1.0) to 22.6% [OR of 0.462 (95% CI: 0.152 to 1.401)] and 6.5% [OR 0.109 (95% CI: 0.022 to 0.543)] from the first, to the second and third tertiles of $\%\Delta P_a$, respectively, without a significant deviation from linearity (p=0.752). Of note, the $\%\Delta P_a$ observed during the assessment of stenoses with IMR ≥30 (n=21) was significantly lower than in those with IMR<30 (n=72) (-5.7 ± 9.8% vs -15.9 ± 11.7%; p<0.001). CFR was also associated with $\%\Delta P_a$ (r=-0.246, p=0.017), and although stenoses assessed during profound-hypotensive responses had higher values of CFR than those assessed in tertiles 1 and 2 of $\%\Delta P_a$ (2.5 ± 1.5 vs 2.2 ±0.9) statistical significance was not reached (p=0.170). However, the observed increase in CFR under profound hypotensive responses seemed to be clinically relevant, because during the latter, the prevalence of vessels with FFR ≤ 0.80 and CFR >2 was higher (35.5% vs 14.5% in tertiles 1 and 2 of $\%\Delta P_a$, p=0.031) [OR 3.24 (95% CI: 1.17, 8.99), p=0.023].

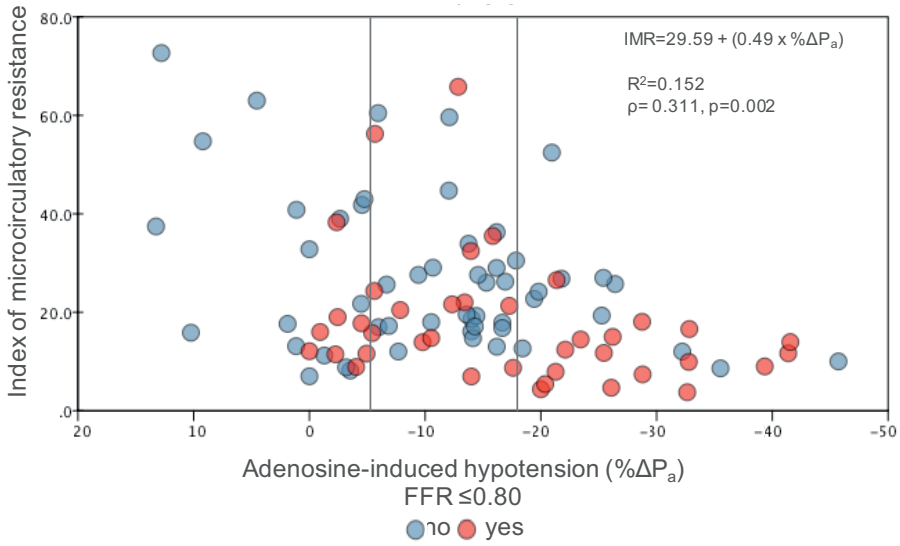

Figure 3 | Microcirculatory resistance values according to fractional flow reserve as distributed among the percentage degree of adenosine-induced hypotension. A significant association between coronary microcirculatory resistance (IMR) and the percentage fall in BP produced by adenosine (%ΔPa) was observed. Vertical lines are located at the %ΔPa tertiles. Please note that FFR values >0.80 are distributed towards higher values of IMR and %ΔPa and, conversely, FFR values ≤0.80 are distributed towards lower values of IMR and %ΔPa.

Integrating adenosine-induced hypotension, fractional flow reserve, microcirculatory resistance and coronary flow reserve

Since IMR and $\%\Delta P_a$ were significantly associated with FFR (at $p<0.10$), multivariable regressions models were performed. These analyses identified that IMR (beta=0.003, $p<0.001$) and not $\%\Delta P_a$ (beta=0.001, p=0.564) was independently associated with FFR. Finally, figure 4 summarizes the hemodynamic findings of the present study: whilst no significant differences were observed between stenoses assessed during mild and moderate adenosine-induced hypotensive responses, those stenoses assessed during profound adenosine-induced hypotension had significantly lower IMR and FFR values as well as a non-significant increase in CFR.

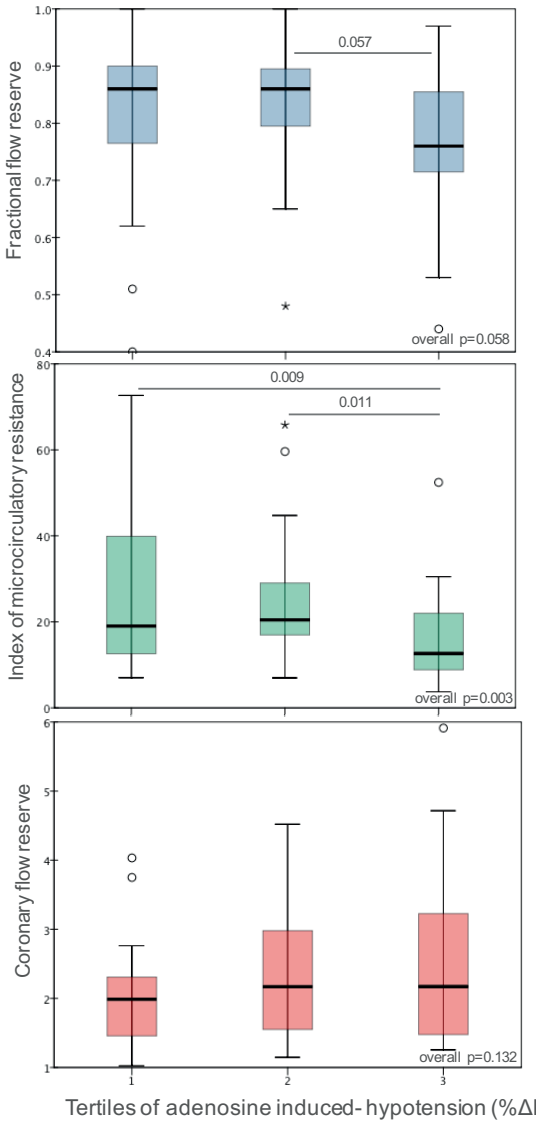

Figure 4 | Fractional flow reserve, microcirculatory resistance and coronary flow reserve as explored across the tertiles of adenosine-induced hypotension. Values of FFR, IMR and CFR across decreasing tertiles of %ΔPa. Only overall p values and post-hoc tests p values <0.10 are shown.

DISCUSSION

To our knowledge, this is first study that investigated differences in the functional assessment of coronary stenoses among different degrees of adenosine-induced hypotension. Our results suggest that such response is heterogeneous, and associated

with relevant differences in clinical and intracoronary physiological characteristics. We observed that adenosine-induced hypotension was associated with BMI, and more pronounced in obese subjects. We also observed a proportionality between the modification in systemic arterial and coronary microcirculatory resistance produced by IV-adenosine. Finally, the obtained FFR values were associated with microcirculatory resistance; with FFR and IMR being lower in those stenoses assessed during profound-hypotensive responses. In the following paragraphs, we discuss the potential clinical implications of our observations in the context of current knowledge of adenosine physiology.

Coronary and systemic effects of adenosine infusion

The most widely recommended coronary hyperemic agent is IV-adenosine because of its safety and ability to produce a steady hyperemic state. Physiologically, adenosine is an endogenous purine nucleoside that interacts with specific cell-surface receptors located on smooth muscle and endothelial cells. This receptors can be divided in four mayor subtypes: A_1, A_{2A}, A_{2B}, and A_3.[16,17] Adenosine-receptors are coupled to G proteins that modulate the activity of adenylate cyclase in different directions: A1 and A3 receptors are coupled to $G_i/G_o/G_q$ proteins that inhibit adenylate cyclase activity, while A_{2A} and A_{2B} receptors are coupled to G_s, that activate adenylate cyclase.[17-19] When activated, adenylate cyclase leads to the production and accumulation of cyclic adenosine 5´-monophosphate that activates protein Kinase A which ultimately produces smooth muscle cells hyperpolarization and relaxation, particularly through the activation of intermediate-conductance K_{Ca} channels.[20-22] Therefore, adenosine-induced peripheral and coronary dilatation is mainly mediated through the activation of A_{2A} and A_{2B} receptors. However, on the other side, it has been consistently observed that the inhibition of adenylate cyclase (mediated by the A_1 and A_3 receptors) leads to vasoconstriction.[20, 23-25] By being the natural agonist, adenosine is able to activate all four receptors (A_1, A_{2A}, A_{2B}, and A_3). Thus, by virtue of differential coupling to either G_s (A_{2A} and A_{2B}) or G_i proteins (A_1 and A_3), adenosine is capable to elicit both, dilatation (A_{2A}- and A_{2B}-mediated) and constriction (A_1- and A_3-mediated) in the peripheral and coronary vascular territories.

In the systemic circulation, IV-adenosine produces a dose-dependent decrease in vascular resistance that is normally paralleled by significant decreases in central venous and left ventricular end-diastolic pressures. Although a reflex sympathetic discharge is also produced (aimed to increase cardiac output) [5, 26, 27], in clinical practice, it is accepted that IV-adenosine decreases mean BP a -10 to -15% during FFR measurements.[2] Interestingly, however, heterogeneous responses in BP to IV-adenosine have been reported in observational[3, 28, 29] and experimental settings[5, 7, 27], ranging from hypertensive to profound-hypotensive. Notwithstanding, the possible clinical signifi-

cance of this heterogeneous BP response to IV-adenosine for FFR measurement has been barely addressed in previous research.

Profound adenosine-induced hypotension and its relationship with obesity

Profound hypotension secondary to adenosine infusion has been related to some pathologies and has been attributed to an inadequate increase in cardiac output due to sympathetic autonomic dysfunction.[30, 31] Interestingly, consistent evidence links obesity with sympathetic autonomic dysfunction, and hyperinsulinemia has been proposed as the underlying mechanism.[32] Hyperinsulinemia simultaneously increases sympathetic activity,[32] desensitizes the baroreflex,[33] increases cardiac output and induces peripheral vasodilatation,[30] Although this is partly the consequence of an expanded body mass, regional hemodynamic studies have observed that limb vascular resistances are either normal or decreased in normotensive obese individuals.[32, 34] Therefore, obesity has been considered a chronic high-output, low-resistance state.[34] Under such conditions, it seems reasonable to speculate that adenosine-induced hypotension could be increased. Another possible explanation for this observation comes from recent insights on adenosine physiology, since some pathological states have been associated with an heterogeneous impairment in adenosine-receptors subtypes.[35] Specifically, it has been proposed that in conditions where A_2 receptors-mediated responses are preserved but A_1 receptors-mediated responses impaired, an increase in adenosine-induced dilation can be produced, due to diminished A_1 constrictive effects.[20, 21, 36, 37] Obesity is one of these conditions. Indeed, A_1 receptor-agonists are less potent in obese animals, and the concentration of A_1 receptors is lower in adipocytes isolated from obese humans as compared to non-obese.[38, 39] Moreover, the decrease in these receptors, which is attributed to down-regulation, is negatively correlated with BMI.[38] Although the translation of these findings from the adipose to the vascular tissue is speculative, proportional changes in subtypes of adenosine-receptors among different human tissues have been observed,[40] providing biological plausability to this hypothesis. Taken all together, our observation is supported by available information that suggests that obesity might be related to profound-hypotensive responses to IV-adenosine either through an impaired sympathetic autonomic or possibly, through an impaired adenosine-A_1 receptor function.

Assessment of coronary stenoses during different degrees of adenosine-induced hypotension

Coronary hemodynamics are influenced by shifting systemic (aortic) and intraventricular pressures, and the coronary perfusion pressure is a result of the difference between diastolic P_a and left ventricular end-diastolic pressure. Challenging the proposal that FFR remains unaltered in shifting hemodynamic conditions,[8] Siebes et al observed in a

resistive model that for a given coronary stenosis, FFR increased with decreasing P_a or increasing microcirculatory resistance.[41] At a low driving pressure, such as that observed in our patients with profound-hypotensive responses, FFR should be higher if predominantly dependent on aortic pressure. For this reason, it might result paradoxical that in our work, stenoses interrogated during profound-hypotensive responses presented significantly lower FFR values. However, this can be explained by a novel observation in our work, namely that microcirculatory resistance significantly decreases as adenosine hypotensive effect becames larger (figure 3). From a hemodynamic point of view, these findings remain congruent with the work of Siebes et al, since these authors also observed resistive changes in the microcirculation as determinants of final FFR values with varying driving pressures.[41]

It remains uncertain if the marked fall in microcirculatory resistance in patients with profound-hypotensive responses to IV-adenosine obeys to an exacerbated response to adenosine -potentially triggered by impaired sympathetic autonomic and/or adenosine-A_1 receptor function- or a decrease in zero flow pressure as a result of decreased left ventricular end-diastolic pressure, that has been reported to influence FFR interrogation.[42,43] Neverthless, the potential contribution of this phenomenon to overestimation of coronary stenosis severity is supported by the obtained CFR measurements in our study, since the observed proportion of vessels with CFR values >2 despite FFR≤0.80 was significantly higher during profound-hypotensive responses. This is of particular relevance, since it has been proposed that patients in this quadrant of the FFR-CFR classification should not be treated on the grounds of documented preserved myocardial flow. Likewise, the fact that the number of perfusion defects was not larger in patients who developed profound hypotension during IV-adenosine in a previous myocardial perfusion imaging study[3] suggests that this phenomenon might selectively affect pressure-derive indices like FFR.

LIMITATIONS

Our study has several limitations. First, our relatively small sample size is a limitation when drawing conclusions and our findings should be interpreted as exploratory and hypothesis generating. Second, coronary collateral wedge pressure was not measured in our study. Although the inclusion of the latter pressure in the calculation of microcirculatory resistance is currently subject of important debate, it has been recently observed that if this pressure is not considered when microcirculatory resistance is calculated with the thermodilution method, IMR might be overestimated.[44] However, other authors that used Doppler velocity to measure coronary flow have observed that the incorporation of wedge pressure as an estimated contribution of collateral

blood flow does not substantially influence the assessment of coronary microcirculatory resistance when FFR >0.6.[45] Being aware of the current debate and to minimize a potential methodological error, we decided to correct IMR values when FFR<0.75 using the regression equation derived by Yong et al for this purpose.[14] However, a separate analysis of our dataset using uncorrected values of IMR (Table 2) revealed similar results to those reported in the manuscript, suggesting that this correction had little effects in our findings.

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CHAPTER 9

Fractional flow reserve and minimum Pd/Pa ratio during intravenous adenosine infusion: very similar but not always the same

Echavarria-Pinto M, Petraco R, van de Hoef TP, Gonzalo N, Nijjer S, Tarkin JM, Ibanez B, Sen S, Jimenez-Quevedo P, Nunez-Gil IJ, Nombela-Franco L, Alfonso F, Fernandez-Ortiz A, Macaya C, Piek JJ, Davies J, Escaned J

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ABSTRACT

Aims

Maximum and stable hyperaemia are critical prerequisites for accurate measurement of fractional flow reserve (FFR). In some patients in which hyperaemia is induced through a central vein (IV), however, the minimum distal coronary pressure to aortic pressure ratio (P_d/P_a ratio) develops before the stabilization of hyperaemia. Herein, we sought to describe the prevalence, magnitude and clinical implications of this phenomenon.

Methods and results

The FFR tracing archive of a single Institution was reviewed, and a total of 104 high-quality IV-FFR recordings from 90 patients were identified. Whenever the minimum P_d/P_a ratio was found before the onset of stable hyperaemia, a search for the lowest P_d/P_a ratio within the steady-state hyperaemic plateau was performed and labeled as FFR_{stable}. Whilst in most cases the minimum P_d/P_a ratio developed during stable hyperaemia, in 19 cases [prevalence of 18.3%, (95% CI: 12.0% to 26.8%)], this value was found before the stabilization of the hyperaemic state. In such cases, the minimum P_d/P_a ratio stabilized later at a higher level (0.77 ± 0.09 vs. 0.81 ± 0.08, $p<0.001$) (mean difference, 0.03 ± 0.02, range, 0.01 to 0.10). In terms of dichotomous classification of stenosis severity and if FFR_{stable} was used to decide upon revascularization, reclassification would have occurred in 3 (2.9%) cases, all presenting a minimum P_d/P_a ratio ≤0.80 with FFR_{stable} >0.80.

Conclusions

During IV-adenosine infusion, the minimum Pd/Pa ratio occurs before the stabilization of hyperaemia in a significant proportion of cases. While the overall difference between the minimum P_d/P_a ratio and its FFR_{stable} counterpart is small, reclassification of stenosis severity might occur, if choosing between the minimum or stable values of FFR within the same trace.

INTRODUCTION

Fractional flow reserve (FFR) was experimentally and clinically validated under conditions of maximum and stable hyperaemia.[1-3] It was convincingly shown that only under these circumstances, myocardial resistance is minimal and constant, and blood flow is proportional to driving pressure. In clinical practice, however, these important considerations were simplified, and FFR is generally defined as "the maximum achievable flow in the presence of a stenosis, divided by the maximum flow expected in the same distribution in the absence of a stenosis.[4] This definition, consequently, implies that maximum achievable flow [corresponding to the minimum distal coronary (P_d) to aortic pressure (P_a) ratio] develops consistently during stable hyperaemia.

Following the initiation of intravenous (IV) adenosine infusion, dedicated consoles identify the minimum trans-stenotic pressure ratio (P_d/P_a) found in the recording period as the FFR. In most cases, this value develops during the steady-state hyperaemic plateau, and therefore the maximum and stable conditions of FFR are both clearly and concurrently present (FFR_{stable}). In some patients, however, the minimum P_d/P_a ratio (corresponding to the maximum flow) develops before the stabilization of shifting haemodynamics, following the initiation of IV adenosine. This is, before the steady-state hyperaemic plateau is reached. In these circumstances, the maximum and stable conditions of FFR do not coincide in time. This frequently- occurring, yet poorly described phenomenon, has not been addressed in previous research, and its clinical consequences when deciding upon revascularization with FFR are unknown.

Consequently, in the present study, we sought to assess the prevalence, magnitude and clinical implications of this phenomenon; namely the development of a minimum P_d/P_a ratio before, and outside the steady-state hyperaemic plateau.

METHODS

Analysis of fractional flow reserve recordings

The FFR tracing and associated clinical database of a single Institution was reviewed. We chose to include only those FFR traces in which 1) hyperaemia was induced with adenosine through a central vein (140 mcgr/kg/min); 2) the recording started before initiation of adenosine infusion and 3) adenosine infusion was maintained for a minimum of two minutes or the steady-state hyperaemic plateau was clearly reached. Traces with artifacts that might affect the quality of the FFR recording, such as loss of P_a or P_d signals, catheter damping, contrast medium injections during recording, automatic calculation pitfalls (identification of FFR during cough, ectopic beats, P_a or P_d noise, etc.) or pressure drift were excluded. In the absence of a formal definition of

the steady-state hyperaemic plateau, we defined stable hyperaemia as the observed plateau in mean P_a after stabilization of changing haemodynamics, following the initiation of adenosine infusion. If a plateau was not clearly established, stable hyperaemia was defined as the period of the recording in which no further systematic fall in P_a was observed, following the initiation of adenosine infusion. Whenever the minimum P_d/P_a ratio was found before the onset of stable hyperaemia (Figure 1), a search for the lowest P_d/P_a ratio within the steady-state hyperaemic plateau was performed and labeled as FFR_{stable}.

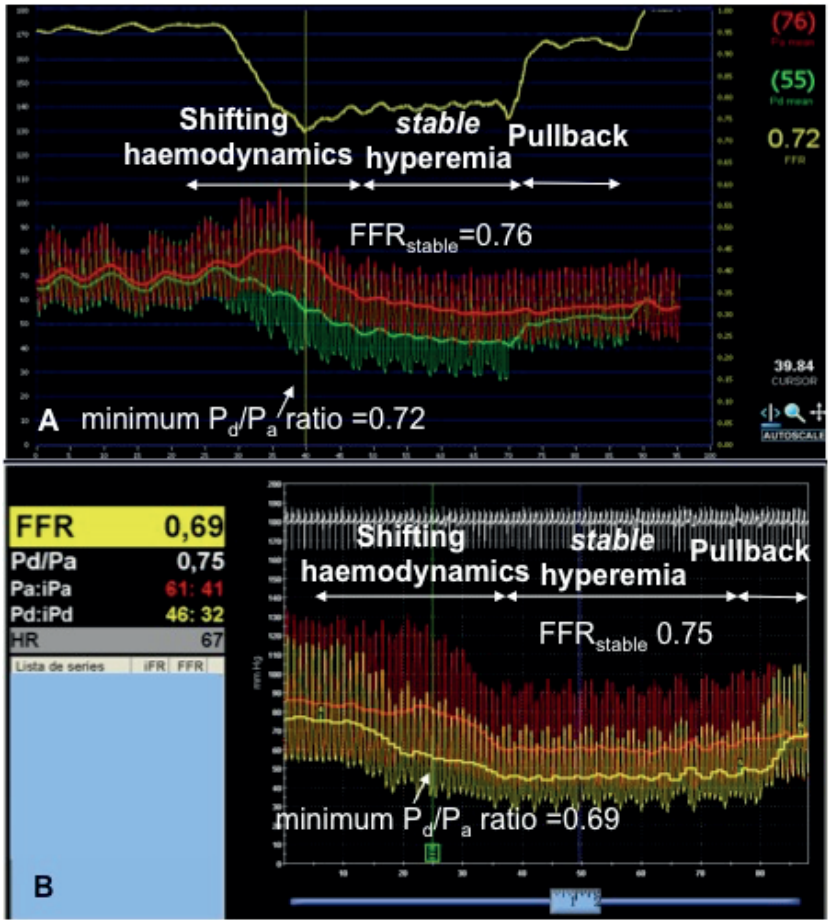

Figure 1 | Panels A and B show examples of the reported phenomenon. Note that the minimum Pd/Pa ratio develops before the stabilization of shifting hemodynamics following the initiation of adenosine IV infusion. Afterwards, FFR stabilizes at higher values (FFRstable). In panel A, please note the upper yellow line showing the minimum Pd/Pa ratio during the recording. In panel B, please note that while the FFR value reported by the console denotes the minimum Pd/Pa ratio, the measure bar is placed within stable hyperaemia, at FFRstable, labeled below FFR as Pd/Pa by the console.

Statistical analyses

Categorical variables are presented as counts or percentages. Continuous variables are presented as mean ± standard deviation. Normality and homogeneity of the variances were tested using the Kolmogorov-Smirnov and Levene tests. Data was analyzed on a per-patient basis for clinical characteristics, and on a per-vessel basis for the rest of calculations. Continuous variables were compared with T tests. Categorical variables were compared with maximum likelihood $\chi 2$ tests. Differences between paired values of P_a, P_d as well as their ratios (P_d/P_a, minimum P_d/P_a ratio and FFR_{stable}) were compared with paired-T tests. For the proportion of cases in which the minimum P_d/P_a ratio developed before stable hyperaemia, Wilson´s exact binomial confidence intervals were calculated. To assess the magnitude of the difference between minimum P_d/P_a ratio and $FFR_{stable,}$ Cohens´ *d* statistics were computed. A p value <0.05 was considered significant. The SPSS 20.0 (IBM Corp, Armonk, New York) statistical software package was used for all calculations.

RESULTS

A total of 104 (90 patients) FFR recordings fulfilled our inclusion criteria: 27 (26%) performed with the S5 Volcano (Volcano Corp.) and 77 (74%) with the RadiAnalyzer Xpress (St Jude Medical, Minnesota, USA) consoles. Figure 2 shows the distribution of FFR values in study population. In general, it can be acknowledged that it is composed by intermediate FFR values, similar to that observed in clinical populations.[5]

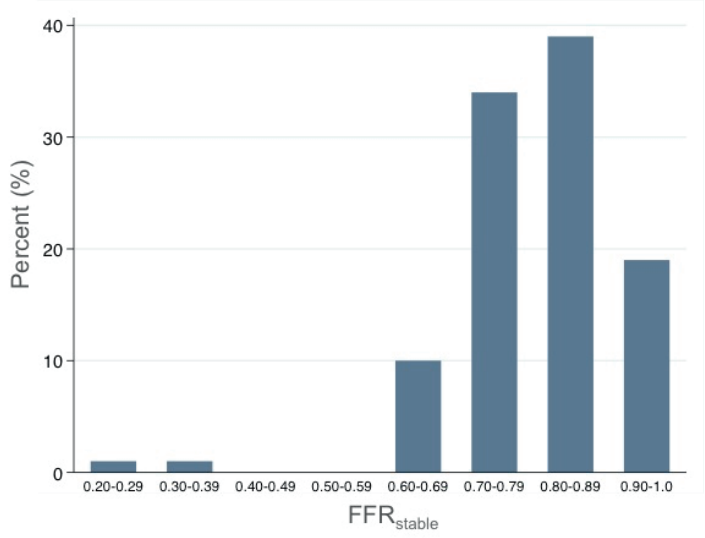

Figure 2 | Distribution of the FFR values in study population.

Overall, the minimum P_d/P_a ratio was significantly lower than FFR_{stable} (0.796 ± 0.111 vs. 0.802 ± 0.110, p<0.001), a difference driven by 19 cases, in which this ratio developed before the stabilization of hyperaemia. Therefore, the prevalence of this phenomenon in study population was of 18.3%, (95% CI: 12.0 to 26.8%). In whole population, Cohens´ *d* equaled 0.06, indicating that the overall mean of FFR_{stable} was at the 52^{th} percentile of the overall mean of minimum P_d/P_a ratio (non-overlapping values= 3.9%). However, in cases in which the minimum P_d/P_a ratio developed before stable hyperaemia, the difference between both values was higher; since a mean minimum P_d/P_a ratio of 0.77 ± 0.09 stabilized later at 0.81 ± 0.08 (FFR_{stable}) (p<0.001) (mean difference, 0.03 ± 0.02, range, 0.01 to 0.10). In such cases, Cohens´ *d* equaled 0.40, indicating that the overall mean of FFR_{stable} was at the 65.5^{th} percentile of the overall mean of minimum P_d/P_a ratio (non-overlapping values= 27.4%). The time to minimum P_d/P_a ratio after initiation of adenosine infusion was significantly shorter than to FFR_{stable} (70 ± 34 sec vs. 77 ± 29 sec, p<0.001). Finally, the clinical profile of the study population is shown in Table 1. No significant differences in the clinical characteristics between patients in whom the minimum P_d/P_a ratio developed before or within stable hyperaemia were found.

The analyses of aortic and distal pressures at baseline, minimum P_d/P_a ratio and FFR_{stable} is shown in Figure 3. It can be observed that a significant drop in P_a and P_d was found when baseline conditions were compared to stable hyperaemia. Moreover, no significant differences in baseline pressures [P_a (92 ± 21 vs. 94 ± 15 mmHg, p=0.534) and P_d (83 ± 20 vs. 87 ± 16 mmHg, p=0.363)] nor in stable- hyperaemic pressures [P_a (76 ± 20 vs. 82 ± 18 mmHg, p=0.179) and P_d (62 ± 20 vs. 67 ± 17 mmHg, p=0.296)] were found between cases that developed the minimum P_d/P_a ratio before or within stable hyperaemia, respectively. However, in the former cases, the minimum P_d/P_a ratio was found at a time point in which P_a remained statistically unchanged, despite that P_d had already dropped significantly, as compared to baseline (Figure 3). The same figure illustrates how the minimum P_d/P_a ratio developed at a time of shifting haemodynamics, revealed by the fact that P_a and P_d, continued to statistically decrease until stabilization at lower values at FFR_{stable}. Of note, at stable hyperemia, the prevalence of vessels with P_d below the autoregulation threshold (<60 mmHg) was numerically higher in those cases that developed the *minimum* Pd/Pa ratio before stable hyperaemia [11 (57.9%) vs. 31 (36.5%)] although statistical significance was not reached (p=0.08).

Table 1 | General characteristics of study population

		Development of minimum P_d/P_a ratio before stable hyperaemia		
	Total population	**Yes**	**No**	**p value**
Per patient analyses (n=88)*	n=90	13 (16.7)*	75 (83.3)*	
Age	67 ± 11	65 ± 14	67 ± 11	0,455
Male	76 (84.4)	10 (76.9)	64 (85.3)	0,463
Left ventricle ejection fraction	62.0 ± 12.1	58.6 ± 11	62.3 ± 11.9	0,321
Cardiovascular risk factors.				
Hypertension	54 (60)	8 (61.5)	44 (58.7)	0,845
Diabetes	18 (20)	5 (38.5)	13 (17.3)	0,102
Dyslipidemia	49 (54.4)	8 (61.5)	40 (53.3)	0,581
Smoker	29 (32.2)	2 (15.4)	27 (36)	0,123
Previous MI	51 (56.7)	7 (53.8)	42 (56)	0,885
Multivessel disease	70 (77.8)	10 (76.9)	58 (77.3)	0,974
Clinical presentation.				
Stable angina	59 (65.6)	7 (53.8)	51 (68)	0,329
Post-MI	31 (34.4)	6 (46.2)	24 (32)	
Per vessel analyses (n=104)	n=104	n=19	n=85	
Diameter stenosis,% (visual assessment)	61 ± 12	61 ± 12	61 ± 13	0,808
Stenosis location				
Left main	9 (8.7)	0	9 (10.6)	0,074
Left anterior descending artery	51 (49)	7 (36.8)	44 (51.8)	
Circumflex	23 (22.1)	8 (42.1)	15 (17.6)	
Right coronary artery	21 (20.2)	4 (21.1)	17 (20)	

Values are mean ± S.D or n(%).
MI: myocardial infarction
*Two patients with >1 interrogated vessels with discrepancy in the development of minimum P_d/P_a ratio before stable hyperaemia within vessels were excluded from per patient analyses.
T-tests or maximum likelihood $\chi 2$ tests were used for comparisons.

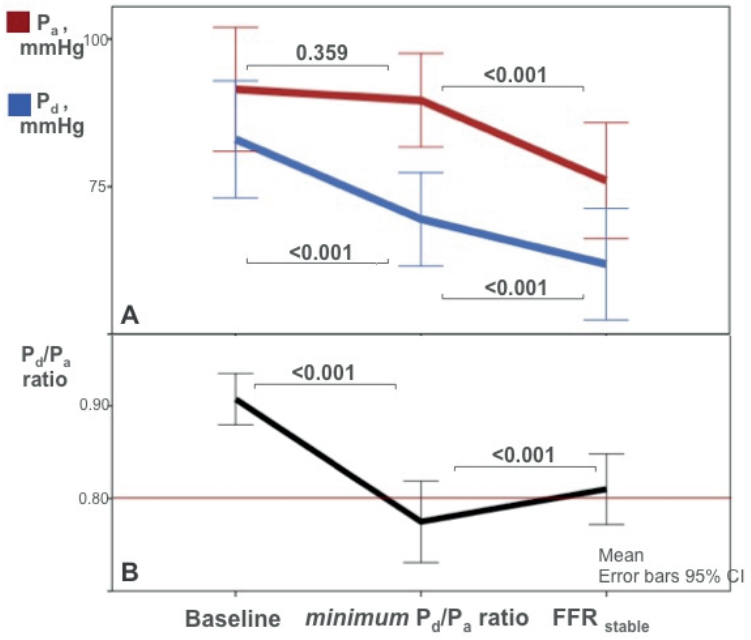

Figure 3

Figure 3 | Panel A shows the changes in Pa and Pd at baseline, minimum Pd/Pa ratio and FFRstable in cases where the minimum Pd/Pa ratio value developed before stable hyperaemia. It can be observed that, at difference with Pd, at the minimum Pd/Pa ratio, a significant fall in Pa has not yet occurred. During FFRstable, however, both pressures stabilize at significantly lower values. Panel B shows the Pd/Pa ratio at the same three moments. The horizontal line is placed at the FFR threshold value of 0.80.

The relationship between the prevalence and cumulative magnitude of this phenomenon across the distribution of FFR values is shown in Figure 4. It can be observed that the per-range, percent of cases in which the minimum P_d/P_a ratio developed before stable hyperaemia was higher in tighter stenoses (FFR<0.70). However, most of the percent- cumulative magnitude of the discrepancy between FFR_{stable} and minimum P_d/P_a ratio (FFR_{stable} - *minimum* Pd/Pa) was found within the 0.70 to 0.90 range. Finally and in terms of dichotomous classification of stenosis severity, reclassification would have occurred in 3 (2.9%) cases, all presenting a minimum P_d/P_a ratio ≤0.80 with FFR_{stable} >0.80. Thus, it is expected that in population showing the same distribution of FFR values as in ours and if FFR_{stable} is used to decide upon revascularization, ≈3% unneeded interventions can be avoided if this phenomenon is identified. Importantly, in non of the cases, a minimum P_d/P_a ratio <0.75 stabilized later over the treatment threshold of 0.80. Finally, a similar prevalence of this phenomenon was observed with the two commercially available systems: 14/77 (18.2%) with the RadiAnalyzer Xpress (St Jude

Medical, Minnesota, USA) and 5/17 (18.3%) cases with the S5 Volcano (Volcano Corporation, San Diego, CA) consoles (p=0.969).

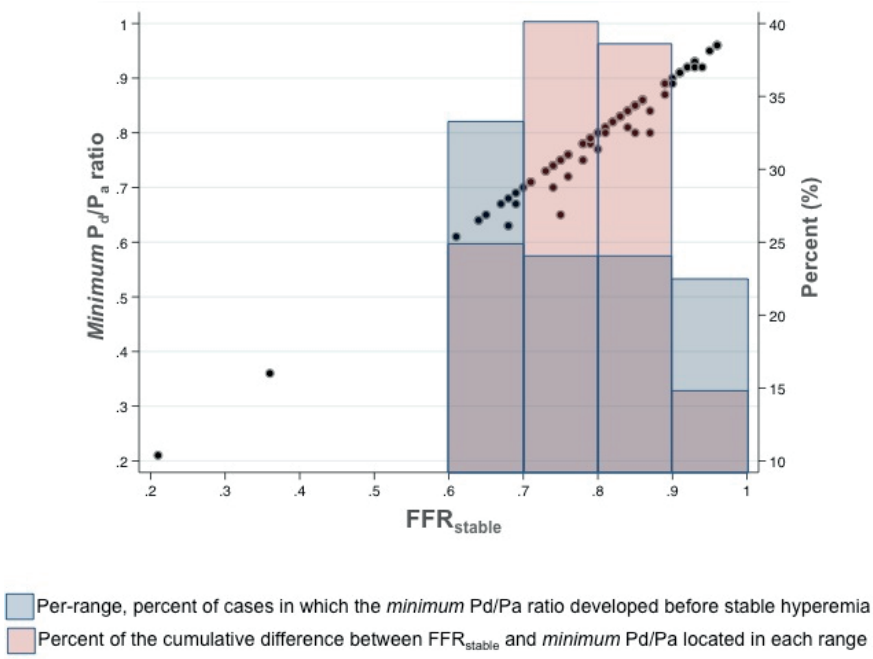

Figure 4 | Scatterplot of the relationship between minimum Pd/Pa ratio and its FFRstable counterpart. Bars in green represent the per-range percent (%) of cases in which the minimum Pd/Pa ratio developed before FFRstable. Bars in red represent the percent (%) of the cumulative sum of the difference between FFRstable and minimum Pd/Pa ratio located in each range.

DISCUSSION

While in most stenosed vessels interrogated with pressure guidewires the minimum value of FFR develops during stable hyperaemia; the main finding of the present study is that in a significant proportion of cases [18.3%, (95% CI: 12.0% to 26.8%)], the minimum P_d/P_a ratio occurs during shifting haemodynamics following the initiation of adenosine infusion, and before the steady-state hyperaemic plateau is reached. This means that overall, FFR_{stable} is slightly higher than what is reported by automated machines (overall, 2% higher in this study). Whilst the overall difference between the minimum P_d/P_a ratio and its FFR_{stable} counterpart is small (reflecting the good performance of this ratio-derived index), reclassification of stenosis severity might occur, if choosing between the minimum and stable values of FFR within the same trace. The

possible physiological basis and clinical implications of this phenomenon are now discussed in detail.

The rationale for FFR calculation relies on pressure sampling during stable hyperaemia, with maximally dilated arterioles and no concomitant shift in other factors influencing coronary haemodynamics, such as extravascular compression, vascular capacitance or central venous pressure. Only then, a modification in the P_d/P_a ratio reflects a proportional change in maximum achievable myocardial flow in the presence of a stenosis relative to the maximum achievable flow in the absence of the stenosis.[6] However, these criteria of haemodynamic stability are not fulfilled immediately after the initiation of adenosine infusion; but only after the stabilization of the steady -state hyperaemic plateau, when constant and minimum microcirculatory resistance is finally achieved. This is the reason why IV-adenosine infusion (over intracoronary boluses) is widely advocated as the method of reference to induce coronary hyperaemia.[7]

When initiated, IV-adenosine has to pass through the pulmonary circulation before reaching the systemic vascular beds.[8] From the arterial territories, adenosine first reaches the coronary circulation, increasing coronary blood flow, which enhances left ventricle contractile function. This is known as Gregg´s phenomenon.[9] A few beats later, adenosine enters the systemic circulation and decreases systemic vascular resistance, triggering a reflex sympathetic discharge that transitorily increases cardiac output and P_a in variable degree.[8, 10] Under such circumstances (enhanced left ventricle contractile function plus systemic sympathetic discharge), there is a short period of time after adenosine initiation in which aortic pressure might increase (or be maintained) while coronary microcirculatory resistance is falling (Figure 5); findings that have shown to increase myocardial blood volume and decrease coronary resistance in humans.[11] Altogether, these situations according to the resistive model of FFR investigated by Siebes et al can dictate a lower FFR value.[12] In addition to this, it can be also argued that coronary capacitance can contribute to this phenomenon, since maximal vasodilation of arterioles with adenosine is followed by a marked increase of coronary capacitance, with a 75% increase in total coronary blood volume in animal models that has been also observed in humans.[11,13] This shift in coronary capacitance might cause a transient dissociation between intracoronary pressure and flow, similar to that observed in early diastole.[14] Finally, the observed statistical trend towards a higher prevalence of vessels with P_d below the autoregulation threshold (<60 mmHg) in cases that developed the minimum Pd/Pa ratio before the stabilization of hyperemia, might also suggest a poorer adenosine- induce increase in coronary collateral flow support[15] as a contributor to the latter phenomenon.

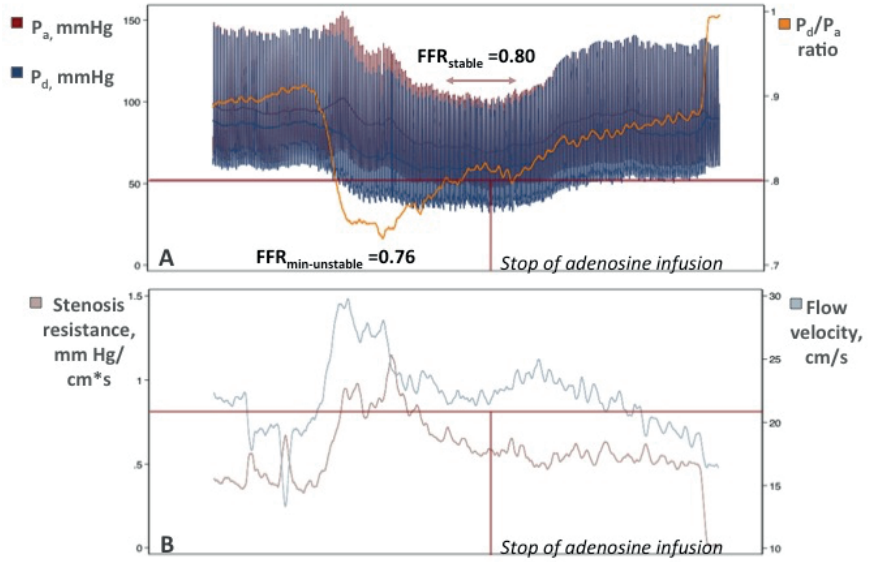

Figure 5 | This figure shows an example of this phenomenon obtained with a guidewire equipped with sensors of pressure and flow velocity (Doppler) (ComboWire® XT, Volcano Corp). Panel A shows Pa, Pd, and the Pd/Pa ratio. Please note that the minimum Pd/Pa ratio was 0.76 and later stabilized at 0.80 (FFRstable). Panel B shows flow velocity (cm/sec) and stenosis resistance (Pa-Pd/flow velocity) [(mmHg/(cm/s)] during the recording. It can be observed that the minimum Pd/Pa ratio developed at a timepoint where hyperaemia was not yet stable and flow velocity and stenosis resistance were higher. Afterwards, at stable hyperaemia, flow velocity and stenosis resistance decreased, and the Pd/Pa ratio (FFRstable) increased. Horizontal lines in both panels are placed at the treatment thresholds of FFR (≤0.80) and HSR (>0.80), respectively. Vertical line indicates the moment when adenosine infusion was stopped. A non- hyperaemic pullback maneuver ruled out pressure drift.

Although the experimental and clinical validation of FFR was done under conditions of maximum and stable hyperaemia,[1, 2] large FFR clinical decision-making studies have not stressed both of these circumstances but only the former. This may have resulted because seminal validation studies did not state exactly when was FFR measured – for example in the PET-validation study, adenosine was given for 4 minutes but it is unclear when within these minutes FFR was measured.[3] Thereafter, subsequent terminology has been open to multiple interpretations. In the DEFER (Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis) trial, adenosine was administered either intravenously or intracoronary to induce maximum hyperaemia, although this was not clearly defined.[15] The FAME study (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) measured FFR after "complete hyperaemia" was achieved with IV adenosine, suggesting that FFR was measured during the steady-state hyperaemic plateau.[16] In FAME 2 (Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease) FFR was measured "during

adenosine-induced hyperaemia" leaving apparently open the possibility to use either the minimum or stable values of FFR.[17] Moreover, a recent study that assessed FFR reproducibility, recalled FFR after the establishment of a stable minimum value.[18] Whilst this rationale protects the simplicity of FFR measurements in clinical practice, our findings shows that in a significant proportion of patients, the minimum and stable values of FFR are close, but not the same and may not concur in time. More importantly, in a small proportion of patients, this difference might lead to different decisions when deciding upon revascularization with FFR.[19] Although the difference between the minimum and stable values of FFR is overall small, this ambiguity might become important in Core Laboratory environments or when studying different hyperaemic routes or agents. A recent statement for standardization, recording and reporting FFR as a Core Laboratory technique recommended making FFR measurements after the administration of IV adenosine for at least 2 minutes and calculating it as "the ratio of P_d to P_a at maximal hyperaemia, the nadir of P_d".[7] As our study suggests, the nadir in P_d may not coincide with the minimum P_d/P_a ratio of the same trace. Therefore, this definition might be improved if the phenomenon described in our study is identified, recalled and corrected.

We finally believe that the discussion of whether the lowest trans-stenotic pressure ratio measured after initiation of IV adenosine consistently fits with the theoretical model of FFR is not a trivial one. In principle, it would be desirable to estimate FFR in clinical practice in the closest possible manner to that expressed in its theoretical form. Moreover, it should be recognized that the theoretical assumptions on which FFR is measured in cases in which the minimum P_d/P_a ratio develops before stable hyperaemia are not fully correct. Whilst this phenomenon appeared to have little impact on stenosis severity classification in our study population (therefore not being in conflict with the value of FFR in decision-making demonstrated in large clinical studies) it remains plausible that selective estimation of FFR during stable hyperaemia might lead to a slightly better diagnostic performance of the test. Moreover and even though in our data no clinical determinants were statistically associated to this phenomenon, it seems reasonable to speculate that conditions affecting the left ventricle systolic and/or diastolic functions as well as the coronary microcirculation or the autonomous nervous system might exert an influence in the development of the described condition. In any case, our study stresses the importance of a correct and standardized methodology for FFR measurement, and it would be desirable that both clinicians and core laboratories take into consideration this phenomenon. Finally, our findings highlight the fact that FFR calculation is not only a number but a complex physiological interrogation above that provided by automated consoles. Further studies towards the understanding and potential implications of this phenomenon are required.

LIMITATIONS

This study has several limitations. Being a retrospective analysis, selection bias cannot be ruled out. Our conclusions are also limited by a relatively small sample size. Finally, being a single-center experience, the external reproducibility of our findings has to be challenged. In spite of these limitations, we believe that the observations gathered can contribute to refine intracoronary physiological guidance with FFR.

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Part C

Influence of the coronary microcirculation on the invasive assessment of ischaemic heart disease

CHAPTER 10

Use of intracoronary physiology indices in acute coronary syndromes

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ABSTRACT

Acute coronary syndromes (ACS) are prevalent, portend a poor prognosis, and represent the most threatening manifestation of coronary artery disease. Whilst very little doubt exists about the clinical benefit of restoring culprit vessels´ patency in patients admitted for ACS, the risk stratification and individual treatment strategy in these complex scenarios is not always straight forward. This is because the extension of myocardial damage and left ventricle recovery are difficult to predict, and a sizable proportion of patients admitted for ACS have bystander multivessel disease. This review summarizes available literature on the adjuvant role of invasive coronary physiology indices in guiding treatment and providing further risk stratification in patients suffering from ACS.

INTRODUCTION

Acute coronary syndromes (ACS) are prevalent, portend a poor prognosis, and represent the most threatening manifestation of coronary artery disease.[1] Whilst very little doubt exists about the clinical benefit of restoring cuplrit vessels´ patency in patients admitted for ACS, the risk stratification and individual treatment strategy in these complex scenarios is not always straight forward. This is because the extension of myocardial damage and left ventricle (LV) recovery are difficult to predict,[2] and a sizable proportion of patients admitted for ACS have bystander multivessel disease (MVD).[3] A growing interest in invasive coronary physiology, coupled with technical developments in wire technology, allows to assess intracoronary pressure and flow in the catheterization laboratory. This review summarizes available literature on the adjuvant role of invasive coronary physiology indices in guiding treatment and providing further risk stratification in patients suffering from ACS.

CORONARY PHYSIOLOGY IN THE CATHETERIZATION LABORATORY AND ITS APPLICATION TO ACUTE CORONARY SYNDROMES

Current technologies allow to measure intracoronary pressure and flow with two different methods: Doppler-tipped guidewires, that estimate coronary flow velocity,[4] and thermal-sensitive guidewires, that based on the coronary thermodilution method estimate mean transit time, an index of absolute coronary flow. [5] When these pressure and flow measurements are obtained during baseline and hyperemia, several physiology indices can be obtained, by relating Ohm´s law to fluids flow.[6] These indices provide valuable information on the status of the epicardial vessel and the coronary microcirculation of the downstream myocardial bed (Figure 1).

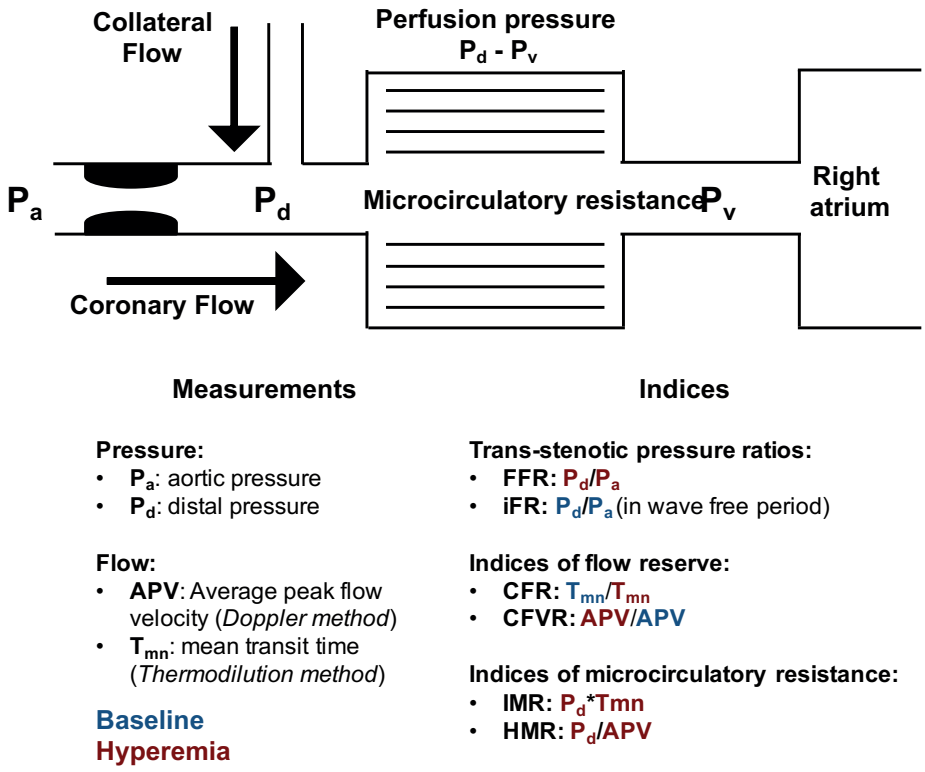

Figure 1 | Schematic representation of the coronary circulation in the presence of an epicardial stenosis. Aortic pressure drives coronary flow through the stenosis and the coronary microcirculation to the right atrium. The application of Ohm´s law to fluid´s flow allows the calculation of several physiology indices. FFR: fractional flow reserve; iFR: instantaneous wave free ratio; CFR: coronary flow reserve; CFVR: coronary flow velocity reserve; IMR: index of microcirculatory resistance; HMR: hyperaemic microcirculatory resistance

FUNCTIONAL ASSESSMENT OF NON-CULPRIT STENOSIS DURING ACS

Bystander MVD is frequent in patients admitted for ACS and is associated with worse short and long-term prognosis. In the APEX-AMI (Pexelizumab in Conjunction With Angioplasty in Acute Myocardial Infarction) trial[7] 41% of the patients admitted with ST-segment elevation myocardial infarction (STEMI) had MVD, and these raised to 54% in the recent PRAMI (Preventative Angioplasty in Acute Myocardial Infarction)) trial.[3] Likewise, in patients with non-ST-elevation acute coronary syndromes (NSTACS), 30-59% of patients have MVD.[8,9] This is important because the occlusion of the infarct related artery may precipitate myocardial ischemia in distant stenosed territories, because of compensatory hyperkinesis or from sudden cease of collateral support. In

this regard, the identification of the culprit artery in STEMI is usually forthright by utilizing information from the surface electrocardiogram and the coronary angiography, but the functional relevance of non-culprit stenosis may be difficult to determine. On the other side, in NSTACS, the identification of the culprit lesion might be challenging, and intracoronary imaging (intravascular ultrasound and optical coherence tomography, for example) is more suited than coronary physiology to unravel the responsable plaque. This highlights the complementariness of the anatomical and functional assessment in patients admitted with ACS.

Fractional flow reserve

Fractional flow reserve (FFR) has become the standard method to assess epicardial stenosis severity in stable patients following the demonstration that decision-making based on FFR results in better outcomes than decision-making based on angiography.[10] However, the theoretical framework of FFR is critically dependent on the ability to achieve maximal hyperaemia, and during ACS, there are multiple factors that might impair hyperaemic response in culprit and non-cuprit territories.[11] Indeed, transitory microcirculatory dysfunction in myocardial beds remote from culprit territories has been described,[12] and local neurohumoral reflexes,[13] vasoconstriction and elevated LV-end diastolic pressure1[4] have been proposed as underlying mechanisms. Notably, a recent angiographic sub-study (n=3,426) of the large ACUITY[14] (Acute Catheterization and Urgent Intervention Triage Strategy) trial demonstrated that a sizable subset of patients (24.8%) undergoing PCI for NSTACS have abnormal non-culprit vessel perfusion as measured by myocardial blush grade.[15] This is important because proof-of-concept studies have suggested that FFR might underestimate stenosis severity in NSTACS as compared to hyperaemic stenosis resistance,[16,17] a more specific index of epicardial stenosis severity.[18] However and in spite of these theoretical limitations, clinically available data (Table 1) suggests that FFR can be reliably used to guide treatment of bystander stenosis during ACS.

Table 1 | Use of physiology indices derived from pressure in acute coronary syndromes

First author	Year	Design	Index	Study outline, objective	Clinical setting	N, total	N, ACS subset	Main findings	FFR-deferral (stenosis) FFR cut-off	Follow-up	Deaths/MI/UA/ TVR
Reliability in culprit vessels											
De Bruyne[36]	2001	Diagnostic, analitical	FFR	A prior- defined comparison of FFR 0.75 cut-off against SPECT in post-MI patients	Culprit vessels of MI≥6 days	57	57	Ss:82%, Sp:87%, Acc 85%, optimal FFR cut-off: 0.78	-	-	-
Usui[75]	2003	Diagnostic, descriptive	FFR	FFR vs SPECT in Stable and post-MI patients	Cuprit vessels<3 months	167	74	post-MI patients: Ss:79%, Sp: 74%, optimal FFR cut-off: 0.76	-	-	-
Samady[37]	2006	Diagnostic, descriptive	FFR	FFR vs SPECT and Contrast Echo in post-MI patients	Culprit vessels of MI<6 days	48	48	Either SPECT or Echo: Ss: 88%, Sp: 93%, Acc: 91%, optimal FFR cut-off: 0.78	-	-	-
Reliability in non-culprit vessels											
Ntalianis[19]	2010	Cohort	FFR	FFR measured acutely and after 35±4 days in non-culprit arteries post ACS	NSTEMI, STEMI	101	101	No significant change in FFR: both acute and follow-up: 0.77± 0.13, p=NS	-	-	-
Wood[20]	2013	Cohort	FFR	FFR measured acutely and after 42±10 days in non-culprit arteries post STEMI	STEMI	47	47	Significant-albeit-modest change in FFR: from 0.84±0.08 to 0.82±0.08, p=0.025	-	-	-
Niccoli[16]	2014	Transversal, analitical	FFR/HSR	FFR vs HSR comparison in NSTEMI vs Stable patients	NSTEMI, Stable	30	15	FFR and HSR discordance more frequent in NSTEMI: 85.7% vs 39.1%, p= 0.04	-	-	-
Indolfi[32]	2015	Transversal, analitical	iFR/FFR	iFR vs FFR comparison in ACS vs Stable patients	UA, NSTEMI, STEMI, Stable	82	53	The diagnostic accuracy of iFR in ACS was not inferior to Stable patients: 79.5% in ACS vs 84.4% in S, p=0.497	-	-	-

Table 1 | Use of physiology indices derived from pressure in acute coronary syndromes (continued)

First author	Year	Design	Index	Study outline, objective	Clinical setting	N, total	N, ACS subset	Main findings	FFR-deferral (stenosis) FFR cut-off	Follow-up	Deaths/MI/UA/TVR
Safety of revascularization deferral in non-culprit vessels											
Hernandez-Garcia[76]	2001	Consecutive cohort	FFR	Prospective ACS cohort deferred if FFR>0.75	UA, MI	43	43	Survival free of MACE: 93.2%	44 0.75	11±6 months	0/0/0/3 in ACS group
Potvin[77]	2006	Consecutive cohort	FFR	Comparison of FFR deferral in ACS vs Stable patients	UA, NSTEMI, STEMI, Stable	201	21	No differences in MACE between ACS and Stable patients (9% vs 13%, p=0.44)	231 0.75	11±6 months	0/2/0/ NA in ACS group
Fischer[78]	2006	Retrospective cohort	FFR	Comparison of FFR deferral in ACS vs Stable patients	UA, NSTEMI, STEMI, Stable	111	35	Trend towards a higher proportion of TLR or cardiac death (53 vs. 30%, p=0.09) in ACS patients	40 0.75	12 months	3/1/0/6 in ACS group
Sels[21]	2011	Sub-study of randomized multicentre trial	FFR	FFR-guidance vs angiophy-guidance in UA/NSTEMI	UA, NSTEMI	328	328	Relative risk reduction of MACE in FFR group: 19%	NA 0.80	24 months	4/12/0/20 in FFR group
Lopez-Palop[22]	2012	Consecutive cohort	FFR	Comparison of FFR-deferral vs FFR-treated in ACS	NSTEMI, STEMI	107	107	No differences in MACE between patients treated or deferred based on FFR (7.7% vs 7.4% respectively, p=0.52)	128 0.75	12 months	5/0/0/8 in FFR group
Clinical-decision making process											
Carrick[79]	2013	Survey	FFR	Simulated decision exercise to test whether FFR would change decisions in NSTEMI	NSTEMI	100	100	Treatment changed in 46% of cases after FFR disclosure. This change favored medical therapy in 26%	- -	-	-

Table 1 | Use of physiology indices derived from pressure in acute coronary syndromes (continued)

First author	Year	Design	Index	Study outline, objective	Clinical setting	N, total	N, ACS subset	Main findings	FFR-deferral (stenosis)	FFR cut-off	Follow-up	Deaths/MI/UA/ TVR
Layland[25]	2014	Randomized multicentre trial	FFR	To assess the management and outcomes of NSTEMI patients randomly assigned to FFR- or angiography-guidance	NSTEMI	350	350	The proportion of patients treated medically was higher in the FFR-guided than in the angiography-guided group [40 (22.7%) vs. 23 (13.2%), p=0.022].	-	-	-	-
Prediction of myocardial viability												
Kim[41]	2012	Cohort	ΔFFR0.80	To assess with pressure ratios the vasodilatory reserve of post-infarcted myocardium using a calibrated upstream balloon obstruction	STEMI	29	29	ΔFFR0.80 was linearly related with the infarct extention by CMR (R2=0.65, P < 0.001)	-	-	-	-

FFR: fractional flow reserve; iFR: instantaneous wave free ratio; HSR: hyperaemic stenosis resistance index; SPECT: myocardial scintography; Echo: echocardiograhy; ACS: actue coronary syndromes; MI: myocardial infarction; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UA: Unstable angina; SS: sensitivity; Sp: Specificity; Acc: Accuracy; MACE: mayor adverse cardiovascular events; TLR: target lesion revascularization; NA: not available

Ntalianis et al. investigated FFR reliability in 101 patients with ACS by measuring FFR acutely and after 35±4 days in non-culprit vessels (75 with STEMI and 26 with NSTACS).[19] No significant difference between the acute FFR value and that at follow-up was observed in patients with STEMI (0.78±0.10 vs. 0.76± 0.10, p=NS) or non-ST-segment elevation infarction (NSTEMI) (0.77±0.10 vs. 0.77±0.20, p=NS). Importantly, only in two stenosis an initial FFR >0.80 subsequently decreased to <0.75. A similar study only in STEMI patients (n=47) observed, however, a significant-albeit-small decrease in the FFR values of non-culprit vessels between the acute presentation and after 41.8±10.2 days of follow-up (0.84±0.08 vs. 0.82±0.08, respectively, p=0.025).[20] Thus and from a pragmatical point of view, FFR measurements in non-culprit vessels during ACS appear to provide reliable estimates of the functional significance of non-culprit stenoses. This notion is now supported by some outcome data. Of the original 1005 patients included in FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) 328 (32.6%) had NSTACS. In these, the use of FFR to guide PCI resulted in similar risk reductions of major adverse cardiac events (MACE) and each MACE components in patients with NSTACS, compared with patients with stable symptoms (absolute risk reduction of 5.1% vs. 3.7%, respectively, p=0.92).[21] Notably, this equipoise in reduction of events was achieved while FFR-guidance reduced the number of stents without increasing in-hospital stay or procedure time. Another study of 107 patients admitted for ACS reported a low rate of MACE (7.4%) at 1 year in 81 stenoses that were deferred because FFR>0.75.[22] As a confirm of FFR aplicability in non-culprit lesions, a prediction model for future interventions of previously deferred lesions according to FFR observed that ACS as clinical presentation did not resulted to be a significant predictor of reintervention at both univariate (hazard ratio: 1.40, 95% CI: 0.82–2.39, p=0.21) or multivariate analysis.[23] Furthermore, deferral of revascularization based on FFR in ACS seems not only safe but also cost-effective, as demonstrated by a randomized study (n=73) in which FFR-guidance reduced the duration (11 ± 2 h vs. 49 ±5 h, p<0.001) and cost (U.S. $1,329 ± $44 vs. $2,133 ± $120, p<0.05) of hospitalization, without increasing procedural time, radiation exposure, or clinical event rates, as compared to stress perfusion scintography.[24]

The FAMOUS-NSTEMI[25] trial (FFR vs. angiography in guiding management to optimize outcomes in NSTEMI) is the first randomized trial on FFR in ACS designed to address whether routine FFR measurements in NSTEMI is feasible and safe, by comparing conventional angiography-guidance (n=174) with FFR-guidance (n=176). The primary endpoint was represented by the proportion of patients treated with medical therapy only that, compared to angiography-guidance, was higher in the FFR-guided group [23 (13.2%) vs 40 (22.7%) respectively, difference 9.5% (95% CI: 1.4%, 17.7%), p=0.022]. Even if no differences were observed in health care outcomes and quality of life between the two study arms, the FFR-guided approach: 1) resulted in changes

in stenosis classification and clinical management in one-fifth of patients, 2) reduced revascularization at the index procedure, and 3) most of these differences were maintained at 12 months. Whilst these randomized findings are encouraging, it shoud be highlighted that this study is limited by a modest sample size, lack of power for clinical outcomes and the fact that most patients were included 3 days after the index episode, suggesting a majority of stabilized ACS. The findings of this trial are in line with a recent French FFR registry (1,075 patients, 19% with recent ACS), in which 43% of the patients had treatment reclassification following FFR disclosure.[26] Altogether, available data supports the inclusion of FFR in the decision making process of patients admitted with ACS, although it should be noted that no FFR trial in ACS has been powered to test for differences in clinical outcomes, making clinical recommendations less clear.

Neither the 2013 and 2014 ACCF/AHA Guidelines for the management of STEMI[27] and NSTACS[10] respectively nor the ESC/EACTS Guidelines on myocardial revascularization[10] currently recommend physiological assessment of non-culprit stenosis during ACS. However, the ACCF/AHA STEMI Guideline[27] recommends PCI of non-culprit vessels before hospital discharge at a separate time from PPCI in patients with spontaneous symptoms of myocardial ischaemia (1C), and in patients with intermediate- or high-risk findings on noninvasive -testing (IIa B). Although these notions have been challenged by the recent PRAMI[3] and CvLPRIT[28] (Complete versus Lesion only PRimary-PCI Trial) trials, available data indeed suggests that FFR-guidance might play a physiology-sound role in deciding upon ACS non-culprit disease.

Instantaneous wave free ratio

The instantaneous wave free ratio (iFR) is a recently introduced index developed to facilitate the functional assessment of coronary stenoses by obviating the need for vasodilator drugs.[29] iFR is derived from the same theoretical framework as FFR (i.e., the relationship between the translesional pressure ratio and the impairment in myocardial blood supply caused by the interrogated stenosis), and is obtained with conventional pressure-wires and appropriate software during baseline conditions. The recent multicentre, prospective, core-laboratory based ADVISE II study (ADenosine Vasodilator Independent Stenosis Evaluation II) demonstrated that the use of a hybrid iFR/FFR approach delivered an overall classification agreement with FFR of 94.2% and obviated the need for hyperemic drugs in 69.1% of patients.[30] iFR seems hence a promising tool to facilitate the physiological assessment of coronary stenosis. Recently, the diagnostic accuracy of iFR in non-culprit vessels of patients admitted for ACS was investigated in a proof-of-concept study with encouraging results.[31] However and because less is known on the baseline status of the coronary circulation during ACS, further studies are needed to accurately establish the place of this novel index in complex clinical settings like ACS.

FUNCTIONAL ASSESSMENT OF CULPRIT STENOSES DURING ACS

In culprit vessels, the early post-STEMI phase is characterized by microvascular platelet plugging, thrombus embolization, coronary vasospasm, endothelial dysfunction, vascular stunning and intramyocardial hemorrhage (Figure 2).[32] This dynamic changes in the infarcted myocardial bed are associated with non-quiescent: 1) microvascular hyperemic response, 2) hyperemic flow, 3) trans-stenotic gradient and as a consequence 4) variable FFR values.[33] Therefore, FFR use in the culprit vessel during the acute phase of STEMI is currently not recommended.[34] However, nuclear imaging studies advocate that as early as 6 days after the infarction, FFR can reliably outline post-STEMI inducible ischaemia (Table 1).[35,36] Still and because after the stabilization of the STEMI process the mass of viable myocardium decreases in the perfusion territory, for a given stenosis, hyperemic flow and trans-stenotic gradient will decrease; thus, the FFR value will be higher.[35] Interestingly, in spite of this reduction in viable myocardium after STEMI, an FFR study performed in chronic infarcted territories (3.7+6.3 months after STEMI) suggests that most culprit stenoses will still be haemodynamically significant (FFR: 0.60+0.14, range 0.26 to 0.77) for the perfused viable mass within the infarction.[37] Since hyperaemic microcirculatory resistance in chronic infarcted and non-infarcted territories appears comparable [39±18 vs 35±11 mmHg/(mL/min/mL of perfusable tissue), p=NS] by fluorodeoxyglucose positron emission tomography, the FFR cut-off established for non-infarcted territories (0.75) seems also dependable in infarct areas.[38]

A contemporary study offered comprehensive insights into temporal changes of coronary physiology in culprit vessels after STEMI.[39] A cohort of 44 STEMI patients was examined with intracoronary pressure, thermodilution-derived indices of flow and cardiac magnetic resonance (CMR) immediately after PPCI, at day 1 and after 6 months. The authors observed that the coronary microcirculation partially recovered within 24 hr after STEMI, with further recovery at 6 months, which lead FFR to decrease in time. Indeed, baseline thermodilution flow and baseline distal-to-aortic pressure ratio remained stable over time but FFR reduced significantly between PPCI and 6 months (p=0.008). This microvascular response was clearer in patients in which the microvasculature was deeply compromised (as assessed with microvascular obstruction by CMR), confirming the limited ability of the coronary microcirculation to exhibit sufficient vasodilation soon after STEMI. In other words, this study showed that FFR decreases as a sign of microvascular recovery, especially in those patients in which the microvascular damage has been large. Notably, this recent findings are consistent with those by Neumann et al. in a cohort of STEMI patients investigated with Doppler flow wires and positron emission tomography, where coronary flow reserve in the infarct region improved in most of the patients 1 hour after PPCI, and further improved within 2 weeks.[40]

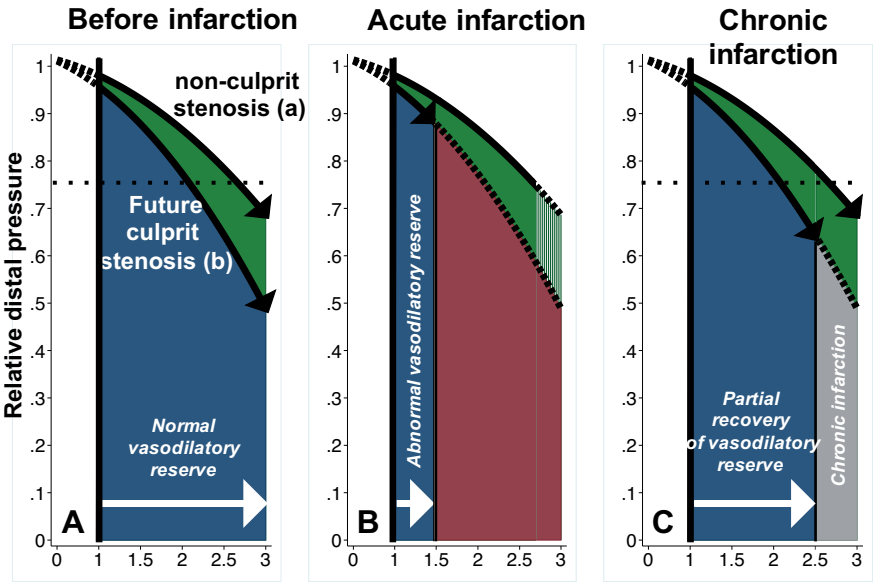

Figure 2 | This schemes represent the pathophysiology of culprit and non-culprit stenosis during STEMI. Relative distal pressure (corresponding to Pd/Pa ratios including FFR) is plotted in y-axis and CFR in the x-axis. A quadratic fit shows the pressure-drop with increasing flow in a non-culprit (a) and culprit (b) stenosed vessel. Panel A shows the hypothetical status before the infarction, with functionally normal myocardium, and normal vasodilatory reserve in culprit and non-culprit territories. Panel B shows the acute pathophysiology at the time of the acute infarction. The culprit territory exhibits a severely abnormal vaosdilatory reserve because of stunned and infarcting myocardium 35. The non-culprit territory might also exhibit an abnormal vasodilatory reserve. In both the culprit 35 and non-culprit vessels16,17 hyperaemic trans-stenotic flow might be impaired and so the trans-stenotic pressure drop. Thus, FFR values might be higher. Finally, in panel C, the infarction has stabilized. Whilst the non-culprit territory will recover its vasodilatory capacity, the viable myocardium within the infarction has decreased, and so the hyperaemic trans-stenotic flow and pressure drop.

PREDICTION OF LEFT VENTRICLE RECOVERY AND RISK STRATIFICATION IN ACS

Survivors of ACS face substantial risk for further MACE. Patients (and family members) often ask what their future holds; thus, information regarding prognosis after ACS is necessary for patient care. Initial risk stratification should start soon after presentation. But risk assessment is a continuous that requires recalibration on the basis of data obtained during the cardiac catheterization and hospital stay. Emerging data indicates that physiology indices can help achieve the former task.

Indices derived from pressure

FFR is an index of stenosis severity. However, Kim et al. put FFR theory to a novel use: the assessment of myocardial viability.[41] After PPCI for STEMI, the authors created temporary artificial stenosis inside the stent with a partially inflated balloon (readily available after PPCI) which was set to a baseline distal-to-aortic pressure ratio of 0.80. Afterwards, customary hypaeremia was induced, and the difference between the baseline and hyperaemic pressure ratio called $\Delta FFR_{0.80}$. This novel index reflects the additional trans-stenotic pressure drop produced by the increase in flow generated by residual myocardium with vasodilatory reserve within the infarct zone. $\Delta FFR_{0.80}$ was linearly related with the extension of the infarction by CMR late gadolinium enhancement (R^2=0.65, P < 0.001), and a $\Delta FFR_{0.80}$ value ≥0.1 had a sensitivity of 100% and specificity of 94.4% to predict absence of transmurality by CMR.

Indices derived from coronary thermodilution

The coronary thermodilution method to assess coronary flow reserve was introduced by De Bruyne[5] and Pijls[42] in the 2,000s and expanded by Fearon[43] to assess microcirculatory resistance in 2003. Its technical ease and a more close correlation to absolute coronary flow reserve than coronary flow reserve from Doppler velocity[44] has expanded its use across the interventional community.

Index of microcirculatory resistance

The index of microcirculatory resistance (IMR) is a technically simple method that combines a thermodilution-derived index of coronary flow (inverse of mean transit time) with intracoronary pressure at hyperaemia to interrogate the minimum achievable microcirculatory resistance of a specific vascular bed (distal pressure divided by the inverse of hyperaemic mean transit time, U).[43] IMR is reproducible,[45] and mounting evidence supports its value as a meaningful diagnostic tool, particularly immediately after PPCI (Table 2). In the first study examining IMR after PPCI, an IMR>32 U (median) was associated with higher infarction size (as assessed by creatine kinase) and worse wall motion score at 3 months by echocardiography. Notably, IMR was the only significant predictor of recovery of LV function at follow-up.[46] This capacity of on-site post-PPCI IMR measurements to discriminate myocardial viability and LV recovery has been further supported by CMR[47,48] and single-positron emission tomography[49] studies and a recent one[50] also observed IMR to correlate significantly with regional fluorodeoxyglucose uptake by positron emission tomography (r=-0.738, p<0.001). Herein, 33 U was the optimal IMR cut-off to predict LV wall motion recovery, with a sensitivity of 73%, specificity of 100% and an area under the receiving operating characteristic curve of 0.89.

Table 2 | Use of physiology indices derived from thermodilution in acute coronary syndromes

First author	Year	Design	Index	Study outline, objective	Clinical setting	N, baseline	N, follow-up	Main findings	Non-invasive imaging	Follow-up
Fearon[46]	2008	Cohort	IMR	To evaluate if IMR after PPCI predicts myocardial damage	STEMI	29	28	IMR correlated significantly with WMS at 3 months (r=0.59, p=0.002), whereas cTFC, TMPG, CFR, and ST-segment resolution did not. IMR was the only significant predictor of recovery of LV function.	Echo	3 months
Lim[50]	2009	Cohort	IMR	To examine if IMR after PPCI predicts myocardial viability and LV recovery	first anterior STEMI	49	40	IMR correlated with regional myocardial FDG uptake (r=0.738, p<0.001) and with WMS (r=0.464, p=0.003)	PET/Echo	6±1 months
Sezer[49]	2010	Cohort	IMR and CFR	To examine temporal changes in infarct region with IMR, CFR, Echo and SPECT	first STEMI	52	35	Baseline infarct size (β=0.6, p<0.001), IMR (β=0.28, p=0.013) and CFR (β=-0.276, p=0.017) were the only Independent predictors of infarct size	SPECT/Echo	5 months
McGeoch[47]	2010	Cohort	IMR	To investigate the relationship between IMR and CMR-infarct findings	STEMI	57	47	IMR was predictor of LV ejection fraction (p<0.001) and infarct volume (p=0.01) on CMR. IMR was independent predictor of LV ejection fraction (p=0.028) and infarct volume (p=0.048)	CMR	3 months
Yoo[80]	2012	Consecutive cohort	IMR	Value of IMR to assess myocardial injury and predict microvascular recovery	first anterior STEMI	34	34	IMR correlated with MVO (r= 0.754, p<0.001), WMS (r= -0.61, p<0.01) and LV (r= -0.52, p<0.01)	CMR/Echo	6.3 months

Table 2 | Use of physiology indices derived from thermodilution in acute coronary syndromes (continued)

First author	Year	Design	Index	Study outline, objective	Clinical setting	N, baseline	N, follow-up	Main findings	Non-invasive imaging	Follow-up
Payne[48]	2012	Cohort	IMR	To determine of IMR after PPCI predicts CMR-myocardial salvage	STEMI	108	96	IMR was a significant multivariable predictor of early myocardial salvage, with a multiplicative effect of 0.87 (95% confidence interval 0.82 to 0.92) per 20% increase in IMR.	CMR	3 months
Fearon[51]	2013	Prospective, multicentre, international cohort	IMR	To determine of IMR after PPCI is predictor of MACE	STEMI	253	253	Patients with IMR>40 U had higher rates of death or rehospitalization for heart failure at 1 year (17.1% vs 6.6%, p=0.027). IMR>40 U was the only independent predictor of death alone (HR, 4.3, p=0.02).	-	2.8 years
Fukunaga[53]	2014	Prospectively designed cohort	IMR, thermodilution curve	To investigate the value of the shape of the thermodilution curve in STEMI	STEMI	88	88	Classification of thermodilution curves in narrow unimodal, wide unimodal and bimodal. All patients with bimodal curve exhibited CMR-MVO (100%, 78%, 30%, p<0.001). Patients with bimodal curves had higher risk of death and heart failure rehospitalization (73%, 6.3, 7.3%, p<0.001)	CMR	6 months
Cuculi[40]	2014	Cohort	IMR, CFR and FFR	To describe how, post-STEMI, IMR, CFR and FFR evolve and are influenced by CMR-MVO	STEMI	82	46	Patients with MVO had lower CFR at PPCI and day 1 (p < 0.05). Baseline flow and Pd/Pa remained stable over time but FFR reduced significantly between PPCI and 6 months (p=0.008)	CMR	6 months

IMR: index of microcirculatory resistance; PPCI: primary percutaneous intervention; CK: creatinin kinase; WMS: wall motion score; LV: left ventricle; Echo: echocardiography; cTFC: corrected TIMI frame count; FDG: 18 fluorodeoxyglucose; PET: positron emission tomography; CFR: coronary flow reserve; SPECT: myocardial scintography; CMR: cardiac magnetic resonance; STEMI: ST-elevation myocardial infarction; MVO: microvascular obstruction; MACE: major adverse cardiac events; Pd/Pa: distal-to-aortic pressure ratio; HR: hazard ratio

Table 3 | Use of index of microcirculatory resistance in stratifying risk of periprocedural myonecrosis and as endpoint of trials

First author	Year	Design	Study outline	Clinical setting	N, total	A	B	C
IMR in periprocedural myonecrosis								
Ng[81]	2012	Cohort	To investigate if pre-PCI predicts peri-MI	Stable patients	50			
Layland[82]	2012	Cohort	To investigate if pre-PCI predicts peri-MI	Stable patients	54			
Wu[83]	2014	Cohort	To investigate if pre-PCI predicts peri-MI	Unstable angina	57			
IMR as endpoint of treatment								
First author	**Year**	**Design**	**Intervention**	**Clinical setting**	**N, total**	**A**	**B**	**C**
Sezer[84]	2007	Pilot randomized trial, halted early for positive results	IC streptokinase (A) vs placebo (B) after PPCI	STEMI	41	21	20	
Cuisset[85]	2008	Randomized, single center trial	Direct stenting (A) vs stent implantation after predilation (B)	Elective PCI	55	25	24	
Sezer[86]	2009	Randomized, single center trial	IC streptokinase (A) vs placebo (B) after PPCI	PPCI after STEMI	95	51	44	
Ito[87]	2011	Randomized, single center trial	Distal protection (A) vs placebo (B) during PPCI	anterior STEMI	36	19	17	
Fuji[88]	2011	Randomized non-blinded, single center trial	Pravastatin 20mg/day (A) vs placebo (B)	Stable angna	80	40	40	
Kirma[89]	2012	Randomized, single center trial	Bolus of IC tirofiban (A) vs bolus oif IV tirofiban plus infusion (B)	first anterior STEMI	49	25	24	
He[90]	2013	Randomized non-blinded, single center trial	Atorvastatin 40mg/day (A) vs atorvastatin 20mg/day (B) for 7 days before PCI	Stable angina	84	43	41	
Ito[91]	2013	Randomized, prospective, cross-over study	IC nicorandril first (A) vs IC nitroglicerin first (B)	first STEMI	60	30	30	

Main findings	N (%), peri- MI	IMR, baseline peri_MI		IMR, post-PCI peri-MI		Best pre-PCI IMR	Ss	Sp	AUC
		yes	no	yes	no				
Univariate predictors of periprocedural MI were pre-PCI IMR (P=0.003) and number of stents (P=0.039). Pre-PCI IMR was the only independent predictor.	10 (20%)	31.6 ± 11.8	17.6 ± 9.7	22.6 ± 18.7	17.5 ± 9.0	27	80	85	0.80
pre-PCI IMR was the strongest independent predictor of periprocedural MI (β=0.7, p=0.02)	33 (61%)	21.2 ± 2.1	15.6 ± 1.8	25.9 ± 3.8	16.1 ± 2.01	-	-	-	0.64
IMR correlated with peak troponin (r=0.805, p=0.001), and with peak CKMB (r=0.608, p=0.003)	22 (39%)	20.1 ± 11.7	16.9 ± 8.8	35.4 ± 13.3	18.3 ± 7.1	31	86	91	0.93

Main findings	Primary endpoint, targeted detectable effect
2 days after PPCI, CFR (2.01±0.57 vs. 1.39±0.31), IMR (16.29±5.06 U vs. 32.49±11.04 U), collateral flow index and coronary wedge pressure were significantly improved in A	Composite of IMR, CFR, wedge pressure, collateral flow index and coronary diastolic deceleration time
B had significantly greater IMR (A: 13±3, B 24±14; p<0.01) than A and tended to have greater post-PCI troponin T (A: 0.035±0.04, B:0.17±0.02; p=0.07)	Difference of 30% in IMR between A and B
At 6 months, infarct size (22.7 vs 32.9%, p=0.003) and LV ejection fraction (77.2% sv 51.8%, p=0.018) were higher in group A as compared to B	Long term LV infarct size at 6 months
IMR was significantly lower in A compared to B (A: 26.6±25.8 U vs 37.2±23.2 U, p=0.032)	Difference of XX% in IMR between A and B
IMR was significantly lower in A compared to B [A: 12.6 U (IQR 8.8 to 18.0) vs 17.6 U (IQR 9.7 to 33.9), p=0.007]	NA
IMR (A: 27±13 vs 35±15U, p=0.08) and CFR (A: 2.2±0.7 vs 1.9±0.6, p=0.25) were not statistically different between A and B	Difference of 30% in IMR and CFR between A and B
IMR was significantly lower in A compared to B (A: 16.5±6.1 U vs 31.2±16 U, p<0.001)	NA
A decreased IMR significantly more than B [Decrease in IMR A: 10.8 U (IQR 5.7 to 20.7) vs 2.1U (IQR 1 to 6), p=0.007]	Change in IMR

Table 3 | Use of index of microcirculatory resistance in stratifying risk of periprocedural myonecrosis and as endpoint of trials(continued)

First author	Year	Design	Study outline	Clinical setting	N, total	A	B	C
Mangiacapra[92]	2013	Randomized, double-blinded study	IC enalaprilat (A) vs placebo (B)	Stable angina	40	20	20	
Hirohata[93]	2014	Randomized non-blinded, single center trial	Nicorandril (A) vs placebo (B) before PCI	Stable angina	62	33	29	
Ahn[94]	2014	Randomized non-blinded, single center trial	IC abciximab vs 10 thrombus aspiration vs IC abciximab and thrombus aspiration	STEMI	40	10	10	20
Woo[95]	2014	Randomized non-blinded, single center trial	Thrombus aspiration (A) vs no thrombus aspiration (B)	STEMI	63	33	30	

IMR: index of microcirculatory resistance; PPCI: primary percutaneous intervention; CK: creatinin kinase; LV: left ventricle; CFR: coronary flow reserve; STEMI: ST-elevation myocardial infarction; peri-MI: periprocedural myocardial necrosis, Ss: sensitivity, Sp: specificity; Ac: area under the receiving operating curve

Main findings	N (%), peri- MI	IMR, baseline peri_MI yes	IMR, baseline peri_MI no	IMR, post-PCI peri-MI yes	IMR, post-PCI peri-MI no	Best pre-PCI IMR	Ss	Sp	AUC
A resulted in significant reduction in IMR (27 ± 11) at baseline vs. 19 ± 9 after drug vs. 15 ± 8 after PCI), whereas a significant post-PCI IMR increase was observed in B (24 ± 15 at baseline vs. 24 ± 15 after drug vs. 33 ± 19 after PCI)				45% reduction in IMR					
post-PCI IMR and troponin 24 hours post-PCI were significantly higher in B compared to A (IMR: 25.4±12.1 vs. 17.9±9.1 U and troponin I: 0.21±0.13 vs. 0.12±0.08 ng/mL, respectivelyl).				NA					
IMR was lower in the C than in A (23.5±7.4 U vs. 66.9±48.7 U, p=0.001) and tended to be lower than in B (23.5±7.4 U vs. 37.2±26.1 U, p=0.07)				IC abciximab and thrombus aspiration would by superior to each treatment alone by 14 IMR U					
IMR (23.5±10.2 U vs 34.2±21.7 U, p=0.018), change in LV ejection fraction (follow-up vs baseline; 3.33±4.6% vs 0.73±1.9%, p=0.005), and change in wall motion score (follow-up vs baseline; -0.121±0.16 vs. -0.004±0.07, p=0.001) were better in A				NA					

A landmark multicentre study[51] (n=253) of STEMI patients undergoing PPCI and IMR measurement immediately after, reported that patients with IMR>40 U (mean) had higher rates of death or re-hospitalization for heart failure at 1 year than patients with IMR ≤40 (17.1% versus 6.6%, p=0.027). Furthermore, IMR>40 U was the only independent predictor of death alone (HR, 4.3 95% CI: 1.3–15.0; p=0.02). Thus, IMR seems to have the potential to identify those patients who may require closer follow-up after STEMI. Altogether, this consistent supporting data has substantiated the use of IMR in ACS and other clinical settings where microcirculatory abnormalities are suspected,[52] including a growing role as endpoint of clinical trials (Table 3). Finally, a word of caution should be urged regarding the IMR cut-off, as up to know, non of the proposed ones has been confirmed in independent validation cohorts. A summary of proposed IMR cut-offs is provided in Figure 3.

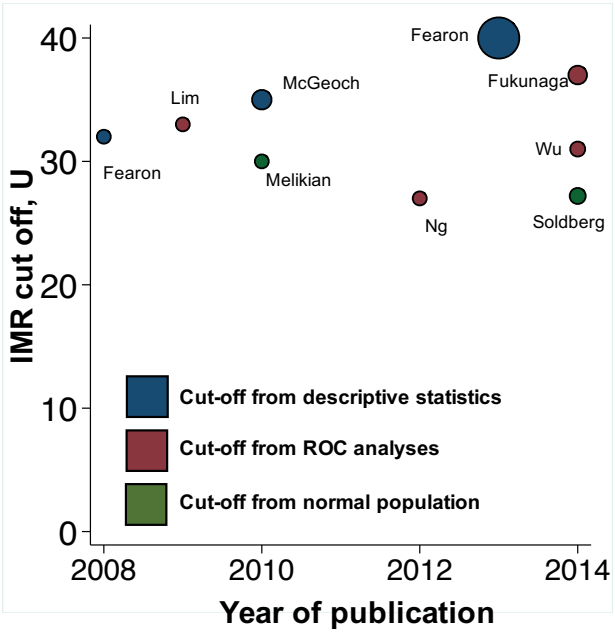

Figure 3 | This figure summarizes the proposed cut-off values for the IMR (y-axis) according to study design (color), year of publication (x-axis) and weighted-sample size (size of marker). ROC: receiver operating curve analyses.

Finally, the effect of upstream epicardial stenosis on the distal microcirculatory resistance in humans has been a subject of debate. Verhoeff et al investigated this phenomena and calculated hyperemic microvascular resistance as distal pressure divided by Doppler-derived flow velocity.[53] These authors concluded that hyperemic

microvascular resistance is elevated distal to the stenoses because of the lower perfusion pressure caused by the trans-stenotic pressure loss. Furthermore, they reported that microvascular resistance was reduced by PCI to a value even lower than in a non diseased reference vessel of the same patient. On the other side, other groups have observed that hyperemic microvascular resistance is independent from epicardial conductance.[54] The main difference between these two arguments results from whether if the effect of collateral flow (as derived from wedge pressure) should be incorporated or not in the calculation of minimal microvascular resistance. Indeed, studies that have corrected IMR for wedge pressure have observed that the difference between uncorrected and corrected IMR is related to FFR such that a more significant stenosis causes a larger discrepancy.[54] The opposite argument is substantiated by the fact that animal and experimental data suggests that wedge pressure does not parallels collateral flow support in a linear fashion, because wedge pressure is also influenced by venous pressure, heart rate, ventricular wall stress and end diastolic left ventricle pressure.[55] Therefore, IMR correction for coronary wedge pressure might overestimate collateral contribution. Whilst this area should be further examined, recent evidence suggest that collateral flow is only of a notable influence with severe stenosis (FFR<0.6),[53] so that the incorporation of wedge pressure into the calculation of microcirculatory resistance might most likely be appropriate only in very severe stenosis.

Thermodilution curve patterns

Not only IMR but also the shape of the hyperaemic thermodilution curve appears to provide incremental information (Figure 4, panel A).[56] A study of 88 patients admitted for STEMI that classified such curves in narrow unimodal, wide unimodal and bimodal observed associated to the latter shape a higher prevalence of microvascular obstruction on CMR when compared with the other groups (100%, 78%, and 30% respectively; p<0.001). Furthermore, patients with bimodal curves had a higher risk of death and heart failure rehospitalization at 6 months (73%, 6.3%, 7.3%; p<0.001). Whilst the authors hypothesize that bimodal patterns may indicate myocardial edema and extrinsic compression of the capillary network, further studies on the reproducibility of this novel index are still needed to accurately establish its clinical relevance.[57]

Indices derived from coronary flow velocity

Doppler flow-velocity systems were firstly introduced to the coronary circulation by Cole in the 1970s,[58] mounted in coronary wires by Doucette in 1992[59] and combined with coronary pressure in humans by Serruys in 1993.[4] Although technically more demanding than the coronary thermodilution method, emerging supportive invasive[60] and non-invasive[61] data as well as the ability to measure rapid-phasic changes in coro-

Table 4 | Use of physiology indices derived from coronary flow velocity in acute coronary syndromes

First author	Year	Design	Index	Study outline, objective	Clinical setting
Kern[60]	1996	Consecutive cohort	Flow velocity	To investigate the relationship between TIMI frame count and Doppler flow velocity in STEMI	recent STEMI
Claeys[96]	1996	Transversal, analitical	CFVR	To compare CFVR in patients with and without STEMI	recent STEMI and stable symptoms
Iwakura[69]	1996	Transversal, analitical	CFVR, flow velocity patterns	To investigate the effect of no-reflow in flow velocity patterns	recent STEMI
Mazur[64]	1998	Cohort	CFVR	To assess if CFVR post-PCI for STEMI CFVR predicts LV function recovery	STEMI
Shimada[72]	2003	Cohort	CFVR, Pzf	To investigate the relation between CFVR and Pzf with residual myocardial viability	Anterior STEMI
Takahashi[63]	2004	Cohort	CFVR	To assess if CFVR post-PCI for STEMI CFVR predicts LV recovery	STEMI
Bax[2]	2004	Cohort	CFVR	To determine predictors of LV function recovery at the time of PPCI	STEMI
Yoon[65]	2008	Cohort	CFVR, DDT, SFR, HMR	To determine predictors of LV function recovery at the time of PPCI	STEMI
Kitabata[67]	2009	Cohort	HMR, CFVR, DDT, Pzf	To investigate if post-PPCI HMR predicts transmural extension of infarction	first anterior STEMI
De Silva[74]	2012	Cohort	Wave intensity analysis, HMR	To determine whether early wave intensity analysis-derived microcirculatory (backward) expansion wave energy predicts late LV viability, defined by functional recovery	non-STEMI
Kitabata[68]	2013	Cohort	HMR, CFVR, DDT	To investigate if post-PPCI HMR predicts transmural LV dilation	first anterior STEMI
Van de Hoef[12]	2013	Cohort	CFVR, DDT, SFR	To identify independent predictors of long term mortality after STEMI	STEMI

TIMI: Thrombolisis in myocardial infarction frame count; PCI: percutaneous intervention; MACE: major adverse cardiac events; LV: left ventricle; STEMI: ST-elevation myocardial infarction; Echo: echocardiography; FDG: 18 fluorodeoxyglucose; PET: positron emission tomography; CMR: cardiac magnetic resonance; CFVR: coronary flow velocity reserve; DDT: diastolic deceleration time; Pzf: zero flow pressure; HMR: hyperaemic microvascular resistance index;

N, baseline	N, follow-up	Main finding	Non invasive imaging	Follow-up
41	41	Post-PCI flow velocity correlated with TIMI frame count (r=0.45,p<.02). However, there was a large overlap in low flow velocity (<20 cm/s) across grades of TIMI flow. Nine of 11 MACE occurred in patients with low coronary flow velocity.	-	18 months
36	-	In patients with a recent MI, CFVR was significantly (p=0.001) lower (80%) than in those without (44%) STEMI both before and after PCI	-	-
42	-	Early systolic retrograde flow and diastolic deceleration rate were significantly higher in patients with no reflow by contrast Echo	Echo	-
32	32	CFVR in the infarct-related artery was significantly higher in the those where LV function recovered (1.43 ± 0.57 vs 0.98 ± 0.70, p=0.0001).	Echo	7 weeks
27	27	Pzf (r=-0.696, p<0.001) and not CFVR (r=-0.07, p=NS) correlate with residual myocardial viability as assessed by FDG uptake by PET	PET	-
67	52	CFVR correlated with the change of wall motion score (r = 0.68, p <0.0001 by Echo. The optimal CFVR cut-off for predicting wall motion recovery was 1.4 (sensitivity 85%, specificity 94%).	Echo	3 weeks
73	73	CFVR was the only independent predictor of global and regional recovery of LV function at six months	Echo	6 months
50	50	Recovery of LV function by Echo was correlated with CFVR (r= −0.442, p=0.002), DDT (r= −0.511, p <0.001), HMR (r=0.443, p=0.002), coronary wedge pressure (r = 0.474, p <0.001), and FDG uptake (r= −0.571, p<0.001).	PET/Echo	6 months
27	27	The area under the curve for transmural extension of infarction tended to be higher for HMR (0.885) than for CFVR (0.848), DDT (0.862) or Pzf (0.853).	CMR	13 days
31	31	Backward-traveling (microcirculatory) expansion wave was inversely correlated with infarct mass (r=–0.81; P<0.0001) and strongly predicted regional LV recovery (r=0.68; P=0.001).	CMR	3 months
24	24	HMR was the only independent predictor for the development of LV remodeling at follow-up (odds ratio: 7.15; 95% confidence interval [CI]: 1.20 to 42.6)	CMR	8 months
100	94	CFVR in the non-culprit vessel was independent predictor of long-term cardiac mortality (hazard ratio, 4.1; 95% confidence interval, 1.2–14.2) whereas CFVR in the culprit vessel, DDT and SFR were not.	-	10 years

nary flow velocity has renewed the interest in this "time-honoured" technique (Figure 4, panel B).

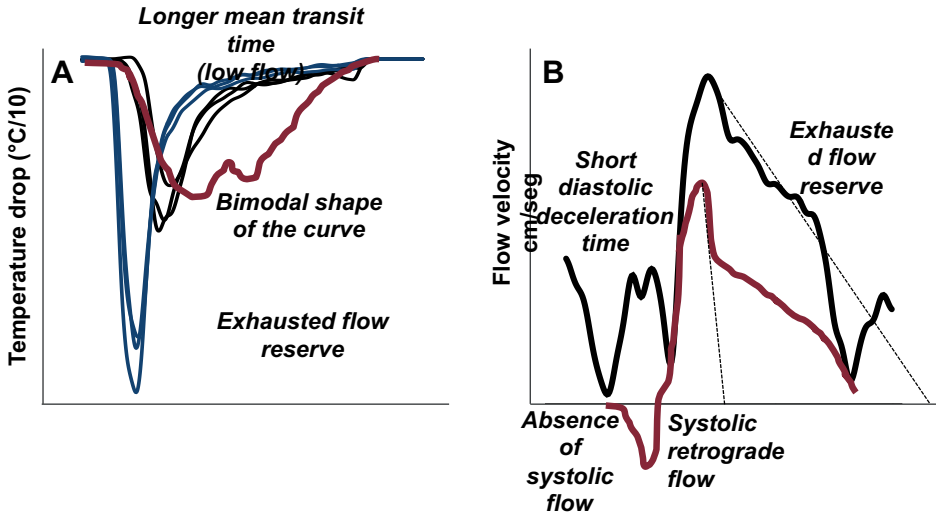

Figure 4 | This figure contrasts normal phasic patterns of intracoronary flow measurements with those observed during STEMI. Panel A shows baseline (black) and hyperaemic (blue) thermodilution curves in triplicate. Signs associated to STEMI are superimposed in red: longer mean transit time and a bimodal shape of the thermodilution curve. Panel B shows in black a normal spectral envelope of Doppler flow velocity. Signs associated to STEMI are superimposed in red: exhausted CFVR, systolic retrograde flow, short diastolic deceleration time and absence of systolic flow.

Coronary flow velocity reserve

Coronary flow velocity reserve (CFVR) is the ratio of hyperemic-to-baseline coronary flow velocity and is a marker of the integrity of both the epicardial and microvascular domains of the coronary circulation. CFVR was introduced to ACS by Kern,[62] and has greatly serve to appraise the human pathophysiology of STEMI (Table 4). For example, the former study early demonstrated that the achievement of successful epicardial vessel´s patency does not homogeneously translate into complete microcirculatory reperfusion after STEMI, as illustrated by the wide variability of flow velocity observed post-PCI in the TIMI-3 vessels of this study.[62]

Post-PPCI CFVR measurements have been inversely related to microvascular obstruction at CMR[63] and have shown to predict infarct size[64] and LV recovery,[2,65,66] even in a comparable way when contrasted to fluorodeoxyglucose positron emission tomography.[67] Notably, in the largest (n=73) available study[2] and among several measurements of microcirculatory function, CFVR was the only independent predictor for regional and global recovery of LV function at six months. This study provided a pragmatic CFVR cut-off, as all patients with CFVR≥2 immediately after PPCI showed some improvement

in LV function at long term follow-up. Recently, van de Hoef et al. reported long-term follow-up in 100 patients admitted for STEMI in whom CFVR, diastolic deceleration time, and systolic flow reversal were measured in both the infarct-related artery and a non-culprit reference vessel.[12] Interestingly, the authors found that CFVR in the non-culprit vessel was an independent predictor of long-term cardiac mortality (hazard ratio, 4.1; 95% confidence interval, 1.2–14.2), with 2.1 as the optimal CFVR cut-off for such event. Diastolic deceleration time, presence or absence of systolic flow reversal, and –surprisingly— the CFVR measured in the infarct-related artery were not predictive of long-term cardiac mortality. This study highlights the importance of microcirculatory function in outlining clinical outcomes [68] and the value of CFVR in assessing risk for further MACE.

Hyperemic microvascular resistance

The combination of hyperaemic distal coronary pressure with coronary flow velocity in the hyperaemic resistance index (HMR) appears an attractive and incremental tool to CFVR as it is not influenced by variations of baseline flow. Kitabata et al.[69] showed that post-PPCI HMR was significantly correlated to peak-CK-MB and infarct size as assessed by CMR. In the same line, HMR has been also correlated to myocardial viability as assessed by fluorodeoxyglucose positron emission tomography and to recovery of LV contractility in patients admitted for STEMI.[67] Finally, HMR has also been found as the only independent predictor of LV remodeling at 8 months (defined as an increase in LV end-diastolic volume of ≥20% by CMR); as compared to myocardial blush grade, ST-segment resolution, CFVR, diastolic deceleration time and CMR defined-microvascular obstruction.[70]

Indices derived from phasic coronary flow velocity patterns

A growing interest in understanding phasic coronary pressure and flow physiology has been nursed by the expectations of appraising more detailed insights into determinants of myocardial perfusion than those provided by traditional means-per-beat methods. Iwakura et al.[71] were the first to describe early retrograde systolic flow and rapid deceleration of the diastolic flow velocity in patients with no reflow phenomenon (Figure 5). Afterwards, Okamura[72] categorized flow velocity patterns according to no reflow phenomenon, and observed that with advancing degrees of microcirculatory damage, diastolic deceleration time shortened first, followed by the appearance of retrograde systolic flow, and finally by disappearance of systolic anterograde flow. Interestingly, these characteristic flow velocity patterns were associated with reduced recovery of regional wall motion and LV ejection fraction. Phasic flow velocity analysis have been combined more recently with distal pressure allowing thus the appraisal of phasic resistance indices. Both the hyperaemic mid-diastolic coronary pressure-flow

relationship (IHDVPS) and, in particular, its intercept with the pressure axis (the zero flow pressure), have a theoretical advantage over CFVR, as they assess coronary flow over a pressure range without the interference of cardiac contraction, providing thus a more comprehensive assessment of the microcirculatory compartment.[14] Theoretically, any decrease in diastolic perfusion due to microcirculatory structural alterations or the effects of the surroundings,[73] such as myocardial edema or haemorrhage during STEMI, should results in a rightward displacement of the diastolic pressure-flow relationship. Under this conditions, the intercept or zero flow pressure shoudl increase, and emerging human data is providing support to this theoretical background.[74]

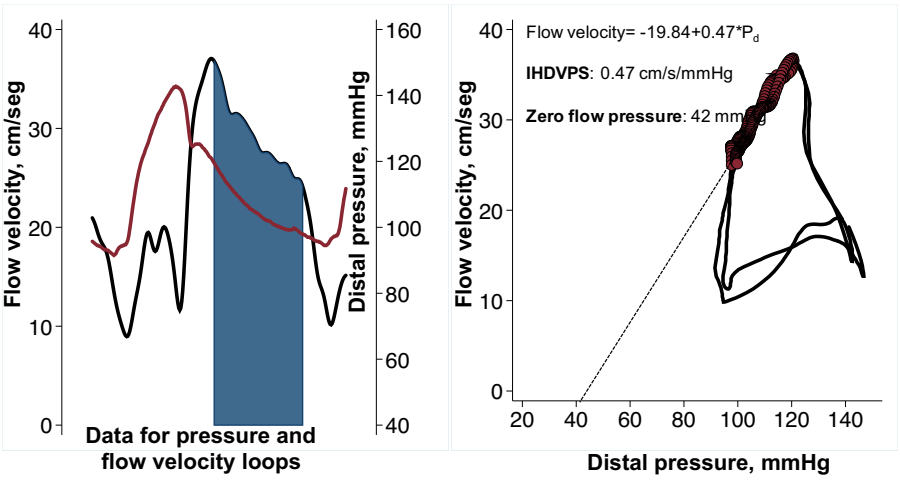

Figure 5 | Panel A shows phasic distal pressure (red) and Doppler flow velocity (black). The period of the cardiac cycle used to calculate the hyperaemic mid-diastolic coronary pressure-flow relationship (IHDVPS) and its intercept with the pressure axis (the zero flow pressure) is highlighted in blue. Panel B shows an example of the former indices.

Finally, the use of wave energetics to analyze phasic flow velocity and coronary pressure [75] has represented a paradigm shift in the evaluation of microcirculatory function. By providing detailed insights into the determinants of myocardial perfusion and the ventriculo-arterial coupling, wave intensity analysis might allow a more-in-deep evaluation of ACS physiopathology. Initial human data in ACS is also encouraging.[76]

RECOMMENDATIONS

From a clinical standpoint, we would offer the following recommendations for the use if physiology indices in ACS, which largely coincide with those proposed by Hennigan et al.[77]:

1. FFR measurements in the culprit vessel of patients with STEMI are not recommended in the acute setting, although FFR is reliable more than six days after the STEMI.
2. Bystander multivessel disease in the ACS setting can be interrogated with FFR, althoug always with caution and after culprit vessel PCI. A clear positive FFR result can be trusted in the clinical decision-making process, but caution should be urged in borderline FFR values, particularly in STEMI, as the recovery of the microciculation might decrease the FFR. Here, it seems appropriate to consider subsequent non-invasive testing or alternatively a repeat FFR assessment at a later date.
3. The use of flow-based physiology indices in the setting of ACS (including resistance indices) should be encouraged, as they provide valuable information in terms of risk stratification.

CONCLUSIONS

Acute coronary syndromes (ACS) are prevalent and portend a poor prognosis. Whilst very little doubt exists about the clinical benefit of restoring culprit vessels´ patency in patients admitted for ACS, the risk stratification and individual treatment strategy in these complex scenario is not always straight forward. This is because the extension of myocardial damage and left ventricle recovery are difficult to predict, and a sizable proportion of patients admitted for ACS have bystander MVD. Available literature clearly underscores the diagnostic value of intracoronary physiology indices in guiding treatment and providing further risk stratification in patients suffering from ACS.

FUTURE PERSPECTIVE

The proportion of patients undergoing cardiac catheterization for ACS is increasing worldwide. Since coronary revascularization based on functional rather than anatomic stenosis assessment has demonstrated to result in better patient outcomes in the stable setting, it can be expected that the use of physiology indices in patients admitted for ACS will also increase. Current data supports the adyuvant role of FFR in guiding treatment of bystander multivessel disease, and flow-based indices such as CFR and resistance indices (IMR, HMR) seem to have the potential to identify those patients who may require closer follow-up because of an increase risk for MACE. Therefore, in the future treatment strategy of patients suffering from an ACS, coronary physiology might play a pivotal role, by providing evidence-based elements for further optimal treatment and risk stratification.

EXECUTIVE SUMMARY

Introduction

1. Risk stratification and individual treatment strategy in patients admitted for ACS is complicated by the facts the extension of myocardial damage and left ventricle recovery are difficult to predict, and a sizable proportion of patients admitted for ACS have bystander MVD.

Functional assessment of non-culprit stenosis during ACS

1. FFR has become the standard method to assess epicardial stenosis severity in stable patients following the demonstration that decision-making based on FFR results in better outcomes than decision-making based on angiography.
2. Available studies supports the inclusion of FFR in the decision making process of bystander MVD in patients admitted with ACS. However, randomized clinical data is lacking.

Functional assessment of culprit stenosis during ACS

1. FFR use in culprit vessels during the acute phase of STEMI is not recommended, although as early as 6 days after the infarction, FFR can reliably outline post-STEMI inducible ischaemia.
2. Hyperaemic microcirculatory resistance in chronic infarcted and non-infarcted territories appears comparable. Therefore, the FFR cut-off established for non-infarcted territories seems also dependable in infarct areas.
3. In the chronic STEMI phase and in spite of this reduction in viable myocardium, most culprit stenoses will still be haemodynamically significant for the perfused viable mass within the infarcted region.

Prediction of left ventricle recovery and risk stratification in ACS

1. Several physiology indices have shown to provide incremental information in terms of risk stratification after ACS
2. In a large study of STEMI patients undergoing PPCI and IMR measurement immediately after, IMR>40 U was the only independent predictor of death alone at one year.
3. In patients admitted for STEMI, culprit and distant vessel CFR has been able to predict left ventricle recovery and stratify the risk of future MACE.

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CHAPTER 11

Impact of age on microcirculatory function and intracoronary physiology indices of stenosis severity

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Submitted

ABSTRACT

Aims

Physiology-guided coronary revascularization has not been specifically studied in elderly patients, even though ageing likely interferes with the applicability of intracoronary physiology indices. We studied the effect of age on intracoronary physiology parameters.

Methods and results

Intracoronary pressure and flow were measured with the Doppler-technique in 299 vessels (228 patients), and thermodilution-technique in 120 vessels (99 patients). In 172 patients, Doppler measurements were also performed in unobstructed vessels. Associations of coronary hemodynamics with ageing were studied in both the stenosed and unobstructed arteries.

Ageing was associated with a progressive increase in hyperaemic microvascular resistance and a progressive decrease in hyperaemic flow. Both in unobstructed (β-0.016±0.005, p=0.001) and obstructed coronary arteries (β-0.015±0.004, p<0.001), age was the strongest independent determinant of coronary flow reserve (CFR), where CFR decreased with advancing age. In obstructed coronary arteries, age was an independent albeit modest determinant of FFR (β 0.002±0.001, p=0.007), where FFR increased with advancing age. Consequently, the adjusted-risk of an FFR/CFR pattern reflective of diffuse or microvascular disease (RR 1.6, 95% CI: 1.1 – 2.3; p=0.017) increased with advancing age, whilst the adjusted risk of a FFR/CFR pattern reflective of non-flow-limiting stenosis with a healthy microcirculation (RR: 0.7, 95% CI: 0.5 – 1.0; p=0.022) decreased.

Conclusion

Ageing is associated with progressive pan-myocardial impairment of coronary vasodilatory capacity. Consequently, for a given stenosis, ageing is associated with a progressive increase in FFR and decrease in CFR, in contrast with any other physiological index of stenosis severity, which should be taken into consideration in clinical decision-making.

INTRODUCTION

Physiology-guided coronary revascularization using fractional flow reserve (FFR) has shown to improve clinical outcomes in stable ischaemic heart disease (IHD) compared with angiographic guidance.[1] However, it should be born in mind that the applicability of these findings to specific patient subsets, such as advanced age, is less clear, as specific supportive data is scarce. This is particularly important for advanced age, because the (patho)physiological changes of the coronary vasculature and alterations in myocardial function commonly associated with the process of ageing may theoretically interfere with the reliability of invasive physiology parameters, like FFR.[2,3] These considerations are essential in an era when, as a result of changing demographics, an increasing number of elderly patients is being referred for percutaneous coronary intervention (PCI),[4] while our understanding of the influence of ageing on coronary indices used to guide coronary revascularization remains limited. Accordingly, in this study, we sought to document the changes in coronary physiology associated with ageing in a clinical cohort of patients with IHD undergoing coronary physiological assessment, both in stenosed coronary arteries and in a sub-cohort of angiographically normal reference coronary arteries, using a comprehensive physiological assessment with combined coronary pressure and coronary flow measurements.

METHODS

Data source

We included patients with a clinical indication for physiological assessment of ≥1 stenosis of intermediate angiographic severity (40 – 70% diameter stenosis) at the Academic Medical Centre (AMC), Amsterdam, the Netherlands, and Hospital Clínico San Carlos (HUCSC), Madrid, Spain. Exclusion criteria were restricted to culprit vessels of acute coronary syndromes, serial stenoses, left main stenosis, significant valvular pathology, and prior coronary artery bypass graft surgery. The local ethical review boards approved the respective study protocols, and all subjects gave written informed consent.

Cardiac catheterization and hemodynamic measurements

Cardiac catheterization was performed according to standard clinical practice. Angiographic images were recorded in a manner suitable for quantitative coronary angiography (QCA) analysis. After diagnostic angiography, sensor-equipped guide wires were used to measure intracoronary pressure and flow. In AMC, coronary flow was assessed using the Doppler-technique,[5] and baseline (bAPV) and hyperaemic average peak

velocities (hAPV) were labelled baseline and hyperaemic flow, respectively. In HUCSC, coronary flow was assessed with the coronary thermodilution-technique.[6,7] Resting and hyperaemic thermodilution curves were obtained in triplicate, and the inverse of the average basal (Tmn_{bas}) and hyperaemic mean transit times (Tmn_{hyp}) was labelled baseline and hyperaemic flow, respectively.[6,7] Coronary flow reserve (CFR) was calculated as the ratio of hyperaemic to baseline flow, where CFR≥2.0 was considered normal, and FFR as the ratio of mean hyperaemic distal pressure (Pd) to mean hyperemic aortic pressure (Pa), where FFR>0.80 was considered normal. Microvascular resistance was calculated from both Doppler and thermodilution-derived data as mean Pd divided by flow, and was determined during both baseline and hyperaemia. Stenosis resistance was calculated from Doppler data only as the mean pressure drop across the stenosis (mean Pa- mean Pd) divided by Doppler flow velocity (at baseline and hyperemia). In AMC, coronary flow was additionally measured in a reference coronary artery, defined as a coronary artery with <30% diameter stenosis on visual assessment, if available. In the absence of obstructive coronary artery disease, reference vessel microvascular resistance was calculated as the ratio between mean aortic pressure and distal flow velocity (during baseline and hyperaemia). Hyperaemia was induced by either intracoronary bolus injection (20-40μg) of adenosine at AMC, or intravenous infusion (140μg/kg/min) at HUCSC.

Statistical analysis

Categorical variables are presented as counts and percentages. Continuous variables are presented as mean ± standard deviation (SD) or median [1st and 3rd quartiles (Q1, Q3)]. Normality and homogeneity of the variances were tested using Shapiro-Wilk and Levene tests. Data was analysed on per-patient basis for clinical characteristics, and on per-vessel basis for the rest of calculations. For descriptive statistics, the study population was stratified in three representative age categories, defined by the quartiles of age. Patients within the 1st quartile were considered "young", patients across quartile 2 and 3 "intermediate", and patients within the 4th quartile "elderly". For vessel-to-patient analyses, robust regressions with Huber-White robust standard errors were used to adjust for clustering of vessels within patients, where appropriate. Overall differences between groups were compared with one-way analysis of variance (ANOVA), Kruskal-Wallis or Chi square test, followed by post-hoc t tests, Mann-Whitney U or Fisher´s exact tests, with Bonferroni-adjusted significance level. The association of age with physiological parameters was tested with robust linear regression analysis, where applicable. Linear mixed models were used to identify independent predictors of FFR and CFR, using Mallow's Cp as criterion for selection of the optimal predictive model, with candidate variables including clinical characteristics (Table 2), clinical presentation, angiographic stenosis severity, and the interrogated vessel (left anterior

descending (LAD), left circumflex (LCx), or right (RCA) coronary artery). These results are presented as beta ± robust standard errors, and standardized coefficients to facilitate comparison. For reference vessel analysis, where all patients had stable symptoms, candidate variables included clinical characteristics (Table 2), and the interrogated vessel. Differences were considered significant at $p<0.05$ (two-sided). The STATA 13.1 (StataCorp, College Station, Texas) statistical software package was used for all calculations.

RESULTS

Patient population

In total, 327 patients with 419 stenosed vessels were investigated: 228 patients (299 vessels) with Doppler-derived flow, and 99 patients (120 vessels) with thermodilution-derived flow. Reference vessel measurements were performed in 172 out of 228 patients (75%) studied with Doppler-derived flow. Clinical characteristics of the complete study population are shown in Table 1. Overall, coronary stenoses were of intermediate severity, both angiographically (mean diameter stenosis: 52.7 ± 11.4%) and physiologically (median FFR: 0.81 (Q1-3, 0.72-0.88)). Moreover, as shown in the Supplementary Figure, the distribution of FFR values reflected a clinical population routinely referred for intracoronary physiological assessment.

Table 1 | Baseline clinical characteristics of the study population

	N=327
Age	61±11
Male gender	242 (75)
Hypertension	159 (49)
Diabetes	57 (17)
Family history	109 (33)
Dyslipidaemia	200 (61)
Smoking	94 (29)
Prior myocardial infarction	133 (41)
Prior percutaneus coronary intervention	97 (30)
Multivessel disease	200 (61)

Data presented as frequency (%)

Clinical and angiographic characteristics according to age

Median age of the patient population was 62 years [Q1, Q3: 54, 69 years]. Accordingly, patients were stratified in young (<55 years; n=87 (27%)), intermediate (≥55 and <70

years of age; n=166 (51%)), and elderly (≥70 years of age; n=74 (23%)). Clinical and angiographic characteristics across these age categories are shown in Table 2. Risk factors for IHD were generally less prevalent in elderly patients, whom were significantly less likely to be male, to have family history of IHD, and to smoke (Table 2). Finally, across these age categories, there were no differences in stenosis location or stenosis severity by QCA.

Table 2 | Clinical, angiographic, and physiological characteristics stratified by age categories

	Age			
	<55 (n=87)	55 - 69 (n=166)	≥70 (n=74)	Overall P-value
Clinical Characteristics#				
Male gender	69 (80)[c]	127 (77)	46 (63)[a]	0.03
Hypertension	37 (43)	86 (52)	36 (49)	0.37
Diabetes	13 (15)	35 (21)	9 (12)	0.19
Family history	35 (40)c	58 (35)	16 (22)[a]	0.04
Dyslipidaemia	61 (70)	97 (58)	42 (57)	0.13
Smoking	34 (39)[b,c]	47 (28)[a]	13 (18)a	0.01
Prior myocardial infarction	38 (44)	72 (43)	23 (31)	0.16
Prior PCI	25 (29)	51 (31)	21 (28)	0.91
Multivessel disease	55 (63)	98 (59)	47 (64)	0.64
Angiographic characteristics*	n=117	n=207	n=95	
Lesion location				0.58
LAD	45 (38 - 53)	45 (39 - 52)	54 (45 - 62)	
LCX	21 (15 - 29)	25 (20 - 31)	20 (13 - 29)	
RCA	33 (26 -42)	29 (24 - 36)	26 (19 - 36)	
Reference vessel diameter, mm	2.9 (2.8 - 3.1)	2.9 (2.8 - 3.0)	3.3 (2.5 - 4.1)	0.53
Diameter stenosis, %	54 (52 - 56)	53 (52 - 55)	50 (48 - 53)	0.09
Intracoronary adenosine	85 (75 - 91)[c]	71 (63 - 77)	57 (44 - 69)[a]	0.002
Pressure measurements*				
Pd/Pa	0.88 (0.86 - 0.91)	0.89 (0.88 - 0.91)	0.89 (0.87 - 0.91)	0.66
FFR	0.76 (0.73 - 0.78)[c]	0.78 (0.76 - 0.80)	0.80 (0.78 - 0.83)[a]	0.03
Delta Pd/Pa (Pd/Pa-FFR)	0.13 (0.11 - 0.14)[c]	0.12 (0.11 - 0.13)[c]	0.09 (0.08 - 0.10)[a,b]	<0.001
Flow measurements*				
CFR (combined)	2.4 (2.2 - 2.5)[c]	2.3 (2.1 - 2.4)[c]	1.9 (1.8 - 2.1)[a,b]	<0.001
CFR (doppler)	2.4 (2.2 - 2.6)[c]	2.3 (2.2 - 2.4)	2.1 (1.9 - 2.2)[a]	0.02
CFR (thermodilution)	2.2 (1.7 - 2.7)	2.2 (1.9 - 2.4)	1.8 (1.5 - 2.1)	0.13
APV baseline, cm/s	17 (15 - 18)	18 (16 - 19)	18 (15 - 20)	0.72
APV hyperemia, cm/s	38 (35 - 42)	39 (36 - 42)	36 (31 - 40)	0.51

Table 2 | Clinical, angiographic, and physiological characteristics stratified by age categories (continued)

	Age			
	<55 (n=87)	55 - 69 (n=166)	≥70 (n=74)	Overall P-value
Tmn baseline, s	0.74 (0.51 -0.97)	0.78 (0.67 - 0.89)	0.61 (0.45 - 0.77)	0.25
Tmn hyperemia, s	0.33 (0.27 - 0.40)	0.37 (0.33 - 0.42)	0.34 (0.27 - 0.42)	0.62
Stenosis resistance measurements* (Doppler only)				
BSR (doppler), mmHg/cm/s	0.92 (0.62 - 1.21)	0.89 (0.62 - 1.17)	1.02 (0.56 - 1.48)	0.90
HSR (doppler), mmHg/cm/s	1.02 (0.72 - 1.31)	1.02 (0.73 - 1.31)	1.14 (0.61 - 1.68)	0.91
Microvascular resistance measurements*				
BMR (doppler), mmHg/cm/s	6.10 (5.54 - 6.66)	5.99 (5.54 - 6.44)	6.27 (5.03 - 7.5)	0.89
BRI (thermo), U	56 (37 - 75)	63 (54 - 73)	51 (37 - 65)	0.36
HMR (doppler), mmHg/cm/s	2.18 (1.97 - 2.38)	2.27 (2.04 - 2.49)	2.73 (2.23 - 3.23)	0.14
IMR (thermo), U	19 (16 - 22)	23 (20 - 26)	23 (18 - 28)	0.17
Change MR (combined), %	-60 (-63 - -57)[c]	-60 (-62 - -58)[c]	-52 (-56 - -49)[a,b]	<0.001
Reference vessel measurements# (Doppler only n=172)	n=54	n=88	n=30	
CFR (doppler)	3.2±0.6 [b,c]	2.8±0.7 [a]	2.6±0.7 [a]	<0.001
APV baseline, cm/s	17 (13 - 21)	17 (13 - 22)	16 (13 - 23)	0.72
APV hyperemia, cm/s	53 (40 - 68)[c]	47 (39 - 60)[c]	39 (34 - 52)[a,b]	0.005
BMR (doppler), mmHg/cm/s	5.75 (4.72 - 7.69)	5.67 (4.5 - 7.47)	5.75 (4.42 - 8.29)	0.92
HMR (doppler), mmHg/cm/s	1.89 (1.30 - 2.25) c	1.93 (1.64 - 2.54)[c]	2.45 (1.95 - 3.08)[a,b]	0.002

#Data presented as mean±standard deviation or frequency (percentage); *Data presented as adjusted mean or adjusted frequency (95% confidence interval)
[a]p<0.05 versus young; [b]p<0.05 versus intermediate; [c]p<0.05 versus elderly
PCI: percutaneous coronary intervention; LAD: left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery; Pd/Pa: resting distal coronary to aortic pressure ratio; FFR: fractional flow reserve; CFR: coronary flow reserve; APV: average peak flow velocity; Tmn: mean transit time; BSR: basal stenosis resistance index; HSR: hyperemic stenosis resistance index; SR: stenosis resistance index; BMR: basal microvascular resistance index; BRI: basal index of microvascular resistance; HMR: hyperemic microvascular resistance index; IMR: hyperemic index of microvascular resistance; MR: microvascular resistance

Influence of age on coronary physiology in reference vessels

In the 172 angiographically normal reference coronary arteries in patients evaluated with Doppler flow, mean CFR was 2.9±0.7. The distribution of reference vessel CFR across age is shown in Figure 1. Reference vessel CFR was negatively associated with age (rho=-0.31, p<0.001; $R^{2=}$0.07, p<0.001), with CFR decreasing with advancing age. (Table 2). Such progressive impairment of CFR occurred in the presence of an age –de-

pendent increase in hyperemic microvascular resistance (rho=0.25, p=0.002; R^2=0.06, p=0.002) and a concomitant decrease in hyperemic flow (rho=-0.22, p=0.006; R^2=0.05, p=0.004: Figure 2); while no significant changes in basal microvascular resistance (rho=-0.01, p=0.93, R^2=0.00, p=0.70) or baseline flow (rho=0.013, p=0.87, R^2=0.00, p=0.98: Figure 2) were documented with advancing age (Table 2).

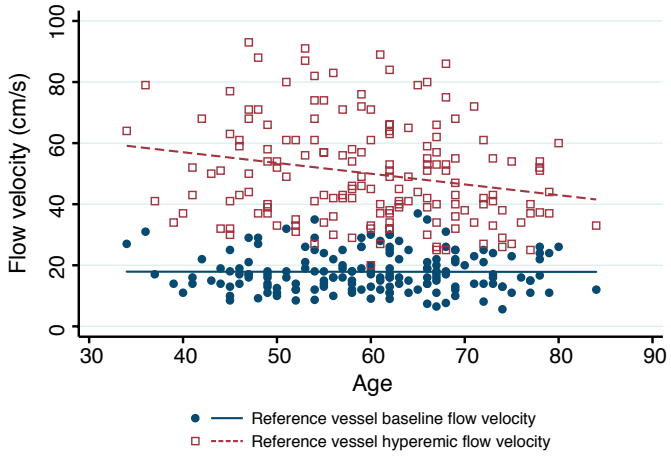

Figure 1 | Scatterplot of reference vessel and target vessel coronary flow reserve (CFR) values according to age. Both in unobstructed reference vessels, and stenosed coronary arteries, ageing is associated with a decrease in CFR.

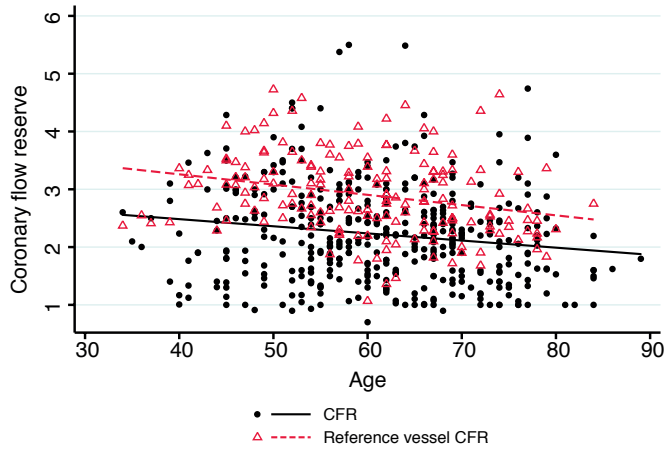

Figure 2 | Scatterplot of reference vessel baseline and hyperemic flow velocity values according to age. With increasing age, a dominant decrease in reference vessel hyperemic flow occurs.

The best multivariable model for the prediction of CFR in reference vessels (R^2=0.11, p<0.001) included age, history of dyslipidemia, and reference vessel (Table 3). Amongst these predictors, age was the strongest independent predictor of CFR in reference vessels, where CFR decreased with advancing age.

Table 3 | Best-fit multivariate linear regression model for the prediction of reference vessel CFR

Variable	Beta	Standard error	Standardized coefficient	p-value
Age	-0.016	0.005	-0.25	0.001
History of dyslipidaemia	0.22	0.105	0.16	0.04
Reference vessel (LAD reference)				
LCx	0.0035	0.111	0.003	0.98
RCA	0.299	0.191	0.12	0.120

LAD: left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery

Influence of age on the physiological assessment of stenosed vessels

The distribution of FFR and CFR values across age in stenosed vessels is shown in Figure 3. FFR showed a significant positive association with age (R^2=0.03, p<0.001) increasing with advancing age. Conversely, CFR showed a significant negative association with age (R^2=0.03, p=0.001). This was also expressed in the overall percent change in microvascular resistance, where the decrease in microvascular resistance from resting to hyperaemia was attenuated with advancing age (R^2=0.03, p=0.002). In contrast, neither resting Pd/Pa in the overall study population (R^2=0.006, p=0.08) nor indices of stenosis resistance in patients studied with Doppler flow (BSR: R^2<0.001, p=0.59; HSR: R^2<0.001, p=0.72) were significantly associated with age. Accordingly, FFR increased significantly and CFR decreased significantly with advancing age (Table 2), while no other index of stenosis severity was significantly associated with age (Table 2).

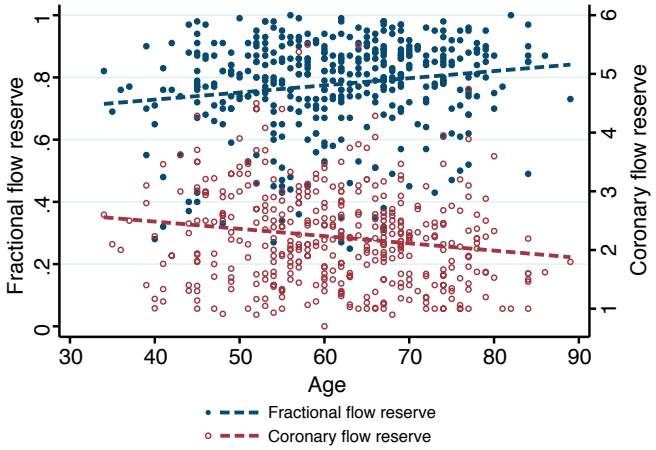

Figure 3 | Scatterplot of FFR and CFR values in stenosed vessels according to age. With advancing age, FFR increases while CFR decreases. These characteristics occurred while no other index of stenosis severity was associated with age.

Notably, hyperaemic microvascular resistance exhibited a significant albeit modest increase with advancing age in those patients studied with Doppler flow (HMR: R^2=0.02, p=0.03), and although trends in microvascular resistance across the age categories were similar between Doppler-derived and thermodilution-derived flow, formal statistical significance was not met in the smaller subcohort of thermodilution measurements (Table 2).

Independent association of age with CFR and FFR in stenosed vessels

The best multivariable model for the prediction of CFR in stenosed vessels (R^2=0.11, p<0.001) included age, prior myocardial infarction, multi-vessel disease, the interrogated vessel, and percent diameter stenosis (Table 4). Amongst these predictors, age was the strongest independent predictor of CFR.

Table 4 | Best-fit multivariate linear regression model for the prediction of CFR in stenosed vessels

Variable	Beta	Robust standard error	Standardized coefficient	p-value
Age	-0.015	0.004	-0.20	<0.001
Prior myocardial infarction	-0.216	0.078	-0.13	0.006
Multivessel disease	0.253	0.080	0.14	0.002
Diameter stenosis	-0.014	0.003	-0.19	<0.001
Lesion location (LAD reference)				
LCx	-0.287	0.098	-0.14	0.003
RCA	-0.097	0.093	-0.05	0.301

PCI: percutaneous coronary intervention; LAD: left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery

The best multivariable model for the prediction of FFR (R^2=0.29, p<0.001) included age, diabetes mellitus, multivessel disease, the interrogated coronary vessel, and percent diameter stenosis (Table 5). Amongst these, diameter stenosis was the strongest independent predictor for FFR. Nonetheless, age was independently associated with FFR, where FFR increased with increasing age.

Table 5 | Best-fit multivariate linear regression model for the prediction of FFR

Variable	Beta	Robust standard error	Standardized coefficient	p-value
Age	0.002	0.001	0.11	0.007
Diabetes	0.033	0.015	0.08	0.029
Multivessel disease	0.034	0.014	0.11	0.018
Diameter stenosis	-0.007	0.001	-0.50	<0.001
Lesion location (LAD reference)				
LCx	0.046	0.017	0.12	0.006
RCA	0.029	0.015	0.09	0.056

LAD: left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery

Effect of age on the CFR and FFR relationship

Age was significantly different across the quadrants of the CFR and FFR relationship (Table 6). Vessels with low FFR and high CFR were more likely observed in younger patients, whilst vessels with high FFR and low CFR were more likely observed in elderly patients.

Table 6 | Accordance and Discordance of FFR and CFR across age categories

	Age			
	<55 (n=87)	55 - 69 (n=166)	≥70 (n=74)	Overall p-value
Pressure/Flow discordance				
FFR>0.80 / CFR≥2.0 *Concordantly normal*	33 (26 - 42)	42 (35 - 48)	32 (23 - 42)	0.15
FFR≤0.80 / CFR≥2.0 *Focal non-flow limiting*	28 (20 - 38)	22 (17 - 28)	15 (9 - 23)	0.08
FFR>0.80 / CFR<2.0 *Diffuse / microvascular disease*	8 (4 - 14)[c]	12 (8 - 17)[c]	26 (18 - 36)[a,b]	<0.001
FFR≤0.80 / CFR<2.0 *Concordantly abnormal*	31 (23 - 40)	24 (19 - 30)	27 (19 - 38)	0.42

Data presented as adjusted frequency, % (95% confidence interval)
[a]p<0.05 versus young; [b]p<0.05 versus intermediate; [c]p<0.05 versus old
FFR: fractional flow reserve, CFR: coronary flow reserve

Figure 4 shows the distribution of FFR and CFR accordance and discordance across decades. After adjustment for independent predictors of FFR and CFR (Table 4 and Table 5), there was an 1.6-fold increase in risk of an FFR/CFR pattern reflective of diffuse or microvascular disease (high FFR, low CFR) (95% CI: 1.1 – 2.3; p=0.017) with each decade increase in age, while there was a decrease in risk of an FFR/CFR pattern reflective of non-flow-limiting stenosis with a healthy microcirculation (low FFR, high CFR) (RR: 0.7 per decade increase in age; 95% CI: 0.5 – 1.0; p=0.022).

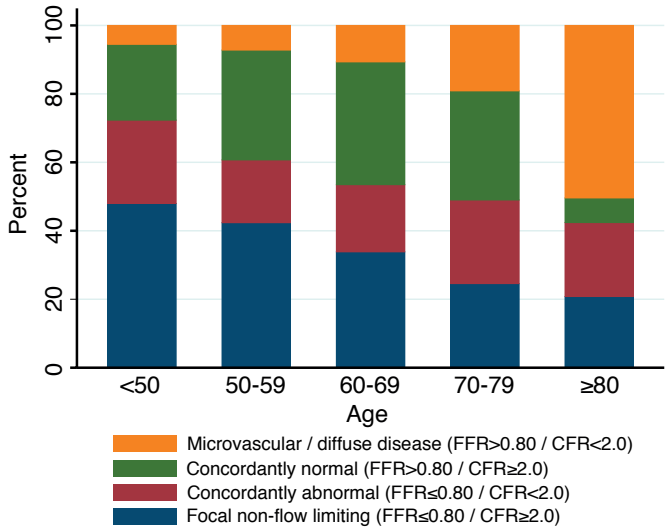

Figure 4 | Prevalence of FFR/CFR accordance and discordance per decade increase in age. With each decade, the prevalence of an FFR/CFR pattern reflective of microvascular and/or diffuse disease increased, whereas the prevalence of an FFR/CFR pattern reflective of a normal circulation or focal stenosis superimposed on a healthy coronary microcirculation tended to decrease.

DISCUSSION

We documented that, in patients with IHD, ageing is associated with microvascular dysfunction, leading to an increased minimal microvascular resistance, and a reduced flow reserve throughout the myocardium. Both in unobstructed and obstructed coronary arteries, age was the strongest independent determinant of CFR, where CFR decreased with advancing age. Similarly, in obstructed coronary arteries, age was an independent determinant of FFR, where FFR increases with advancing age, despite no influence of ageing on stenosis severity as determined either by angiography or other physiological indices of stenosis severity. Importantly, ageing was associated with an increased prevalence of and FFR/CFR pattern associated with microvascular dysfunction or diffuse coronary artery disease. These observations imply a potential impact of

the patient´s age on intracoronary physiological indices routinely used to interrogate the coronary circulation and to guide coronary revascularization.

Ageing, coronary flow reserve, and fractional flow reserve

In our study, advancing age was associated with a decrease in CFR, on the basis of a pathological impairment of microvascular vasodilator function leading to an increased minimal microvascular resistance. This finding is in agreement with previous studies documenting a decrease in CFR with advancing age in unobstructed coronary arteries.[2] The impairment in microvascular vasodilator function with advancing age was associated with a significant albeit modest increase in FFR, despite equivalent stenosis severity with advancing age by several standards, and despite a lower prevalence of cardiovascular risk factors in elderly patients. From a clinical perspective, these findings suggest that the detection of inducible ischaemia with FFR decreases with ageing, whilst the overall burden of ischaemia diagnosed with CFR increases with advancing age. Our findings concur with previous data showing an increased prevalence of exercise related ischaemia on non-invasive testing associated with ageing despite equivalent extent of angiographic coronary artery disease.[8] Hence, our observations confirm that for a given stenosis, FFR may unaccountedly be elevated, and CFR may unaccountedly be impaired, because of (patho)physiological ageing of the microcirculation that influences FFR and CFR in opposite directions. As a result, advancing age is associated with a higher prevalence of vessels with normal FFR but reduced CFR, typically attributed to the presence of diffuse disease or microcirculatory dysfunction, and to a lower prevalence of vessels with abnormal FFR and normal CFR, typically attributed to a focal non-flow limiting stenosis in the presence of a healthy coronary microcirculation.[9-11]

Clinical implications

Our study is the third to report increased FFR values with advancing age, which has until now been attributed to the absence of functionally significant coronary artery disease.[12,13] However, our study is the first to concomitantly assess FFR and physiological stenosis severity derived from the combined assessment of coronary pressure and flow, and to describe the physiological basis of this finding. A higher prevalence of microvascular dysfunction and diffuse atherosclerosis with advancing age[9,11,14] implies that ageing of the coronary vasculature might interfere with the conclusions of such FFR interrogation.[15] With advancing age, FFR progressively underestimates the physiological severity of coronary stenoses due to an increase in minimal microvascular resistance and decrease in hyperaemic flow. This is important, since a normal FFR in an elderly patient might not imply a healthy vasculature, but may reflect the limitations of FFR to detect microcirculatory dysfunction or diffuse disease-related IHD, highly prevalent in such a population. Moreover, a normal FFR might not exclude the presence of coronary flow impairment

well documented to be associated with myocardial ischemia, and unequivocally related to impaired prognosis.[16] Physicians should be aware that, despite the fact that revascularisation might not be indicated in theses vessels, these anomalies might be a cause of ischaemia and thereby justify the clinical presentation, and have important implications for patient prognosis.[17,18] It may even be hypothesised that objective assessment of physiological stenosis severity, with tools independent of microvascular vasodilator function, such as indices of stenosis resistance, might be indicated to identify patients that could benefit from stenosis alleviation despite relatively normal FFR values. The results of the present study substantiate the limitations of using coronary pressure measurements as a surrogate of coronary flow in the diagnosis of the spectrum of ischemic heart disease,[19] should urge broadened clinical judgment to guide clinical decision-making in the individual patient, particularly in the elderly, and substantiate on-going efforts to re-introduce coronary flow-based parameters into routine decision-making.

LIMITATIONS

Our conclusions refer to patients with clinical indication for intracoronary interrogation of epicardial stenosis. Intracoronary flow was assessed with both the Doppler and thermodilution technique; the two available methods for this purpose. Nonetheless, most findings were consistent between technologies, which strengthens the extrapolation of our findings to the clinical setting. Additionally, different administration routes and doses of adenosine were used to induce hyperemia. Although this limits the internal validity of our findings, it enhances their generalization, since this better reflects real-world use of hyperemic agents.

CONCLUSIONS

Advanced age is associated with an increased prevalence of coronary physiological characteristics associated with microvascular dysfunction and diffuse atherosclerosis. The resulting impairment of the vasodilatory capacity of the coronary circulation is associated with a relative increase in FFR and decrease in CFR for a given stenosis, in contrast with any other physiological index of stenosis severity. Moreover, many vessels with normal FFR display abnormal vessel flow characteristics, which become more prevalent with advancing age. Hence, FFR is at risk of progressive underestimation of coronary flow impairment with advancing age, which should be taken into consideration as part of clinical decision-making.

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CHAPTER 12

Influence of the amount of myocardium subtended to a coronary stenosis on the index of microcirculatory resistance. Implications for the invasive assessment of microcirculatory function in ischemic heat disease

Echavarría-Pinto M, van de Hoef TP, Nijjer SS, Gonzalo N, Nombela-Franco L, Ibañez B, Sen S, Petraco R, Jimenez-Quevedo P, Nuñez-Gil I, Cerrato E, Salinas P, Quirós A, García-García HM, Fernandez-Ortíz A, Macaya C, Davies J, Piek J, Escaned J

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ABSTRACT

Aims

The index of microcirculatory resistance (IMR) is growingly used to quantify microcirculatory function. However, in normal coronary arteries, resistance increases with the branching structure of the coronary tree, which suggest that IMR could be influenced by the amount of downstream myocardial mass (MM). We aimed to evaluate the influence of the amount of MM subtended to an intermediate stenosis on the IMR.

Methods and results

IMR, fractional flow reserve and coronary flow reserve (CFR) were measured in 123 coronary arteries (102 patients) with intermediate stenosis. Jeopardized MM was estimated with the Myocardial Jeopardy Index (MJI). MM was inversely associated with IMR (R^2=0.16, p<0.001). Differently, CFR was MM-independent (R^2=0.0). Vessels with IMR ≥30 U subtended lower amounts of MM than vessels with IMR<30 [MJI: 13.0% (Q1-3, 12.5-18.2%) vs 20.4% (Q1-3, 15.10-25.5%), p<0.001], and at multivariate analyses, MM, aortic pressure, minimum lumen diameter and age were independent IMR predictors (R^2=0.24, p<0.001). Vessels with IMR ≥30 U and preserved CFR supplied the smallest MM amounts, suggesting an anatomically reduced but functionally preserved vascular bed.

Conclusions

The amount of myocardium subtending to a coronary stenosis is inversely associated with the IMR, while is not associated with the CFR.

CONDENSED ABSTRACT

We investigated the influence of the amount of myocardial mass (MM) subtended to an intermediate coronary stenosis on the index of microcirculatory resistance (IMR) and the coronary flow reserve (CFR). For this, jeopardized MM was estimated with the Myocardial Jeopardy Index (MJI) in 123 stenosed coronary arteries in whom IMR and CFR were assessed. At univariate analyses, MM was inversely associated with IMR (R^2=0.16, p<0.001) whilst CFR was MM-independent (R^2=0.0). At multivariate analyses, MM, aortic pressure, minimum lumen diameter and age were independent IMR predictors (R^2=0.24, p<0.001). Hence, MM is inversely associated with the IMR, while is not associated with the CFR.

INTRODUCTION

Myocardial flow impairment in ischemic heart disease (IHD) can be due to obstructive or non-obstructive coronary involvement.[1] Fractional flow reserve (FFR) is a valuable tool to assess obstructive causes of IHD, but it does not informs if concomitant non-obstructive involvement, generally caused by microcirculatory dysfunction, is present.[2] The index of microcirculatory resistance (IMR) allows the clinical assessment of microcirculatory resistance, and given its technical simplicity, is growingly used as tool to appraise microcirculatory function in the catheterization laboratory.[3] Yet, a theoretical concern that arises for the widespread use of the IMR is that, in normal coronary arteries, resistance increases across the branching structure of the coronary tree, because coronary flow decreases while the driving pressure remains virtually unchanged.[4] This implies that IMR values could be influenced by the amount of myocardial mass (MM) subtended to the sensor or the epicardial stenosis, in a similar fashion as it has been proposed for FFR.[5] If this physiology basis applies also in clinical pathological settings where IMR is currently used, however, has not been addressed by previous research.

In this study of patients with IHD, we sought to describe how subtended MM influences the IMR. For this purpose, stenosed coronary arteries undergoing FFR interrogation were further investigated with the IMR, and the amount of MM subtended to the index stenosis was estimated with well-validated angiographic indices specifically adapted to this purpose. Additionally, coronary flow reserve (CFR) was also investigated, to achieve additional insights on the functionality of the downstream myocardial bed.

METHODS

Study population

Patients with a clinical indication for FFR interrogation of ≥1 intermediate coronary stenosis [40% to 70% diameter stenosis (DS) by quantitative coronary angiography (QCA)], investigated at Hospital Clinico San Carlos, Madrid, Spain, were prospectively studied. Patients with myocardial infarction <5 days, contraindications to adenosine, left ventricle (LV) ejection fraction <30% or left main disease were excluded, as well as vessels supplying previously known infarcted territories (either by electrocardiographic findings or clinical history), with serial stenoses, marked diffuse narrowings or with surgical grafts. Approval from the Institutional Review Board was obtained and all patients gave informed consent.

Angiographic analysis and estimation of subtended myocardial mass

Optimal angiographic views were obtained following intracoronary nitrates (0.2 mg). Two experienced reviewers blinded to physiology data performed QCA (CASS II, Pie Medical, Maastricht, The Netherlands). DS, lesion length and reference and minimum lumen diameter (MLD) were measured. One experienced reviewer blinded to physiology calculated three well-validated angiographic indices of jeopardized myocardium, first from all angiograms and after 3 months in a random subsample of 30 patients. Specifically, to calculate MM in our study, we followed the methodology modified by Leone et al.[5] We used the Myocardial Jeopardy Index (MJI) as primary jeopardy score because it has been widely used as method to calculate jeopardized myocardium.[6] The MJI incorporates the size, number and distribution of the coronary arteries as well as coronary dominance. The three main coronaries and their terminal branches are graded based on vessel length and size. A score of 0 indicates a minor terminal artery, and a score of 3 represents a large vessel extending more than two thirds of the distance from base to apex. Septal branches are arbitrarily assigned a maximum total score of 3, and right-ventricular marginals and posterior descending septal branches are not scored. To calculate the amount of MM jeopardized by the investigated stenosis, all scores of branches distal to the lesion are summed and divided by the global score supplying the entire LV. This index expresses jeopardized MM as LV percentage.

Two other angiographic indices were also calculated as supportive analyses: The 2) APPROACH Jeopardy Score (AJS), which according to pathological data provides the percentage of LV supplied by a vessel or its branches.[7] The amount of MM jeopardized by the index lesion is calculated taking into account the downstream area and is expressed as LV percentage. When the stenosis is not located in the proximal part of the vessel, the amount of jeopardized MM is reduced to two thirds of the region if the lesion is located in the middle part of the vessel and to one third when located in the distal segment. Finally, the 3) Duke Jeopardy Score (DJS), which divides the coronary tree into 6 segments: LAD, diagonal, septal branches, circumflex, obtuse marginal branches and the posterior descending coronary artery.[8] Two points are assigned to each, and the sum of all distal to the stenosis is considered to be jeopardized.

Intracoronary physiology measurements

Pressure wires fitted with thermistors (PressureWire™ Certus™, St. Jude Medical, St. Paul, Minnesota) were used according to described methodologies.[9,10] Sensors were placed approximately three centimeters distal to the stenosis of interest to allow for pressure recovery and in proximal stenosis, six centimeters were attempted to be left between the guiding catheter and the sensor.[9] FFR was calculated as the ratio of distal coronary pressure (P_d) to aortic pressure (P_a) at stable hyperemia during adenosine infusion (140µg/kg/min) through a central vein. Persistence of calibration was checked.

IMR was calculated as the product of hyperemic P_d and hyperemic mean transit time (Tmn_{hyp}), and was corrected for collateral flow in arteries with FFR<0.75 using proposed methods.[10,11] Uncorrected IMR values (IMR_u) are provided as well. CFR was calculated as the ratio of baseline mean transit time (Tmn_{bas}) to $Tmn_{hyp.}$[9] FFR ≤0.80 and CFR <2 were used as cut-offs,[2] and based on the reported variability of IMR in patients with and without IHD, values of IMR ≥30 U were considered abnormal.[12]

Statistical analysis

Continuous variables are presented as mean ± SD or median [quartile 1 and quartile 3 (Q1-3)] and categorical variables as counts and percentages. Normality and homogeneity of the variances were tested using Shapiro-Wilk and Levene tests. Data was analyzed on per-patient basis for clinical characteristics, and on per-vessel basis for the rest of calculations. Independence was assumed for vessel-level analyses. Continuous variables were compared with Student *t* tests or Mann-Whitney U tests, and categorical variables with χ^2 or Fisher´s exact tests. Overall differences were compared with one-way analysis of variance (ANOVA), Kruskal-Wallis, χ^2 or Fisher´s exact tests followed by post-hoc *t* tests, Mann-Whitney U or Fisher´s exact tests, with Bonferroni-adjusted significance level. Tests of linear trend across ordinal categories (polynomial contrasts for continuous and Mantel-Haenszel tests for categorical) were conducted. Correlation coefficients (Pearson´s r or Spearman´s ρ) were calculated, and for multiple comparisons, significance level was adjusted with Bonferroni´s method. The intraobserver reproducibility of jeopardy scores was assessed with intraclass correlation coefficients (ICC) in a random subsample of 30 patients. Linear and nonlinear regressions with *F*-tests were used to obtain curves of best fit, following Box-Cox transformations to achieve approximate normality of residuals, when appropriate. Finally, linear mixed models were used to identify independent predictors of IMR, FFR and CFR, where clinically relevant variables[5,13] (age, sex, hypertension, diabetes, dyslipidemia, body surface area (BSA), smoking, previous myocardial infarction, clinical presentation, QCA variables, P_a and MJI) were modeled using Mallows´s Cp as criterion for best-fit. In order to account for the lack of vessel independence, mixed models were fitted adding the effect of patient as a random component. Results are presented as beta ± robust standard errors, p values and standardized beta (that represent standardized partial regression weights of each parameter) to facilitate comparisons. Differences were considered significant at p<0.05 (two-sided). The STATA 12.1 statistical software package was used for calculations.

RESULTS

Baseline characteristics

Clinical, angiographic, and physiological characteristics of the study population (123 arteries in 102 patients) are shown in Tables 1 and 2. The study comprised coronary stenoses of intermediate severity, both angiographically (DS: 48.6 ± 12.1%) and physiologically [median FFR=0.83 (Q1-3, 0.74-0.89)]. Median IMR was 16.8 U (Q1-Q3, 10.1-26.2), and the median percentage of LV jeopardized by the investigated stenoses (MJI) was 19.2% (Q1-3, 13.6-25.0%). The intraobserver reproducibility of all jeopardy scores was satisfactory [ICC=0.99, (95% CI: 0.98 to 0.99), p<0.001 for MJI; ICC=0.99, (95% CI: 0.98 to 0.99), p<0.001 for AJS; and ICC=0.93, (95% CI: 0.86 to 0.96), p<0.001 for DJS] (Supplemental Figure 1).

Table 1 | General characteristics of patients included in the study n=102

Age	**64 ± 11**
Male	82 (80.4)
Left ventricle ejection fraction, %	62 ± 8
Cardiovascular risk factors	
Hypertension	75 (73.5)
Diabetes	25 (24.5)
Dyslipidemia	67 (65.7)
Obesity (BMI≥30 kg/m^2)	37 (36.3)
Smoker	28 (27.5)
Previous myocardial infarction	52 (50.9)
Multivessel disease	54 (52.9)
Clinical presentation	
Stable angina	53 (52.0)
Post-myocardial infarction (>5 days)	32 (31.4)
- STEMI	18 (17.6)
- NSTEMI	14 (13.7)
Unstable angina	17 (16.6)
Medical treatment	
Aspirin	89 (87.3)
Statins	82 (80.3)
ACE inhibitors	65 (63.7)

Values are mean ± S.D or or n (%).
II B: primary angina, at rest, within past month but not within preceding 48 hr; III B: primary angina, at rest, within preceding 48 hr.

Table 2 | General characteristics of stenosed vessels included in study

		Angiographic and physiological characteristics across tertiles of jeopardized myocardium (MJI)			
	Total vessels	Tertile 1 (<16%)	Tertile 2 (16 to 22%)	Tertile 3 (>22%)	p value (overall)
	n=123	n=41	n=44	n=38	
Stenosis location					
Left anterior descending artery	53 (43.1)	9 (22.0)	15 (34.1)	29 (76.3)[a]	0,003
Circumflex	25 (20.3)	11 (26.8)	11 (25)	3 (7.9)	
Right coronary artery	45 (36.6)	21 (51.2)	18 (40.9)	6 (15.8)	
Quantitative coronary angiography					
Reference diameter, mm	2.78 (2.37-3.29)	2.63 (2.27-3.05)	2.77 (2.42-3.10)	3.21 (2.71-3.77)[a,b]	0,003
Minimal lumen diameter, mm	1.22 (1.05-1.53)	1.17 (1.0-1.49)	1.22 (1.09-1.47)	1.35 (1.11-1.58)	0,362
Diameter stenosis, %	48.6 ± 12.1	47.8 ± 12.8	47.6 ± 11.4	50.7 ± 12.2	0,596
Lesion length, mm	8.1 (5.4-11.1)	7.1 (4.6-9.5)	9.1 (6.5-12.5)	8.2 (5.2-10.8)	0,066
Physiological parameters					
P_a, mmHg	79 (68-89)	77 (71-89)	79 (63-93)	83 (71-87)	0,755
P_d, mmHg	64 (53-74)	68 (58-76)	64 (53-78)	59 (44-68)	0,083
FFR	0.83 (0.74-0.89))	0.86 (0.82-0.9)	0.81 (0.76-0.90)	0.75 (0.68-0.85)[a,b]	<0,001[l]
FFR ≤ 0.80	52 (42.3)	8 (19.5)	20 (45.5)[a]	24 (63.2)[a]	<0,001[l]
CFR	1.90 (1.35-2.67)	2.19 (1.63-2.90)	1.56 (1.10-2.21)[a]	2.04 (1.25-2.80)	0,007
CFR < 2	67 (54.5)	17 (41.46)	31 (70.45)[a]	19 (50)[b]	0,022
IMR_u, U	16.8 (10.1-26.2)	24.2 (17.0-32.5)	18.0 (12.4-26.8)	16.0 (10.3-21.7)[a]	0,003[l]
IMR, U	16.8 (10.1-26.2)	22.7 (15.6-32.5)	16.4 (11.7-24.8)	11.2 (8.0-17.1)[a,b]	<0,001[l]
IMR ≥ 30 u	23 (18.7)	13 (31.7)	8 (18.2)	2 (5.3)[a]	0,009[l]
Tmn_{bas}, sec	0.60 (0.32-0.91)	0.79 (0.57-1.18)	0.52 (0.26-0.85)[a]	0.57 (0.30-0.84)[a]	<0,001[l]
Tmn_{hyp}, sec	0.31 (0.22-0.45)	0.36 (0.25-0.49)	0.30 (0.21-0.50)	0.28 (0.2-0.39)	0,055[l]

Values are mean ± S.D, median (25^{th}-75^{th}) or n(%).

P_a.: hyperemic aortic pressure; P_d: hyperemic distal pressure; FFR: fractional flow reserve; CFR: coronary flow reserve; IMR_u: index of microcirculatory resistance (uncorrected); IMR: index of microcirculatory resistance (corrected); Tmn_{bas}: basal mean transit time; Tmn_{hyp}: hyperemic mean transit time.

[a] P<0.05 compared to tertile 1

[b] P<0.05 compared to tertile 2

[l] P<0.05 for linear trend

Jeopardized myocardium, coronary dimensions and physiological indices

Correlations between QCA parameters, physiological indices, and scores of jeopardized MM are provided in Table 2 and 3. Additional analyses of such variables across tertiles of MM are provided in Table 2. IMR correlated negatively with all jeopardy scores, with IMR decreasing with increasing MM (Figure 1). FFR was also inversely correlated with MM (Supplemental Figure 2), with FFR decreasing with increasing MM, whilst CFR was not correlated with any of the jeopardy scores (Figure 2, Table 3). Similar findings were observed after dichotomizations of the physiology indices, where 23 (18.7%), 52 (42.3%) and 67 (54.5%) vessels had abnormal IMR (≥30 U), FFR (≤0.80) and CFR (<2), respectively. Indeed, vessels with IMR ≥30 U (n=23, 18.7%) subtended lower amounts of MM than vessels with IMR<30 U (MJI: 13.0% (Q1-3, 12.5-18.2%) vs 20.4% (Q1-3, 15.10-25.5%), p<0.001); vessels with FFR≤0.80 subtended larger MM than vessels with FFR>0.80 (MJI: 21.3% (Q1-3, 16.7-26.5%) vs 16.7% (Q1-3, 13.0-21.7%), p<0.001) and, differently, vessels with CFR<2 subtended an statistically similar amount of MM than vessels with CFR≥2 (MJI: 20.0% (Q1-3, 15.4-24.0%) vs 17.0% (Q1-3, 13.0-26.1%), p=0.535) (Figure 3).

Table 3 | Correlations between intracoronary physiology indices, stenoses characteristics and scores of jeopardized myocardium n=123

	Myocardial Jeopardy Index	Approach Jeopardy Score	Duke Jeopardy Score
Intracoronary physiology indices			
IMR_u	-0.346***	-0.351***	-0.238**
IMR	-0.408***	-0.383***	-0.276**
FFR	-0.338***	-0.333**	-0.263*
CFR	-0.103	-0.078	-0.093
Quantitative coronary angiography			
Reference diameter, mm	0.317**	0.167	0.163
Minimum lumen diameter, mm	0.185	0.175	0.085
Diameter stenosis, %	0.075	-0.029	0.107
Lesion length, mm	0.111	0.072	0.117

Abbreviations as Table 2
All Spearman´s ρ
Bonferroni-adjusted significance level: *p<0.05, **p<0.01, ***p<0.001

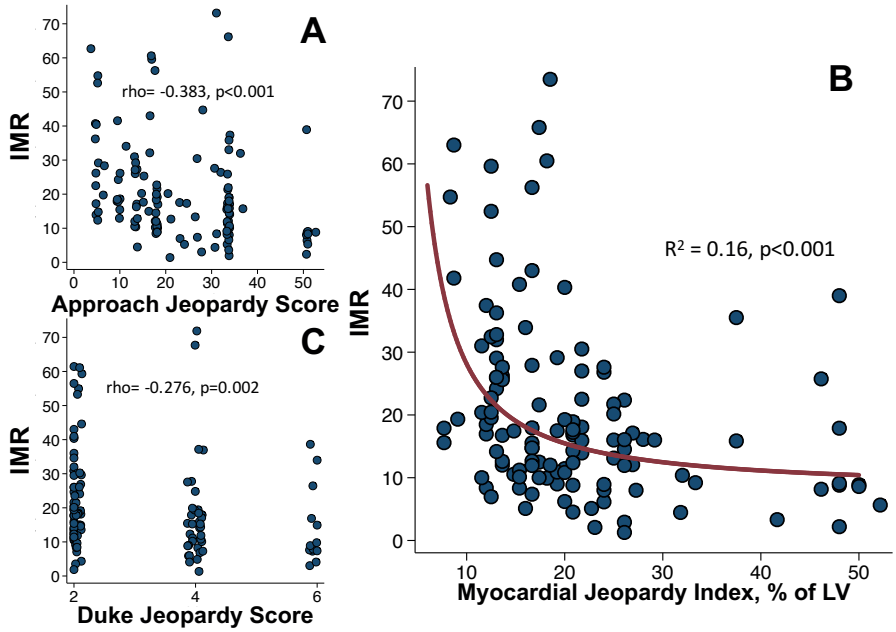

Figure 1 | Relationship between IMR and indices of jeopardized myocardium. Equation denote the best fit regression model and the R2 the model fit. In A and C "jitter" was added to avoid overlapping of dots.

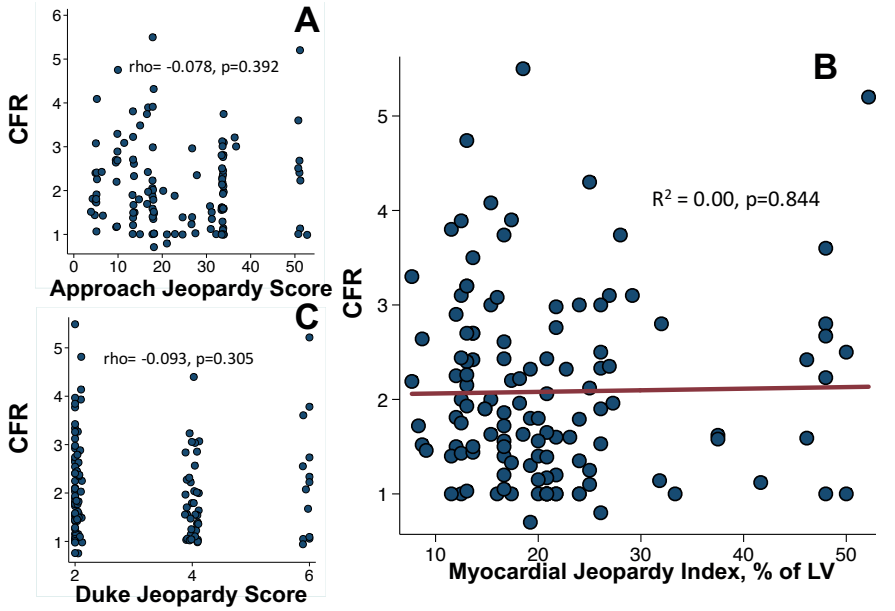

Figure 2 | Relationship between CFR and indices of jeopardized myocardium. In A and C "jitter" was added to avoid overlapping of dots.

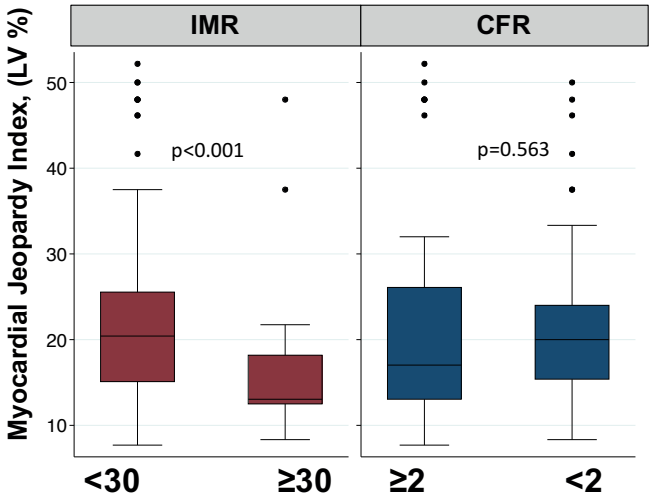

Figure 3 | Boxplots of the amount of myocardial mass (MJI) subtended to the coronary stenosis according to categorized values of IMR and CFR.

Finally, multiple regression analyses were performed to test the independence of the observed univariate associations of MM with IMR and FFR. Notably, MM was a strong independent predictor for both IMR and FFR (Table 4). CFR, however, could not be satisfactory modeled, as the best attempt (age, previous remote myocardial infarction and reference diameter, R^2=0.04) did not reached statistical significance (p=0.156).

Influence of jeopardized myocardium on the relationships between IMR and mean transit times

As theoretically expected in normal coronary arteries, increasing amounts of MM were associated with increasing magnitudes of baseline and hyperemic flow, as demonstrated by a negative association of MM with baseline [ρ= -0.284, (95% CI: 0.112 to 0.439), p=0.001] and hyperemic [ρ=-0.271, (95% CI: 0.098 to 0.427), p=0.002] mean transit times. IMR exhibited a comparable but inverse behavior (Figure 4), since it increased with increasing baseline [ρ=-0.579, (95% CI: -0.686 to -0.448), p<0.001)] and hyperemic mean transit times [ρ=-0.636, (95% CI: -0.730 to -0.517), p<0.001)]. Therefore, as MM decreased, baseline and hyperemic mean transit times increased, and IMR increased. Figure 4 provides detailed analyses of these relationships from the perspective of the IMR. High IMR values were distributed towards higher values of baseline and hyperemic mean transit times (i.e., lower magnitudes of absolute flow) and lower values of MM.

Table 4 | Multivariate predictors of IMR and FFR

	Beta	Robust Standard Error	P value	95% CI	Standardized Beta
IMR: R^2=0.24, p<0.001					
Myocardial Jeopardy Index	-0,538	0,106	0,000	-0,746 to -0,330	-0,381
P_a, mmHg	0,211	0,066	0,001	0,082 to 0,340	0,294
Minimum lumen diameter, mm	5,440	2,945	0,065	-0,331 to 11,211	0,156
Age	0,191	0,098	0,051	-0,001 to 0,384	0,140
Intercept	-4,419	8,190	0,589	-20,471 to 11,633	-
FFR: R^2=0.30, p<0.001					
Myocardial Jeopardy Index	-0,005	0,001	0,000	-0,006 to -0,003	-0,391
Minimum lumen diameter, mm	0,088	0,019	0,000	0,050 to 0,126	0,304
Body surface area, m^2	-0,148	0,062	0,017	-0,270 to -0,027	-0,210
Hypertension	0,045	0,025	0,070	-0,004 to 0,094	0,162
Age	0,002	0,001	0,104	0,000 to 0,004	0,153
Intercept	0,930	0,158	0,000	0,620 to 1,240	-

Predictors are ordered according to standardized beta coefficients
Variables included: age, sex, hypertension, diabetes, dyslipidemia, body surface area (m^2), smoking, previous myocardial infarction, clinical presentation, diameter stenosis, minimum lumen diameter, reference diameter, lesion length, hyperemic aortic pressure (P_a) and myocardial jeopardy index (MJI).
CFR could not be satisfactory modeled

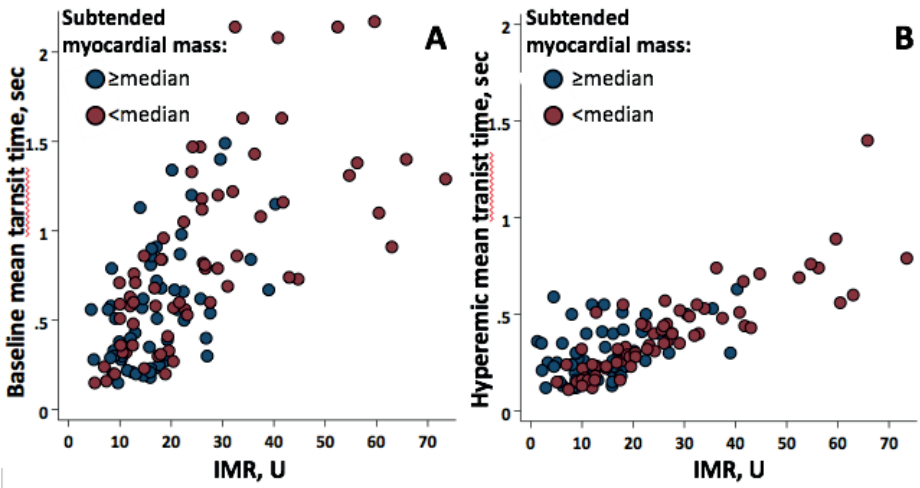

Figure 4 | Relationship of the IMR with baseline and hyperemic mean transit times. High IMR values were distributed towards higher values of mean baseline and hyperemic transit times (i.e., lower magnitudes of baseline flow and hyperemic flow, respectively) . Furthermore, vessels subtending smaller amounts of myocardial mass (below the median value of MJI) were distributed towards lower values of baseline flow, lower values of hyperemic flow, and higher values of the IMR.

Influence of jeopardized myocardium on the relationship between IMR and CFR

The relationship between IMR and CFR is provided in Figure 5. MM was significantly different across the quadrants of the IMR and CFR relationship (overall p=0.010). Vessels supplying perfusion to the largest amounts of MM (highest tertiles of MJI) were distributed towards lower values of IMR irrespectively of CFR. Finally, vessels with high IMR and normal CFR supplied perfusion to the smallest amounts of MM.

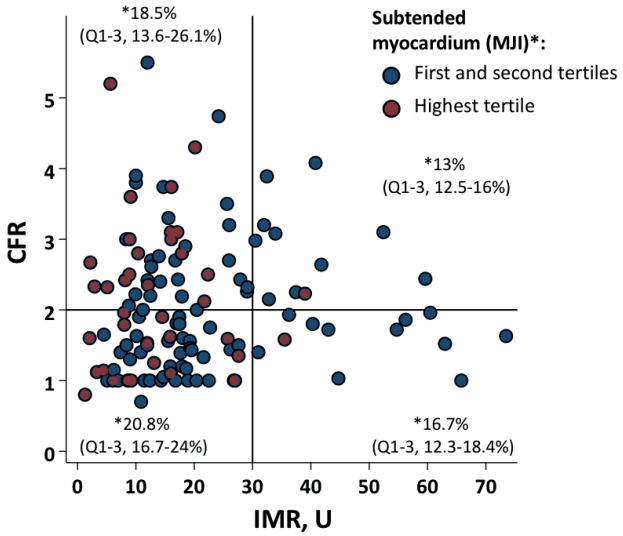

Figure 5 | This scatterplot shows the relationship of IMR with CFR. The horizontal line is placed at the CFR cut-off value of 2, and the vertical line at the IMR cut-off value of 30 U. MJI was significantly different across such quadrants (overall p=0.010). Vessels supplying perfusion to the highest amounts of MM are highlighted in red (highest tertile of MJI). Please note how these vessels are distributed towards lower of the IMR, irrespectively of the CFR. Finally, vessels with normal CFR (>2) and high IMR (>30 U) subtended the smallest amounts of MM.

DISCUSSION

This study addressed a theoretical concern for the clinical use of resistance indices to assess microcirculatory function. Namely, the physiologically expected increase in estimated coronary resistance across the branching structure of the coronary tree.[4] This is important at a time when, in addition to obstructive involvement, microcirculatory dysfunction is increasingly acknowledged as determinant of clinical outcomes[1], and when the IMR appears to many as its soundest diagnostic invasive clinical test.[3] Our findings suggest an influence of the amount of MM subtended to a coronary stenosis

on the IMR; however, this influence seems to be rather modest. Furthermore, this study suggests that CFR is not significantly affected by MM, which as explained below, could refine the interpretation of high IMR values in selected cases. In the following paragraphs, these aspects and their possible clinical implications are discussed in detail.

Clinical pertinence of combined intracoronary pressure and flow measurements

Multimodality physiological assessment of coronary vessels with combined intracoronary measurements of pressure and thermodilution-derived flow allows the calculation of FFR, CFR and IMR.[9] Not only does this more comprehensive approach has contributed to understand the complex interplay between focal stenosis, diffuse epicardial disease and microcirculatory dysfunction in patients with IHD,[14,15] but most importantly, all of its components (FFR,[16] CFR,[14] and IMR[17]) have independently shown to provide valuable information in terms of the stratification of cardiovascular risk. Since current coronary wires allow the calculation of all these three indices simultaneously, this combined diagnostic approach is both technically feasible and physiologically incremental.

Clinical value of the IMR

Coronary resistance indices have been demonstrated to correlate better with histologically-demonstrated anomalies of the coronary microcirculation than relative indices like CFR.[18] The IMR is a technically simple method that combines a thermodilution-derived index of coronary flow with intracoronary pressure to interrogate the minimum achievable microcirculatory resistance of a specific vascular bed.[10] IMR is reproducible, and mounting evidence supports its value as a meaningful diagnostic tool in both acute an chronic IHD settings.[3,17] Indeed, high IMR values have been associated with larger myocardial infarctions, worse myocardial recovery after an infarction, larger periprocedural myonecrosis, and most importantly, with worse survival at long term.[3,17] However, it has to be kept in mind that, as any new diagnostic tool, IMR should be subject of scrutiny. Although initial experimental studies demonstrated a moderate correlation of the IMR with true microcirculatory resistance,[10] the possible influence of subtended MM on the IMR has not been explored. This is important because in normal coronary arteries, theoretical coronary resistance should increase in every bifurcation, because coronary flow decreases while the driving pressure remains almost unchanged.[4] Our study substantiates this physiological background, because IMR values increased as the amount of subtended MM to the stenosis decreased, and such influence persisted as independent after multivariate statistical adjustments. Moreover, high IMR values were distributed towards higher values of mean transit times (i.e., lower magnitudes of baseline and hyperemic flow), a phenomenon expected in vascular beds with an abnormal function but also in anatomically reduced normal vascular beds. Hence, our study suggests that IMR

might reflect not only the functionality of the microcirculatory bed under interrogation, but also to some degree its extent. Nevertheless and of importance for the applicability of the IMR as tool to appraise the coronary microcirculation, we observed that the physiological influence of MM on the IMR was only modest, as it only explained a small percentage (16%) of IMR variability. We believe this substantiates the clinical use of a single IMR cut-off for pragmatic clinical assessment of microcirculatory function, which is further supported now by two studies in normal coronary arteries that have reported the highest limit for "IMR normality"— <27.2 U[19] and <30 U[12]— within a very narrow range.

Possible adjuvant role of CFR for the interpretation of high IMR values

Finally, an interesting finding from our study is the absence of association between CFR and subtended MM. This also fits theoretical basis, since by normalizing hyperemic flow to baseline flow, CFR should intrinsically correct for the magnitude of flow within the myocardial bed under investigation.[20] Therefore, CFR should be comparable in arteries of different length and diameter, and should not be affected by downstream MM. It is reasonable to speculate, consequently, that under particular conditions, CFR could help refine IMR interpretation. Specifically, functionally normal but anatomically reduced vascular territories should theoretically exhibit preserved CFR and concomitant high IMR values. Given the preserved flow supply, territories with a frankly normal CFR but a high-IMR value seem more likely reflections of anatomically reduced normal vascular beds than of territories affected by microcirculatory disease. Nonetheless and because our study was performed in vessels with intermediate stenosis, this possible adjuvant role of CFR should be considered cautiously and only in cases where CFR is preserved, because an exhausted CFR could mean either epicardial or microcirculatory disease.[9]

How do these considerations conciliate with the gathered evidence supporting the clinical value of IMR[3,17]? Simply stated, high IMR values could be general reflections of "low-flow states", which in most of the cases can be attributable to microcirculatory dysfunction, or lesser residual viable myocardium. In some other cases, however, lower magnitudes of flow might be normal, if the vascular bed under interrogation is anatomically reduced but functionally preserved, as suggested by a normal CFR. This proposal requires further validation in dedicated studies.

LIMITATIONS

Firstly, MM was not measured directly. An ideal study would require metabolic demonstration of the functionality and viability either by cardiac magnetic resonance or positron emission tomography) of the interrogated vascular bed. However, the used angiographic scores have been clinically used to assess the influence of MM on other indices of

coronary physiology like FFR,[5] and have been thoroughly validated against either pathological data or cardiac magnetic resonance.[7,21] Furthermore, we included patients with history of remote myocardial infarctions. Whilst some have suggested an influence of myocardial infarction on distant microcirculatory function,[22] others have found that IMR does not change significantly after a few days or weeks following an acute infarction in non-culprit territories.[23] Furthermore, the mean period of time between the infarctions and the physiological interrogation in our small population with stabilized acute coronary syndromes was long [8.2±3.8 days (min 5, max 20 days) in the STEMI and 7.2±1.8 days (min 5, max 11 days) in the non-STEMI populations], and all patients were stabilized and asymptomatic several days before the index procedure. In this regard, we find reassuring that the mean IMR values observed in our study were similar to those reported by other investigators that have assessed IMR only in populations of stable patients.[12,24] Next, IMR is also influenced by the haemodynamics of the LV and the coronary wedge pressure which were not measured. Because of this, we decided to correct IMR values for possible collateral flow contribution when FFR<0.75 using proposed methods.[11] A separate analyses (not shown) using uncorrected IMR values lead to the same conclusions reported in this manuscript. Also, our conclusions are limited by a relatively small sample size, and being a single-center experience, the external reproducibility of our findings has to be challenged. Finally, the translation of our findings to resistance indices derived from Doppler flow velocity is unknown. Theoretically and although technically more demanding, resistance indices derived from Doppler flow velocity should be less influenced by MM, because the decrease in flow velocity from proximal to distal segments is smaller than the decrease in volumetric flow.[20] Nonetheless an in spite of this limitations, we believe the gathered observations contribute to improve the interpretation of the available invasive methods to assess IHD.

SUPPLEMENTAL RESULTS

Supplemental Table 1 provides Spearman´s correlations between intracoronary physiology indices and the amount of myocardial mass subtended by the interrogated stenosis as assessed by the myocardial jeopardy index (MJI) according to clinical presentation. MJI was associated with IMR and FFR in both acute an stable patients. Supplemental Figure 1 shows a Bland Altman continuous agreement plot between the first and second reading of MJI.). The mean bias between the first and second MJI measurements was -0.003, with a lower and upper bound of -0.024 and 0.017, respectively. The relationship between fractional flow reserve (FFR) and the amount of myocardium subtended by the stenosis as assessed by MJI is provided in Supplemental Figure 2. FFR was inversely associated with MJI. Line represents best fit line, equation best fit regression and the R2 the model fit.

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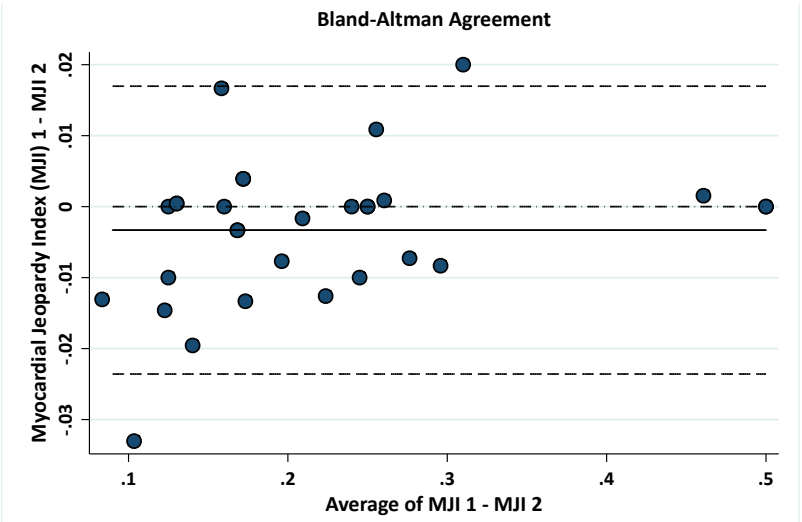
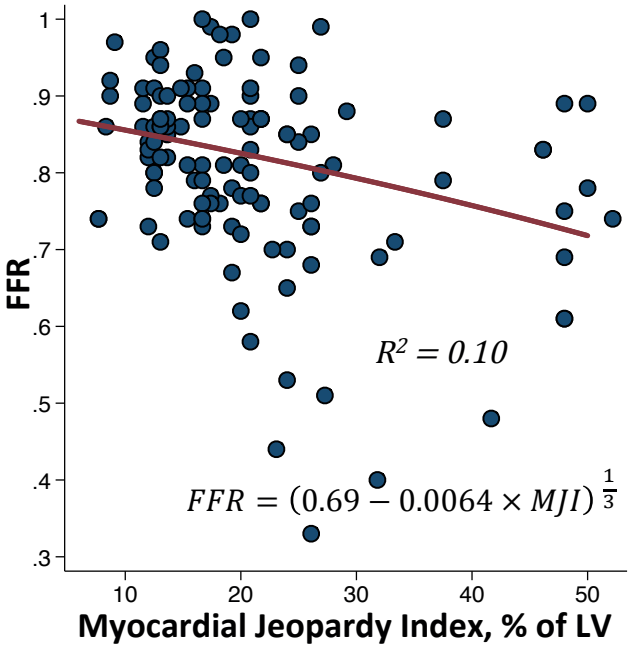

Bland-Altman Agreement
Myocardial Jeopardy Index (MJI) 1 - MJI 2
-.03
-.02
-.01
0
.01
.02
.1
.2
.3
.4
.5
Average of MJI 1 - MJI 2


FFR
1
.9
.8
.7
.6
.5
.4
.3
$R^2 = 0.10$
$FFR = (0.69 - 0.0064 \times MJI)^{\frac{1}{3}}$
10
20
30
40
50
Myocardial Jeopardy Index, % of LV

Supplemental Table 1 | Correlations of the Myocardial Jeopardy Index with the intracoronary physiology indices

	Myocardial Jeopardy Index
Stable patients, n=53 patients (69 vessels)	
IMR_u	-0.5379**
IMR	-0.390***
FFR	-0.286*
CFR	-0.065
Stabilized ACS patients, n=49 patients (54 vessels)	
IMR_u	-0.326*
IMR	-0.489***
FFR	-0.385**
CFR	-0.153

IMR_u: index of microcirculatory resistance (uncorrected); IMR: index of microcirculatory resistance (corrected); FFR: fractional flow reserve; CFR: coronary flow reserve
Spearman´s ρ
Significance level: *p<0.05, **p<0.01, ***p<0.001

Part D

Comprehensive invasive physiological assessment of ischaemic heart disease

CHAPTER 13

Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve

A combined analysis of epicardial and microcirculatory involvement in ischemic heart disease

Echavarria-Pinto M, Escaned J, Macías E, Medina M, Gonzalo N, Petraco R, Sen S, Jimenez-Quevedo P, Hernandez R, Mila R, Ibañez B, Nuñez-Gil IJ, Fernández C, Alfonso F, Bañuelos C, García E, Davies J, Fernández-Ortiz A, Macaya C

Circulation. 2013 Dec 17;128(24):2557-66

ABSTRACT

Background

In chronic ischemic heart disease (IHD), focal stenosis, diffuse atherosclerotic narrowings (DAN) and microcirculatory dysfunction (MCD) contribute to limit myocardial flow. The prevalence of these IHD levels in fractional flow reserve (FFR) interrogated vessels remains largely unknown.

Methods and results

Using intracoronary measurements, 91 coronaries (78 patients) with intermediate stenoses were classified in four FFR and coronary flow reserve (CFR) agreement groups, using FFR>0.80 and CFR<2 as cutoffs. Microcirculatory resistance (IMR) and atherosclerotic burden (Gensini score) were also assessed. MCD was assumed when IMR≥29.1 (75th percentile). Fifty-four (59.3%) vessels had normal FFR, from which only 20 (37%) presented both normal CFR and IMR. Among vessesl with FFR>0.80, most (63%) presented disturbed haemodynamics: abnormal CFR in 28 (52%) and MCD in 18 (33%). Vessels with FFR>0.80 presented higher IMR [adjusted mean 27.6 (95% CI: 23.4 to 31.8)] than those with FFR≤0.80 [17.3 (95% CI: 13.0 to 21.7), p=0.001]. Atherosclerotic burden was inversely correlated with CFR (r=-0.207, p=0.055), and in vessels with FFR>0.80 and CFR<2 (n=28, 39%), IMR had a wide dispersion (7-72.7 U), suggesting a combination of DAN and MCD. Vessels with FFR≤0.80 and normal CFR presented the lowest IMR, suggesting a preserved microcirculation.

Conclusions

A substantial number of coronary arteries with stenoses showing an FFR>0.80 present disturbed haemodynamics. Integration of FFR, CFR and IMR supports the existence of differentiated patterns of IHD that combine focal and diffuse coronary narrowings with variable degrees of MCD.

INTRODUCTION

Chronic ischemic heart disease (IHD) is a multifactorial entity that occurs both in the presence or absence of obstructive coronary artery disease (CAD).[1] Fractional flow reserve (FFR) has become a standard method to assess obstructive CAD in the catheterization laboratory[2] following the demonstration that decision-making based on FFR results in better patients outcomes than angiography-guided revascularisation.[3] However, identification of other factors contributing to IHD, such as diffuse atherosclerotic narrowing (DAN) and microcirculatory dysfunction (MCD), remains largely elusive to the simplified model of physiological assessment provided by the FFR. This diagnostic gap is important because it remains plausible that patients with normal FFR values and MCD might have a worse prognosis.[4] The same applies to the presence of DAN, frequently overlooked during angiography, which may cause myocardial ischemia[5] and influence long-term outcome.[6]

When combined with FFR, coronary flow reserve (CFR) and microcirculatory resistance could provide additional insights on the contribution of obstructive CAD, DAN and MCD to IHD. In this study, we performed a comprehensive assessment of coronary haemodynamics in vessels with intermediate stenoses, using FFR, CFR and the index of microcirculatory resistance (IMR).[7,8] In addition, the Gensini score was recalled as a surrogate of atherosclerotic burden[9]. The obtained data was combined to outline three separate patterns of atherosclerotic involvement in IHD: focal epicardial stenoses, DAN and MCD.[8]

METHODS

Study population

Patients with a clinical indication for FFR interrogation of 1 or more intermediate coronary stenoses (40% to 70% diameter stenosis by quantitative coronary angiography [QCA]), investigated at Hospital Clinico San Carlos, Madrid, Spain, were prospectively studied. Culprit vessels of acute coronary syndromes, serial stenoses and marked diffuse narrowings were excluded. Very distal narrowings, not amenable for revascularisation (vessel diameter <1 mm), were allowed. Other exclusion criteria were left main stenosis, surgical grafts, contraindications to adenosine, hemodynamic instability and severe vessel tortuosity or calcification. All patients gave informed consent and Institutional Review Board approval was obtained according to current regulations.

Angiographic analysis

Angiographic data was collected by two experienced reviewers blinded to physiology data. Angiographic views were obtained following intracoronary nitrates (0.2 mg) administration. Offline QCA was performed in optimal projections using validated software (CASS II, Pie Medical, Maastricht, The Netherlands). Minimum lumen diameter [MLD], percent diameter stenosis (DS), lesion length and reference lumen diameter were measured. Atherosclerotic burden was assessed using the Gensini score.[9] This score limited to the vessel interrogated with the guidewire (arterial-Gensini score) was also recalled.

Intracoronary physiological indices

Coronary guidewires with pressure and temperature sensors (St. Jude Medical, St. Paul, Minnesota) were used according to described methodology.[7, 10, 11] FFR was calculated as the ratio of distal coronary pressure (P_d) to proximal coronary pressure (P_a) at stable hyperemia induced by intravenous adenosine (140µg/kg/min through a central vein). Persistence of calibration was checked. CFR was measured simultaneously with FFR using the thermodilution method, as described elsewhere.[11] Resting and hyperaemic thermodilution curves (in triplicate) were obtained, and CFR was calculated as the ratio of mean transit time (Tmn_{bas}) divided by mean hyperemic transit time (Tmn_{hyp}). IMR was calculated as the product of mean distal coronary pressure during maximal hyperemia and Tmn_{hyp}.[7] In arteries with FFR<0.75, IMR was corrected for coronary wedge pressure using the method proposed by Yong et al.[12] A meticulous technique was followed to avoid potential pitfalls affecting these indices.

Cut-off values for physiological indices

FFR ≤0.80[3] (low-FFR) and CFR <2 (low-CFR)[13] were used as threshold values. Based on the reported variability of IMR in patients with and without CAD,[14] values ≥75 percentile of IMR in the overall study population were assumed abnormal (high-IMR) and suggestive of MCD.

Classification of focal, diffuse epicardial and microcirculatory compartments

In identifying relative contributions of epicardial conductance (focal or DAN) and microcirculatory resistance to myocardial flow impairment, we used the four-quadrant distribution of the agreement between FFR and CFR proposed by Johnson et al:[8] (A) predominantly focal epicardial involvement (low-FFR and high-CFR); (B) adequate and concordant (high-FFR and high-CFR); (C) reduced and concordant quadrant (low-FFR and low-CFR) and (D) predominantly diffuse epicardial involvement (high-FFR and low-CFR). In the latter quadrant, those with CFR<2 and FFR near 1.0 (pressure loss less than 5mm) were labeled as lone-MCD[8] (Figure 1).

Statistical analysis

All continuous variables are presented as mean ± SD or median (interquartile range), according to their normal or non-normal distribution. Categorical variables are presented as numbers or percentages. Normalcy and homogeneity of the variances were tested using the Kolmogorov-Smirnov and Levene tests. Data was analyzed on per-patient basis for clinical characteristics, and on per-vessel basis for the rest of calculations. From per-patient analyses, those with more than 1 interrogated vessel showing differences in quadrant classification between vessels were excluded. Continuous variables were compared with t test or Mann-Whitney U test, as appropriate. Categorical variables were compared by the maximum likelihood $\chi 2$ test. Linear regression analyses were used to determine correlation coefficients (Pearson or Spearman, as appropriate) between quantitative variables. At patient-level, overall differences between quadrants were compared with maximum likelihood $\chi 2$ tests. At vessel-level, mixed effect regression models were used to correct for additional variability of arteries from the same subject. From these models, adjusted means ($_{adj}$mean) and 95% coinfidence intervals are presented. If significant, between-quadrants differences were compared with maximum likelihood $\chi 2$ tests or mixed effect regression models, as appropriate. No post-hoc corrections were performed. A p value <0.05 was considered significant. The SPSS 20.0 (IBM Corp, Armonk, New York) statistical software package was used for all calculations.

RESULTS

Baseline characteristics

Clinical, angiographical, and physiological characteristics of the study population (91 arteries studied in 78 patients) are shown in tables 1 and 2. Mean FFR value was 0.81±0.12 (min 0.4-max 1.0). FFR was ≥0.75 in 70 (76.9%) cases, >0.80 in 54 (59.3%), between 0.7-0.9 in 62 (68.1%), and <0.70 in only 12 (13.1%). Mean CFR was 2.0 ± 0.85 (min 1.0-max 4.74). A CFR <2 was documented in 53 (58.2%) cases; 9 (10.9%) had a CFR >3 and only 2 (2.2%) >4. IMR mean and median values were 26.3±16 and 18.1 (12.1-29.1), respectively (min 3.7-max 72.7). A 75th IMR percentile value of 29.1 U was documented and used as cutoff for high-IMR cases (MCD).

Table 1 | General characteristics of study population n =78

Age (years)	**65.8±10.5**
Men	64 (82.1)
Cardiovascular risk factors.	
Hypertension	57 (73.1)
Diabetes	20 (25.6)
Dyslipidemia	54 (69.2)
Smoker	20 (25.6)
Obesity	31 (39.7)
Previous MI	42 (53.8)
Multivessel disease	37 (47.4)
Gensini score	34 (24-57)
Clinical presentation.	
Stable angina	40 (51.3)
Post-MI	24 (30.8)
Unstable angina II B	11 (14.1)
Unstable angina III B	3 (3.8)

Values are mean ± S.D, median (25^{th}-75^{th}) or n (%).
MI: myocardial infarction; II B: primary angina, at rest, within past month but not within preceding 48 hr; III B: primary angina, at rest, within preceding 48 hr.

Table 2 | General characteristics of epicardial stenoses included in study n=91

Stenosis location.	
Left anterior descending artery	39 (42.9)
Circumflex coronary artery	21 (23.1)
Right coronary artery	31 (34.1)
Quantitative coronary angiography.	
Reference diameter, mm	3.05 ± 0.64
Minimum lumen diameter, mm	1.31 ± 0.43
Diameter stenosis, %	46.99 ± 12.25
Lesion length, mm	7.80 ± 3.56
Coronary physiological parameters.	
P_a, mmHg*	79.4 ± 20.7
P_d, mmHg*	64.7 ± 20.8
FFR	0.81 ± 0.12
CFR	1.94 ± 0.80
IMR, U	18 (12.1-29.1)
Tmn_{bas}, seg	0.73 ± 0.48
Tmn_{hyp}, seg*	0.37 ± 0.21

Values are mean ± S.D, median (25^{th}-75^{th}) or n (%).
Pa: aortic pressure; Pd: distal pressure; FFR: fractional flow reserve; CFR: coronary flow reserve; IMR: index of microcirculatory resistance; Tmn_{bas}: basal mean transit time; Tmn_{hyp}: hyperemic mean transit time. *During stable hyperemia

FFR, CFR and IMR values were similar among patients with and without hypertension, diabetes, obesity, current smoking or history of prior myocardial infarction; findings that could be limited by our small sample size (Supplemental Table 1). Also, FFR, CFR and IMR values were not significantly different between clinical presentations, either as acute coronary syndromes or as stable angina ($_{adj}$means, p for overall comparisons: FFR=0.359, CFR=0.995 and IMR=0.540).

Angiographic analysis

Table 2 shows relevant QCA data. Stenosis severity correlated with FFR [positively with MLD (r=0.258; p=0.024) and negatively with DS (%) (r=-0.331; p=0.003)], but not with CFR (MLD: r=-0.056, p=0.631; DS: r=-0.124, p=0.287) or IMR (MLD: r=-0.064, p=0.585; DS: r=-0.025, p=0.829).

Correlations between FFR, CFR and IMR

FFR was not significantly correlated with CFR (r=0.171; p=0.105). A significant and positive correlation between FFR and IMR was found (r=0.451; p<0.001), illustrating the haemodynamic dependance of FFR on microcirculatory status (Figure 1). However, in arteries with FFR>0.80 (n=54), this correlation became non-significant (r=0.128; p=0.358). CFR and IMR were not correlated in the overall vessel population (r=0.112; p=0.293) nor in only those with FFR>0.80 (r=-0.040; p=0.774).

Findings in non-significant coronary stenoses (FFR >0.80)

In total, 54 arteries (59.3%) had a FFR >0.80. When compared with arteries with FFR≤0.80, vessels with FFR>0.80 presented higher IMR [27.6 (95% CI: 23.4 to 31.8) vs 17.3 (95% CI: 13.0 to 21.7); p=0.001] and CFR values [2.1 (95% CI: 1.8 to 2.3) vs 1.8 (95% CI: 1.5 to 2.0); p=0.035] ($_{adj}$means). Remarkably, when CFR and IMR were used as dichotomous variables, a high number of vessels with normal FFR presented abnormal CFR or IMR: 28 (51.9%) had low-CFR and 18 (33.3%) high-IMR. Consequently, only 20 (37%) vessels with FFR >0.80 had concordant normal values of all three indexes.

Finally, within the normal FFR group, classification agreement between dichotomized values of CFR and IMR was low (kappa of -0.098; p=0.441). They were concordant only in 24 (44.44%); and in 30 (55.6%) arteries a classification disagreement was observed: CFR<2 but normal-IMR (<75th percentile) in 20 (37%) and CFR≥2 with high-IMR in 10 (18.5%) arteries.

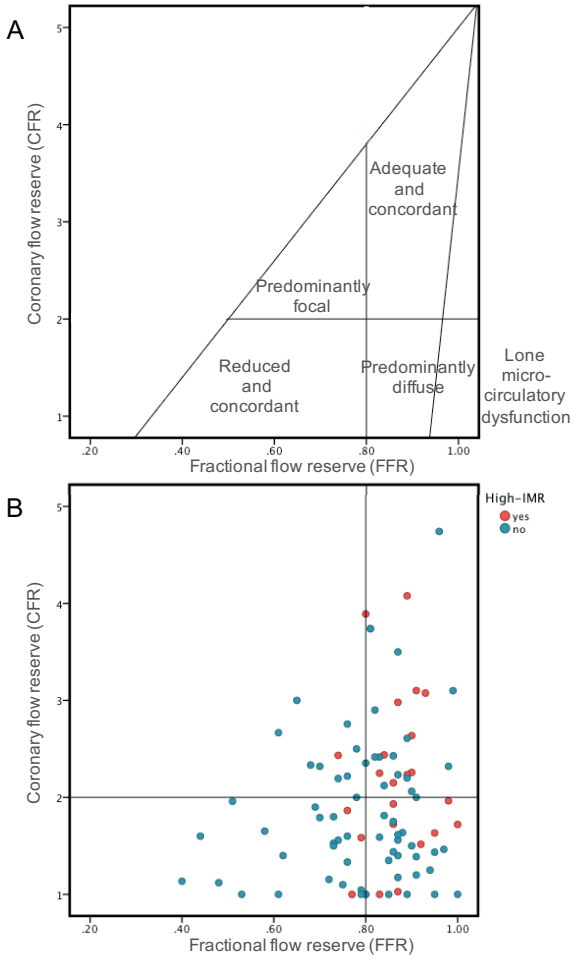


Figure 1 | Conceptual and documented plots of the FFR/CFR relationship. Panel A: Conceptual plot of the FFR/CFR relationship showing the four different quadrants (modified from reference 8). Panel B: Scatterplot of FFR and CFR values in our study with high-IMR values (>29.1 U) highlighted.

Construction of the four-quadrant model of IHD based on the FFR/CFR relationship

Further assessment of the FFR/CFR relationship was performed in a four-quadrant scatterplot[8] (figure 1). Categorical agreement between FFR and CFR was low (kappa of 0.147, p=0.135). FFR and CFR were concordant in 51 (56.1%) cases: B in 26 (28.6%) and C in 25 (27.5%). Classification disagreement occurred in 40 vessels (44.0%): A in 12 (13.2%) and D in 28 (30.9%). Within D, 6 vessels (representing 6.6% of overall, and 21.4% of vessels in D) met the definition of lone-MCD. Table 3 reports clinical and

Table 3 | Clinical and physiological differences among the four-quadrant distribution of the FFR/CFR relationship

	Predominantly focal (A) (FFR≤0.80 and CFR≥2)	Adequate and concordant (B) (CFR≥2 and FFR>0.80)	Reduced and concordant (C) (CFR<2 and FFR≤0.80)	Predominantly diffuse (D) (CFR<2 and FFR>0.80)	•p value
Per-patient analyses (n=73)*	9(12.3)	21(28.8)	22(30.1)	21(28.8)	
Age	68±9	62±9	63±11	70±11[b,c]	0,039
Hypertension	8(88.9)	14(66.7)	15(68.2)	16(76.2)	0,540
Diabetes	3(33.3)	8(38.1)	9(40.9)	1(4.8)[a,b,c]	0,015
Dyslipidemia	7(77.8)	16(76.2)	15(68.2)	13(61.9)	0,721
Obesity	1(11.1)	11(52.4)[a]	12(54.5)[a]	5(23.8)[b,c]	0,025
Smoker	3(33.3)	4(19.0)	5(22.7)	6(28.7)	0,818
Previous MI	7(77.8)	9(42.9)	12(54.5)	12(57.1)	0,346
Per-artery analyses (n=91)	12(13.2)	26(28.6)	25(27.5)	28(30.8)	
Physiological parameters					
FFR	0.73(0.70 to 0.77)	0.88(0.86 to 0.90)[a,c]	0.68(0.63 to 0.73)	0.90(0.88 to 0.92[a,c]	<0,001
CFR	2.56(2.29 to 2.83)	2.76(2.50 to 3.02)[c]	1.39(1.25 to 1.52)[a]	1.43(1.33 to 1.54)[a,b]	<0,001
IMR, U	15.8 (9.8 to 23.10)	25.9 (20.8 to 31.0)[a,c]	18,0 (12.3 to 23.8)	29.1 (22.9 to 35.4)[a,c]	0,007
High-IMR	2(16.7)	10(38.5)	3(12.0)	8(28.6)	0,123
P_a, mmHg°	70(57 to 83)	81(74 to 89)	75(66 to 84)	85(78 to 92)	0,154
P_d, mmHg°	52 (42 to 63)	72(64 to 78)[a,c]	51(44 to 57)	77(69 to 84)[a,c]	<0,001
Tmn_{bas}, seg	0.83(0.53 to 1.13)	1.01(0.80 to 1.2)[c]	0.56(0.41 to 0.70)	0.57(0.44 to 0.70)[b]	0,001
Tmn_{hyp}, seg°	0.31(0.22 to 0.40)	0.36(0.30 to 0.43)	0.40(0.29 to 0.50)	0.39(0.31 to 0.46)	0,599

Table 3 | Clinical and physiological differences among the four-quadrant distribution of the FFR/CFR relationship (continued)

	Predominantly focal (A) (FFR≤0.80 and CFR≥2)	**Adequate and concordant (B) (CFR≥2 and FFR>0.80)**	**Reduced and concordant (C) (CFR<2 and FFR≤0.80)**	**Predominantly diffuse (D) (CFR<2 and FFR>0.80)**	**•p value**
Angiographic analyses					
Gensini score	70.5(37.2 to 103.7)	34.8(28.4 to 41.2)	46.3(32.6 to 59.9)	41.4(31.9 to 51.0)	0,097
Vessel only-Gensini score	18.7 (11.2 to 26.3)	10.1 (7.7 to 12.4)	17 (10 to 23)	15(10 to 20)	0,063

Values are mean ± S.D., $_{adj}$mean (95% CI) or n (%).

*Patients with stenosed vessels in discordant quadrants were excluded

MI: myocardial infarction; Pa: aortic pressure; Pd: distal pressure; FFR: fractional flow reserve; CFR: coronary flow reserve; IMR: index of microcirculatory resistance; $Tmnb_{as}$: basal mean transit time; Tmn_{hyp}: hyperemic mean transit time. °During stable hyperemia

[a]P<0.05 compared to group A

[b]P<0.05 compared to group B

[c]P<0.05 compared to group C

•Mixed effect regression models or maximum likelyhood $\chi 2$ tests were used for overall and between groups' comparisons.

physiological differences among the four quadrants. Patients in D were older and had less diabetes and obesity than those in B and C.

Microcirculatory resistance and FFR/CFR relationship

Subsequently, the microcirculatory resistance was investigated among the four-quadrant distribution of the FFR/CFR relationship. This revealed a significant difference in IMR values between groups ($_{adj}$mean, p for overall comparison=0.007) (figure 2A, table 3). The highest microcirculatory resistance was observed in D [29.1 (95% CI: 22.9 to 35.4)] and the lowest in A [15.8 (95% CI: 9.9 to 21.8)]. IMR values in D were significantly higher than those in C [29.1 (95% CI: 22.9 to 35.4) vs 18.0 (95% CI: 12.3 to 23.8); p=0.010] and A [vs 15.8 (95% CI: 9.9 to 21.8); p=0.003]. The second quadrant ranking in IMR values was B [25.9 (95% CI: 20.8 to 31.0)]. These values were significantly higher than those in C [vs 18.0 (95% CI: 12.3 to 23.8); p=0.045] and A [vs 15.8 (95% CI: 9.9 to 21.8; p=0.013]. No significant differences in microcirculatory resistance were found between D and B (p=0.412)(all, $_{adj}$means). Figure 2B shows the prevalence of vessels with IMR values suggestive of MCD. Importantly, 78% (18/23) of vessels with MCD had an associated FFR>0.80.

Inclusion of the "lone-microcirculatory dysfunction" region in the conceptual plot of the FFR/CFR relationship

Six arteries of D (representing 6.6% of total and 21.4% of D vessels) met the definition of lone-MCD. These analyses rendered the results visually represented in figure 2 ($_{adj}$mean, p for overall comparison=0.016). It can be acknowledged that these arteries had the highest microcirculatory resistance [38.6 (95% CI: 21.1 to 56.1)] in the study population and this was significantly higher than that in A [vs 15.8 (95% CI: 9.9 to 21.8); p=0.021] and C [vs 18.0 (95% CI: 12.6 to 23.8); p=0.028] (all, $_{adj}$means).

Gensini score as a surrogate of atherosclerotic burden

In univariate analysis, the Gensini score revealed more diffuse atherosclerotic burden in patients with diabetes [52.5(28.5-86) vs 32.3(23.5-51); p=0.018], prior MI [48(29.5-65.5) vs 28.8(19-44); p<0.001] and a statistical trend was also observed in patients with dyslipidemia [43(28-57.3) vs 29.5(21.5-51); p=0.056]. No significant correlation between age and Gensini score was found (r=-0.050;p=0.670) (table 3). Overall, this score was not significantly different between the four quadrants of the FFR/CFR relationship ($_{adj}$mean p=0.097). However, when diffuse atherosclerosis was analyzed at a per-vessel level (arterial-Gensini score), trends towards higher degree of this index in A and C vessels were observed. No significant associations between arterial-Gensini score and FFR (r=-0.171, p=0.113) or IMR (r=-0.015, p=0.889) were documented. How-

ever, a marginal, negative association between the latter and CFR was found (r=-0.207, p=0.055).

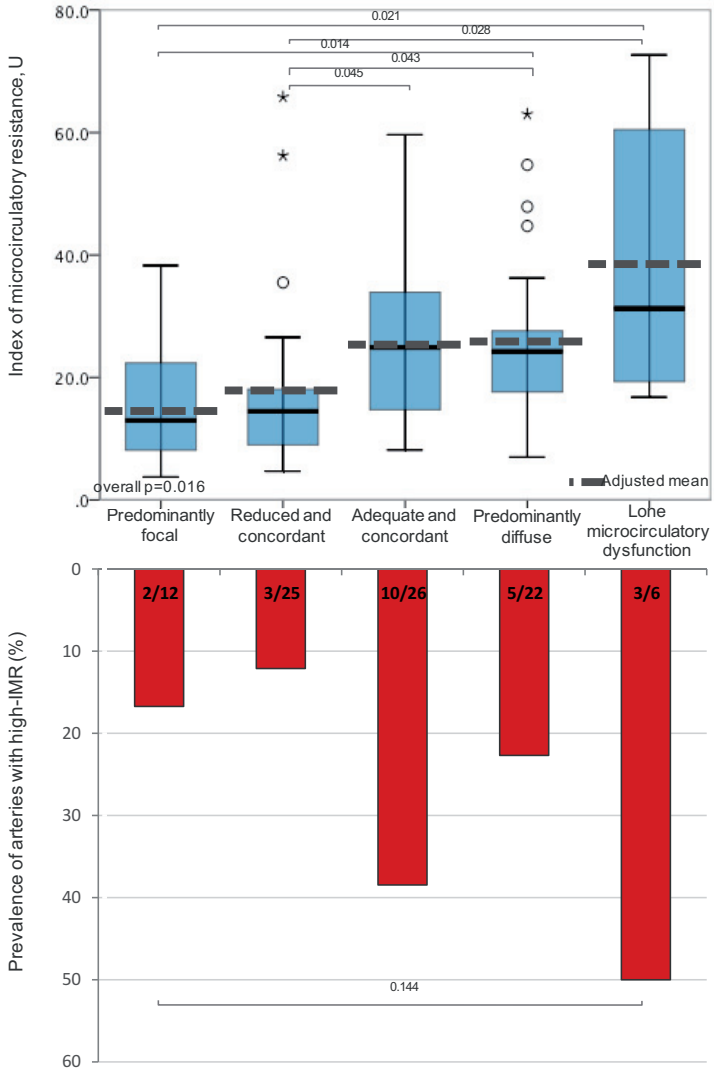


Figure 2 | Coronary microcirculatory resistance within the FFR/CFR relationship. Upper panel: Microcirculatory resistance among quadrants of the FFR/CFR relationship. Only p<0.05 values are shown. Lower panel: Prevalence of arteries with high-IMR. Numbers within columns represent n/total within each quadrant of the FFR/CFR relationship. Please also note that arteries meeting the "lone-MCD" definition were subtracted from quadrant D. All p values are of $_{adj}$means.

DISCUSSION

The main conclusions of this study are: 1) more than half (59%) of the coronary vessels with intermediate stenoses and an associated normal FFR (FFR>0.80) present data suggestive of abnormal haemodynamics associated with IHD (CFR<2 in 52%; high IMR in 33%); 2) abnormal FFR values (FFR≤0.80) are highly unlikely when MCD is present and 3) integration of FFR, CFR and IMR supports the existence of differentiated patterns of atherosclerotic disease that combine focal and DAN with variable degrees of MCD. In the following paragraphs these aspects are discussed in detail.

Fractional flow reserve and myocardial flow impairment in ischemic heart disease

Obstructive CAD in angiography has been customarily taken as indicative of IHD.[1] However, impairment of myocardial blood supply in IHD has a multilevel origin. In epicardial vessels, both focal and diffuse atheromatous narrowings increase vascular resistance, with an added component of vasoconstriction triggered by endothelial dysfunction.[5] At a microcirculatory level, increased resistance may result from structural remodelling (arteriolar obliteration and capillary rarefaction),[15] vasoconstriction of large arteriole resulting from endothelial dysfunction or alpha-adrenergic stimulation,[16, 17] and extravascular compression of capillaries and venules.[18] Despite that, assessment of IHD in clinical practice largely focuses in the identification of ischemia-generating epicardial stenoses that can be targeted with revascularisation. Gaining insights on other levels of IHD is important from the two-fold perspective that abnormal microcirculatory haemodynamics have been identified as predictive of cardiac events in patients without epicardial stenoses,[19, 20] and that patients allocated to the revascularisation deferral arm in pivotal FFR randomized trials were not free from long-term cardiac events (21% mayor adverse cardiovascular event (MACE) rate in DEFER trial, 33% and 20% long-term angina at 5 and 2 years follow-up in the DEFER and FAME trials, respectively). [21, 22]

Dual assessment of the coronary circulation with FFR and CFR

In this research we focus on the information encoded in the classification agreement between FFR and CFR. This approach provides a richer perspective of coronary haemodynamics and might help to identify patients that, despite a normal FFR, have impaired myocardial blood supply and, potentially, poorer prognosis (figure 3).[23] Both CFR and FFR were originally used to assess functional stenotic significance; however, beyond the close concordance initially reported,[24] a significant disagreement between both methods has been consistently found, like in our study. [23, 25, 26] Recently, a new interpretation of the classification agreement between FFR and CFR was proposed by Johnson et al[8] on the grounds of published studies and original findings with CFR derived from

non-invasive positron emission tomography (PET) (figure 1A). A fluid dynamic model fitting their observations suggests that the distribution of values in the four quadrants of the FFR/CFR relationship obeys to the relative contributions of focal stenosis, DAN and MCD.[8]

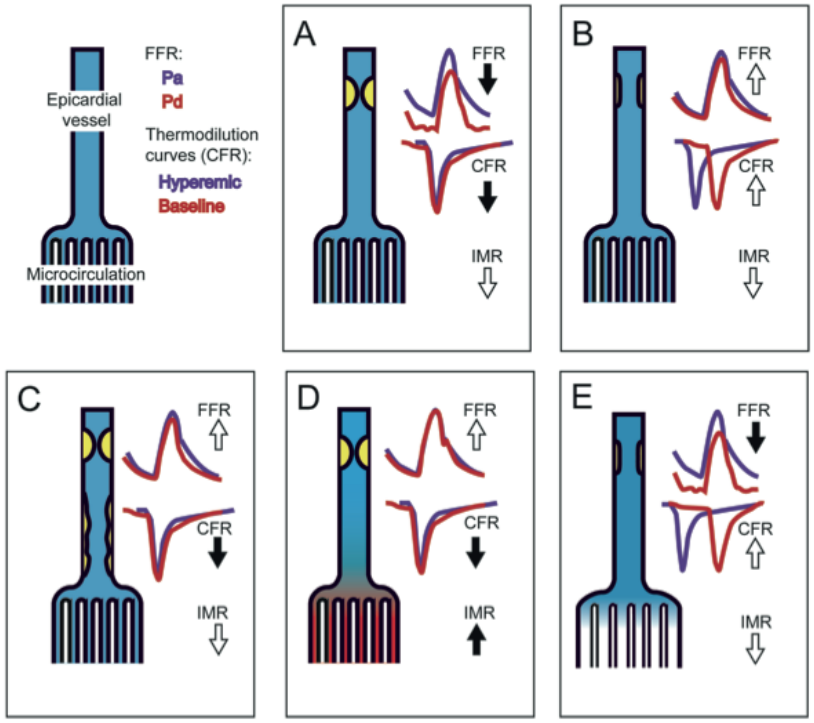


Figure 3 | Schematic representation of the coronary hemodynamic patterns documented in this study. Panel A: vessel located in the C of the FFR/CFR relationship, with concordantly abnormal FFR and CFR and normal (low) IMR. Panel B: vessel in B with a non-severe focal stenosis without associated DAN or MCD. Panel C: vessel in D with a focal stenosis and DAN. Despite a normal FFR, an abnormal CFR with low IMR suggests that diffuse epicardial atherosclerosis is the predominantly affected compartment. Panel D depicts a stenosis located also in D. At a difference with the case shown in panel C, the presence of MCD, and not DAN, may account for the discrepancy between FFR and CFR. The abnormal hemodynamics illustrated in panel C and D can be only identified by combining information of FFR, CFR and IMR. Panel E: vessel with a stenosis located in A that, despite showing an abnormal FFR, has preserved CFR as a result of well-preserved microcirculation and absence of significant DAN.

We applied this concept to patients with intermediate coronary stenoses, which constitute the current recommendation for FFR in clinical practice guidelines. Microcirculatory resistance was measured to obtain additional information on vessels included in the four quadrants of the FFR/CFR classification agreement. In the absence of well-defined cutoffs to identify MCD, the 75th quartile of overall IMR was used as

a threshold for identification of MCD. This IMR threshold (29.1 U) seems reasonable because it is very similar to the highest "limit of IMR normality" (<30 U) reported by Melikian et al. in patients without clinical evidence of atherosclerosis.[14]

Impact of microcirculatory dysfunction (MCD) on FFR interrogation.

Fractional flow reserve has greatly contributed to make decisions on coronary revascularisation by applying a restricted model of coronary physiology.[3, 27] Being a translesional hyperemic pressure ratio, FFR is a relative index of epicardial conductance, and therefore it is influenced by the limits to maximal achievable blood flow caused by MCD and/or distal epicardial stenoses. It has been proposed that the presence of MCD is not an obstacle to take decisions based on FFR, provided that MCD is deemed to be non-reversible.[28] Yet, the actual prevalence of MCD in cases in which revascularisation is deferred based on FFR is largely unknown.

In our study, microcirculatory resistance was significantly higher in vessels with non-severe stenoses (FFR>0.80). As a matter of fact, 33.3% of FFR non-severe stenoses had high IMR values suggestive of MCD. As shown in a separate analysis (figure 2), this was particularly pronounced in stenoses meeting the "lone-MCD" (high FFR, low CFR and pressure loss <5 mmHg), providing support to the model of Johnson et al.[8] An important message of our research is that, in intermediate stenoses, an FFR >0.80 does not identify only "healthy" vessels, but rather a mix of vessels with impaired and non-impaired myocardial circulation. As a corollary, an important proportion of patients in whom revascularisation is deferred on the grounds of FFR>0.80, have abnormal coronary haemodynamics.

Alternatively, vessels with FFR<0.75 stenoses frequently presented low or normal IMR values (IMR quartiles 1 to 3). This suggests that FFR classifies as hemodynamically severe only those stenoses located in vessels without MCD. In vessels with FFR<0.75, low microcirculatory resistance aimed to compensate high epicardial resistance, was found. Finally, the high microcirculatory resistance found among vessels in B is unclear. Whether this represents an incipient state of MCD (in which CFR is still preserved) or a heterogeneous response to hyperemic stimulies remains to be adressed by future research.

Relationship between angiography and intracoronary physiological indices

Angiographic and physiological indices correlated poorly, reinforcing the well-known limitations of angiography in depicting functional severity of intermediate stenoses. Despite being also an angiographic index, the Gensini score is widely used[29, 30] and has demonstrated to provide relevant prognostic information.[29] Interestingly, the documented trend towards a negative, significant association between arterial-Gensini score and CFR (r=-0.207, p=0.055) is in agreement with the proposal made by Johnson et al[8]

regarding the effect of DAN on CFR. It has to be kept in mind that, being a pre-requisite for FFR interrogation, patients with distal coronary stenoses that might interfere with FFR measurements were excluded from our study, and that therefore the effect of DAN on CFR may have been more evident in the study of Johnson et al based on PET.[8]

Classification disagreement between FFR and CFR

In the discordant A group (FFR≤0.80 and CFR≥2), the expected physiological substrate would be the presence of a focal epicardial narrowing with normal distal epicardial conductance and functionally preserved microcirculation. A CFR>2.0 would therefore reflect that diffuse disease and microcirculatory impairment are minimal. At a difference with FFR, CFR has a large inter-individual variability, influenced by age, gender and physical training among other factors.[31, 32] IMR measurements suggest that MCD was absent in group A vessels, supporting previous observations based on Doppler-derived microcirculatory resistance in the same FFR/CFR classification quadrant.[25] Since normal CFR values in group A vessels suggests adequate myocardial blood supply, the benefit of revascularisation of epicardial stenoses, despite abnormal FFR, might be challenged. Further investigation on this hypothesis is required.

DAN causes pressure losses and influences FFR values.[5] Vessels without focal stenoses but with angiographic signs of atherosclerosis present lower FFR values, compared with angiographically normal coronaries.[14] DAN has also been proposed as the dominant cause for group D discrepancy (FFR>0.80 and CFR<2.0). In theory, MCD could also account for group D vessel classification. In support of this, we documented significantly higher microcirculatory resistances in D than in C or A vessels. However, within this quadrant, IMR had a wide dispersion of values (from 7 to 72.7 units), supporting the concept that discrepancies in group D have a dual origin in DAN and MCD. (figure 4 and 5).

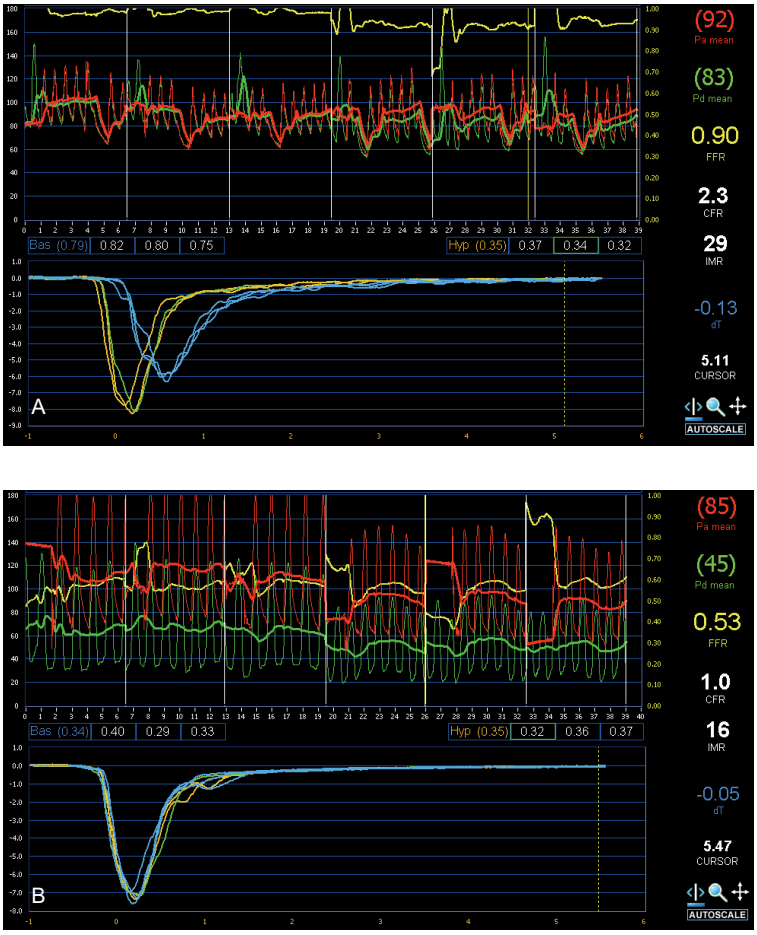


Figure 4 | Representative cases of vessels with adequate and concordant and reduced and concordant values of FFR and CFR. Panel A: vessel located in B with a non-severe stenosis with normal FFR and CFR values (note the well separated baseline and hyperemic thermodilution curves); IMR is close to the 75% percentile value. Panel B: vessel located in C, with a severe stenosis, showing abnormal FFR and an exhausted CFR (CFR=1.0, baseline and hyperemic thermodilution curves are overimposed) and low microvascular resistance.

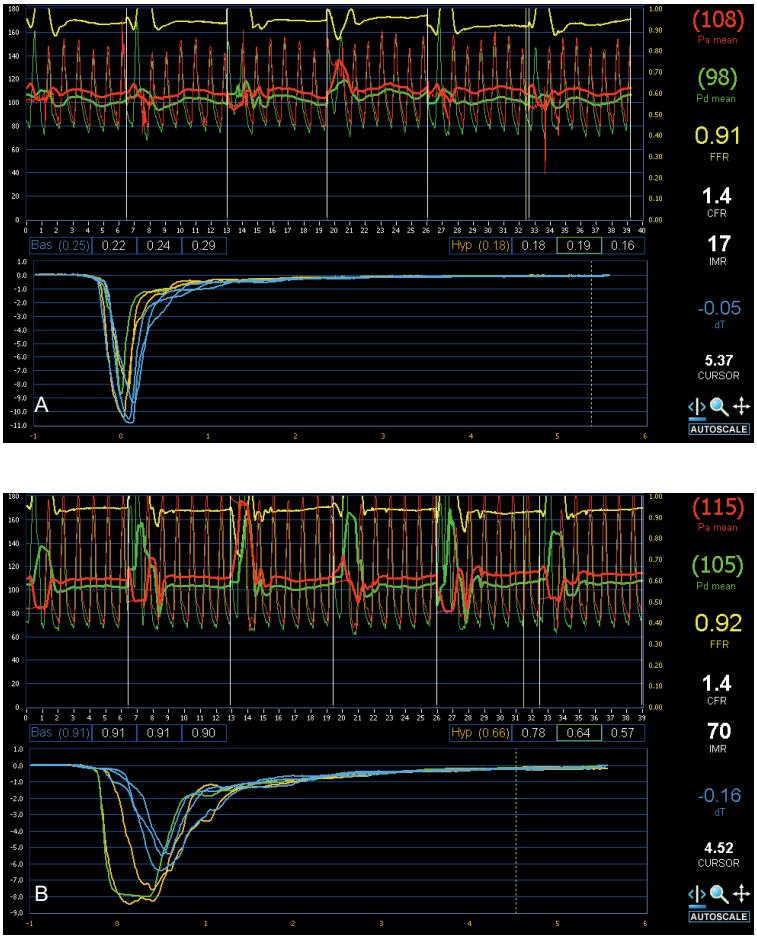


Figure 5 | Representative cases of vessels with normal FFR and abnormal CFR. These two tracings illustrate the separate contribution of DAN and MCD to abnormal coronary hemodynamics in some vessels with normal FFR. Panel A: vessel located in D, in which the dominant feature is an abnormal CFR with normal IMR. The theoretical explanation is that DAN is the dominant cause of abnormal hemodynamics. Panel B: vessel also in D, with virtually identical FFR and CFR values than the one in Panel A that, however, shows very high IMR values suggestive of MCD.

Implications for prognosis and future directions

Do these haemodynamic patterns convey prognostic information? As already mentioned, the rates of MACE and persistent angina at follow up in landmark FFR studies suggests that the invasive diagnosis of IHD can be still potentially improved. In this regard, for example, other authors have reported a worse prognosis in patients with D group vessels. Among 159 patients with FFR≥0.75, Meuwissen et al. found that those

(n=28) with abnormal Doppler-derived CFR presented a significantly higher MACE rate (17%) at 1-year follow-up than those (n=129) with normal CFR (5% MACE rate).[23] Similar conclusions come from non-invasive studies. In 103 patients with normal myocardial perfusion by single-photon emission computerized tomography (a surrogate of stenoses with FFR>0.75[33]), Herzog et al found that abnormal PET-derived CFR (n=32) was associated with a significantly higher MACE (6.25% vs. 1.4% per year; p <0.05) and cardiac death rates (3.1% vs. 0.5% per year; p <0.05) during follow-up, compared with normal CFR patients (n=71).[34] Recently, Murthy et al reported in a large population an adjusted 3.2 and 4.9-fold increase in cardiac death rate for diabetics and non-diabetics patients, respectively, showing impaired PET-derived CFR (p=0.0004).[35] Finally, DAN in the absence of focal stenosis has been associated with an increased risk of MACE [HR of 1.85 (1.51-2.28)][6]. Overall, this evidence suggests that both, DAN and MCD may have prognostic implications that could, in addition to obstructive CAD, improve IHD risk stratification.

LIMITATIONS

Our study can be envisaged as hypothesis generating due to our relatively small sample size. Our study reflects the recommended use of FFR-guided revascularization. Patients with intermediate stenoses may have a lower risk than those with more severe stenoses included in other studies. Coronary wedge pressure was not measured. This might lead to overestimation of IMR[36] in tight stenoses with significant collateral support. Even when overestimation should be minimal in intermediate severity stenoses, corrected IMR values as proposed by Yong et al[12] were used to minimize that effect. A separate analysis of our dataset using uncorrected IMR revealed similar results to those reported in the manuscript. Finally, a comparative survival analysis of patients with vessels belonging to the different categories contemplated in our study (A, B, C and D) was not performed due to limited sample size.

CLINICAL PERSPECTIVE

Although impairment of myocardial blood supply in ischemic heart disease (IHD) results from both obstructive and non-obstructive coronary involvement, its diagnosis is largely stenosis-centred. Fractional flow reserve (FFR) informs on whether treating epicardial stenoses may benefit the patient, but not on whether concomitant non-obstructive coronary disease, that might also influence outcome, is present. To investigate this, a comprehensive assessment of coronary hemodynamics with FFR (abnormal

≤0.80), coronary flow reserve (CFR, abnormal <2.0) and microcirculatory resistance (IMR) was performed in 93 vessels with intermediate stenoses. Interestingly, 63% of vessels with normal FFR>0.80 presented disturbed hemodynamics, revealed by abnormal CFR (52%) and/or microcirculatory disease (MCD, defined as IMR≥29.1) (33%). Indeed, and as theoretically expected, the presence of MCD almost invariably implied non-significant (>0.80) FFR values that could be wrongly interpreted as absence of significant disease. Four coronary hemodynamic patterns were generated based on dichotomous classification of FFR and CFR; non-agreement groups (accounting for 63% of vessels) seem to result from the presence of diffuse epicardial disease (CFR≤2.0 and FFR>0.80) or from focal epicardial narrowing with preserved microcirculatory function (FFR≤0.80 and preserved CFR>2.0). Future research should address whether in the first group might have a worse prognosis despite an FFR >0.80, while in the latter revascularisation might be spared despite an FFR≤0.80 (due to preserved CFR). Overall, the observations serve as a preamble to a more comprehensive, yet required, intracoronary assessment of IHD, which may improve prognostic characterisation and guide therapeutic strategies aiming to both obstructive and non-obstructive coronary disease.

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Supplemental Table 1 | Summarized values of FFR, CFR and IMR among patients with and without cardiovascular risk factors. n =78

	Yes	No	P value*
Men, n (%)	64 (82.1)		
FFR	0.81 (0.78 to 0.83)	0.82 (0.78 to 0.87)	0.597
CFR	1.96 (1.75 to 2.17)	1.90 (1.6 to 2.19)	0.728
IMR	23.3 (19.7 to 26.8)	23.9 (16.3 to 31.5)	0.876
Hypertension, n (%)	57 (73.1)		
FFR	0.80 (0.75 to 0.86)	0.81 (0.78 to 0.84)	0.758
CFR	2.01 (1.80 to 2.23)	1.73 (1.48 to 1.99)	0.097
IMR	22.74 (19.1 to 26.3)	25.5 (18.6 to 32.3)	0.495
Diabetes, n (%)	20 (25.6)		
FFR	0.82 (0.79 to 0.85)	0.79 (0.74 to 0.84)	0.326
CFR	1.90 (1.56 to 2.25)	1.96 (1.76 to 2.17)	0.780
IMR	19.22 (14.50 to 23.93)	24.81 (20.91 to 28.71)	0.073
Dyslipidemia, n (%)	54 (69.2)		
FFR	0.81 (0.78 to 0.84)	0.81 (0.77 to 0.85)	0.977
CFR	2.03 (1.82 to 2.26)	1.75 (1.49 0 2.02)	0.104
IMR	23.3 (19.3 to 27.2)	23.7 (18.2 to 29.1)	0.903
Smoker, n (%)	20 (25.6)		
FFR	0.80 (0.74 to 0.87)	0.81 (0.79 to 0.84)	0.688
CFR	1.89 (1.61 to 2.17)	1.97 (1.75 to 2.18)	0.673
IMR	22.8 (16.5 to 29.1)	23.6 (19.9 to 27.3)	0.839
Obesity, n (%)	31 (39.7)	54 (59.3%)	
FFR	0.80 (0.76 to 0.85)	0.82 (0.79 to 0.85)	0.698
CFR	2.01 (1.72 to 2.30)	1.90 (1.67 to 2.12)	0.549
IMR	23.0 (18.3 to 27.7)	23.7 (19.3 to 28.0)	0.839
Previous MI, n (%)	42 (53.8)		
FFR	0.80 (0.76 to 0.83)	0.83 (0.80 to 0.86)	0.169
CFR	1.88 (1.67 to 2.10)	2.03 (1.74 to 2.31)	0.422
IMR	21.0 (16.6 to 25.4)	26.2 (21.6 to 30.8)	0.110
Multivessel disease, n (%)	37 (47.4)	43 (47.3%)	
FFR	0.82 (0.79 to 0.86)	0.80 (0.76 to 0.84)	0.385
CFR	1.92 (1.64 to 2.21)	1.97 (1.78 to 2.17)	0.779
IMR	21.12 (17.2 to 25.2)	25.9 (20.8 to 30.9)	0.154

Values are n (%) or $_{adj}$means (95% CI).
*Mixed effect regression models

CHAPTER 14

Moving beyond coronary stenosis: has the time arrived to address important physiological questions not answered by fractional flow reserve alone?

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MAKE EVERYTHING AS SIMPLE AS POSSIBLE, BUT NOT SIMPLER.

—Albert Einstein

Fractional flow reserve (FFR) is an intracoronary pressure- derived index that circumvents many of the limitations of angiography in assessing stenosis severity.[1] From a broad perspective, the greatest achievement of the investigators from Aalst, Eindhoven, and Houston who developed FFR was incorporating intracoronary physiology to routine clinical practice. Key elements in FFR success were (1) the simplicity of the technique, (2) the use of a welldefined cutoff (initially 0.75; since the FAME study, 0.80) that facilitated interpreta tion of the results, and (3) the gathering of evidence in prop erly designed trials.[2] But, above all, the key aspect was the relevance of the question answered by FFR: Does this stenosis requires revascularization?

The latter is an important issue, which largely explains why physiology indices used in the pre-FFR era did not reach clinical application. Leaving aside a few exceptions, the most important studies using Doppler-derived coronary flow reserve (CFR) in the 1990s, such as Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE), DEBATE II, French Randomized Optimal Stenting Trial (FROST), and Doppler Endpoint STenting INternational Investigation (DESTINI) (including in total 1734 patients), explored whether optimi zation of the results of balloon angioplasty with CFR could reduce restenosis or avoid the use of coronary stenting (the so called provisional stenting strategy).[3,4] A posteriori, it is easy to understand why, despite the positive results of several of these studies, the Doppler guidewire never became indicated for this purpose not a part of the interventionalists toolbox.

On the contrary, the robustness of the question behind FFR (focused on revascularization appropriateness) increased over time, becoming maximal in current scenario, domi nated by major doubts on the overall benefit of percutaneous coronary intervention, concerns on percutaneous coronary intervention overindication, and urge for costeffectiveness in a context of economical crisis. Also in the noninvasive field—and mainly because of the strength of outcome data— FFR has become a standard of reference, and FFR like indi ces obtained by applying computational fluid dynamics to multidetector computer angiography compete now with ischemia detection techniques.

Which are the challenges for coronary physiology in FFR era? Without any doubt, the first challenge is to increase its adoption, which remains low in most countries. Simpler adenosine-free indices based on the pressure–flow relationship have been proposed to foster this purpose.[5] In addition, a new set of important questions has arrived. After a 50-year stenosis-centered culture of myocardial ischemia, growing evidence indicates that ischemic heart disease is a multilevel condition that affects both the epicardial and the microcirculatory domains of the coronary circulation, as well as the myocardium.[6]

Postponing the development of tools aiming comprehensive ischemic heart disease diagnosis is no longer tenable; otherwise, it will not be possible to ascertain prognostic implications of multilevel coronary involvement to create awareness of the problem among the cardiovascular community, or to assess the effect of treatments addressing the coronary microcirculation.

Several groups, including ours, have strived in making possible this type of comprehensive assessment by combining FFR and CFR, envisaged as complementary rather than competing techniques.[7–9] In this issue of *Circulation: Cardiovascular Interventions*, van de Hoef et al[10] present the results of a research performed in a large cohort of patients investigated with multimodality physiological assessment in whom percutaneous coronary intervention was deferred whenever Doppler-derived CFR and FFR were not concordantly abnormal (using CFR<2.0 and FFR<0.75 as cutoff values). Importantly, the patients included in this cohort were followed up for a long period of time (median, 12 years), providing unique insights on the prognostic relevance of the hemodynamic findings done with FFR and Doppler-derived CFR.

The first important observations made by these researchers refer to the interaction between microcirculatory dysfunction and FFR. By definition, FFR is a stenosis-centered technique that uses the hyperemic translesional pressure ratio as a surrogate of myocardial flow impairment caused specifically by the interrogated stenosis. The rationale behind FFR acknowledges that microcirculatory dysfunction, by impairing myocardial blood flow, modulates FFR values. Yet, since the matter before a coronary stenosis is deciding whether revascularization is appropriate or not, operators have been reassured that issues about concomitant, longstanding microcirculatory dysfunction, which would not be solved by stenting, can be left out of the decision-making process.

The data from the Amsterdam group put an end to any peace-of-mind generated by this attitude, showing that the outcome of patients with FFR>0.80 and impaired myocardial blood supply (low-CFR) is unacceptably high when compared with those with preserved CFR. The most immediate question that comes to mind is whether these patients could be similar to those that developed major cardiac events or persistence of angina after being allocated to the deferral revascularization study arm (on the grounds of FFR≥0.75 or >0.80)[11] in FFR trials. It is beyond the scope of this editorial comment to discuss whether, on the grounds of the microcirculatory resistances reported by van de Hoef et al,[10] such CFR impairment obeys just to microcirculatory disease or also to diffuse atheromatous involvement,8 which influences patient outcome.[12] In any case, the take-home message is that this hemodynamic pattern cannot be obtained with FFR alone, and that while revascularization is not currently indicated, physicians involved in the management of the patient should become aware that coronary hemodynamic are abnormal, and that this has been associated to a worse outcome. We can only provide tentative answers on how to proceed; for the time being, the diagnosis of abnormal

hemodynamic in patients with stenosis and FFR>0.80 should be followed up by optimization of secondary prevention, anti-ischemic treatment, and close patient follow-up.6 Future studies will demonstrate whether this attitude, born of more comprehensive physiological information, contributes to improve outcome in patients with multilevel coronary involvement.

The second set of observations refers to the alternative discordant FFR/CFR group, namely vessels with FFR≤0.80 and CFR>2.0. The rationale of FFR implies that the hyperemic trans-stenotic pressure ratio reliably identifies ischemia-generating stenoses, irrespective of the magnitude of coronary flow. However, investigators measuring both FFR and coronary flow have been puzzled by the fact that a substantial number of stenoses have abnormal FFR, despite preserved CFR and low microcirculatory resistances[7,9] (both suggestive of preserved blood supply and absence of microcirculatory dysfunction). The most plausible explanation for this paradox is that, under certain conditions, an FFR below the diagnostic cutoff may reflect the existence of high coronary flow and not of a significantly flow-limiting stenosis. In other words, being FFR a surrogate of coronary flow, the documentation of a nonpathological value of a flow-based index, such as CFR, should raise the concern that such cases are FFR false-positives, and that therefore revascularization might be deferred. This attitude is supported by the long-term outcome of these patients in the present study during the first 3 years of follow-up because the major adverse cardiac events rate was relatively low. Interestingly, there is a long-term catch up of events in this FFR/CFR discordant group. Because a less pronounced phenomenon also occurred over time in the reference group (that in which both FFR and CFR were concordantly normal), the authors interpret this finding as a result of atherosclerosis progression.

How to read the study of van de Hoef et al?[10] On one hand, the hemodynamic findings are consistent with observations performed by other groups using different methodologies (positron emission tomography, FFR, and thermodilutionderived CFR).[9,13] This provides strong support to the feasibility of performing multilevel physiological interrogation of the coronary circulation with FFR and CFR. On the other, the documentation of differentiated outcomes by their combination is of great importance and suggests that the invasive diagnosis of ischemic heart disease can be still potentially improved beyond FFR. The demonstrated benefit of FFR when compared with angiography should not impede revisiting its diagnostic efficiency in settings, such as the FFR<0.80/CFR>2.0 subgroup discussed above. This is important because the extremely high diagnostic accuracy reported in initial FFR validation was derived from a small number of patients selected with stringent inclusion and exclusion criteria.[14] Finally, in translating the findings of van de Hoef et al[10] to current practice, it is also important to remember the retrospective, nonrandomized design of the study, and the differences with contemporary secondary prevention and optimal medical treatment.

As cardiologists, we are now exposed to a double tension: to simplify physiology as FFR has done, to foster its adoption and, thus, to translate patients the benefits demonstrated in FFR studies and, on the contrary, to face the complexity of ischemic heart disease, which involves not only the epicardial but also the microcirculatory domains of the coronary circulation and the myocardium. The article of van de Hoef et al[10] serves in this way as a reminder of the limits of simplicity and parsimony in medical sciences.

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CHAPTER 15

Diagnostic and prognostic implications of coronary flow capacity: *A comprehensive cross-modality physiological concept in ischemic heart disease*

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ABSTRACT

Background

Although ischemic heart disease (IHD) results from a combination of focal obstructive, diffuse, and microcirculatory involvement of the coronary circulation, its diagnosis remains focused on focal obstructive causes. Coronary flow capacity (CFC) comprehensively documents flow impairment in IHD, regardless of its origin, by interpreting coronary flow reserve (CFR) in relation to maximal flow (hAPV), and overcomes the limitations of using CFR alone. This is governed by the understanding that ischemia occurs in vascular beds with substantially reduced hAPV and CFR, while ischemia is unlikely when hAPV or CFR is high.

Objectives

To evaluate whether CFC improves discrimination of patients at risk for major adverse cardiac events (MACE) compared with CFR alone, and to study the diagnostic and prognostic implications of CFC in relation to contemporary diagnostic tests for IHD, including fractional flow reserve (FFR).

Methods

Intracoronary pressure and flow were measured in 299 vessels (228 patients), where revascularization was deferred in 154. Vessels were stratified as normal, mildly reduced, moderately reduced, or severely reduced CFC. The occurrence of MACE after deferral of revascularization was recorded during 11.9 years of follow-up (Q1,Q3: 10.0, 13.4 years).

Results

Combining CFR and hAPV improved the overall prediction of MACE over CFR alone ($p=0.01$). After stratification in CFC, MACE rates throughout follow-up were strongly associated with advancing impairment of CFC ($p=0.002$). After multivariate adjustment, mildly and moderately reduced CFC were associated with 2.1-fold (95%-CI: 1.1–4.0,$p=0.017$), and 7.1-fold (95%-CI: 2.9–17.1,$p<0.001$) increase in MACE hazard, respectively, compared with normal CFC. Severely reduced CFC was identified by FFR≤0.80 in 90% of cases, while ≥40% of vessels with normal or mildly reduced CFC still had FFR≤0.80.

Conclusion

CFC provides a robust cross-modality platform for the diagnosis and risk-stratification of IHD, and enriches the interpretation of contemporary diagnostic tests in IHD.

INTRODUCTION

Although ischemic heart disease (IHD) is a complex multilevel process that originates from a combination of focal obstructive, diffuse, and microcirculatory causes of myocardial flow impairment,[1] contemporary clinical practice remains focused on focal epicardial coronary artery obstruction. However, the presence of a strong link between myocardial blood flow impairment and adverse clinical outcome regardless of its origin, urges a comprehensive diagnostic approach towards IHD, not restricted to the epicardial domain.[2-4]

The coronary flow reserve (CFR)[5] is a well-validated index that allows the assessment of blood flow impairment originating from either obstructive, diffuse, or microcirculatory involvement of the coronary circulation. However, its use has been limited due to a reported sensitivity towards resting hemodynamics. As a result, the coronary pressure-derived fractional flow reserve (FFR) is considered the preferred surrogate for blood flow impairment in the catheterization laboratory.[6] Nonetheless, FFR is an invasive tool that was introduced to identify significant epicardial coronary artery obstruction by means of trans-stenotic pressure drops, which by definition do not occur in the presence of diffuse coronary artery disease or microcirculatory involvement in IHD, and can be concealed when obstructive, diffuse, and microcirculatory causes coincide.[7] Therefore, both CFR and FFR seem insufficient to comprehensively diagnose IHD.[4,7-10]

An alternative approach towards the diagnosis of IHD can be found in the concept of coronary flow capacity (CFC), which integrates both CFR and maximal hyperemic flow to depict myocardial blood flow impairment due to a combination of obstructive, diffuse, and microcirculatory involvement of the coronary vasculature.[11] First derived from positron emission tomography (PET), CFC may potentially provide a comprehensive and robust physiological platform, likely applicable to all invasive and non-invasive modalities aiming to detect myocardial blood flow impairment, and which may overcome many of the limitations of using CFR or FFR alone. However, the complementarity of CFR and hyperemic flow in terms of risk-stratification in IHD has not been documented, nor its comparison with other contemporary invasive and non-invasive diagnostic tests in IHD. In the present study, we aimed to document 1) the applicability of the CFC concept to invasive measurements, 2) whether the physiological complementarity of CFR and hyperemic flow translates into an improved discrimination of patients at risk for adverse outcome, and 3) the diagnostic and prognostic implications of CFC in relation to contemporary diagnostic tests for IHD.

METHODS

Data source

Between April 1997 and September 2006, we evaluated patients with stable IHD referred for evaluation of ≥1 coronary artery stenosis (40-70% diameter stenosis at visual assessment). Patients were enrolled in a series of study protocols,[10,12-14] and data were entered in a dedicated database. These protocols excluded patients with renal function impairment (calculated glomerular filtration rate <30mL/min/1.73m^2), significant left main disease, atrial fibrillation, recent myocardial infarction (<6 weeks prior to screening), prior coronary artery bypass graft surgery, as well as vessels with ostial stenosis, serial stenoses, or visible collaterals. The institutional ethics committee approved the study procedures, and all patients gave written informed consent.

Myocardial perfusion scintigraphy (MPS)

MPS was performed prior to coronary angiography using ^{99m}Technetium sestamibi or ^{99m}Technetium tetrofosmin, according to a two-day stress/rest protocol. A blinded expert panel evaluated the scintigraphic images. Perfusion defects were classified as dubious, mild, moderate or severe. Improvement at rest of >1 grade was considered a "reversible" perfusion defect, and improvement of ≤1 grade a "persistent" perfusion defect. The result was considered positive when a reversible perfusion defect was allocated to the perfusion territory of interest.

Coronary angiography and physiological measurements

Coronary angiography was performed according to standard practice. Quantitative coronary angiography (QCA) analyses were performed offline using validated software (QCA-CMS version 3.32, MEDIS, Leiden, The Netherlands). Intracoronary pressure was measured with a 0.014" pressure sensor-equipped guide wire (Volcano Corp., San Diego, USA), and coronary blood flow velocity was subsequently measured with a 0.014" Doppler crystal-equipped guide wire (Volcano Corp., San Diego, USA). Hyperemia was induced by an intracoronary bolus of adenosine (20-40 µg). Flow velocity measurements were additionally performed in a reference vessel, defined as a coronary artery with less than 30% epicardial narrowing, if available.

Long-term follow-up

Three-, 6-, 12-month, and long-term follow-up was performed by clinical visits or telephone contact to document major adverse cardiac events (MACE), defined as the composite of cardiac death, myocardial infarction not clearly attributable to non-target vessels, and clinically driven (urgent) revascularization of the target vessel. All patient-

reported adverse events were adjudicated after evaluating hospital records, or contacting treating physicians.

Definition of physiological parameters

FFR was calculated as the ratio of mean distal-to-aortic pressure during hyperemia, where FFR≤0.80 was considered abnormal.[15] CFR was calculated as the ratio of hyperemic to basal average peak blood flow velocity (hAPV and bAPV, respectively), where CFR<2.0 was considered abnormal.[16] We additionally determined the hyperemic stenosis resistance index (HSR)[14] as the ratio of the trans-stenotic pressure drop to hAPV, where HSR>0.80 mm Hg was considered abnormal,[16] and the hyperemic microvascular resistance index (HMR), as the ratio of distal coronary pressure to hAPV.[9] Parameter definitions are detailed in Table 1.

Table 1 | Physiological parameter definitions

FFR = mean Pdistal /mean Paorta (during hyperemia)
CFR = hyperemic flow velocity (hAPV) / basal flow velocity (bAPV)
HSR= (mean Paorta – mean Pdistal)/ APV (during hyperemia)
HMR = mean Pdistal / APV (during hyperemia

Pdistal (P_d): distal coronary pressure, Paorta (P_a): aortic pressure, APV: average peak flow velocity distal to the coronary lesion, HSR: hyperemic stenosis resistance index, HMR: hyperemic microvascular resistance index

Derivation of the invasive coronary flow capacity map

Figure 1 shows the invasive coronary flow capacity (CFC) map. Analogous to the PET-derived CFC concept, coronary flow was categorized into clinically meaningful ranges using well-documented thresholds of CFR derived from invasive measurements. The highest coronary flows are encountered in patients without significant epicardial coronary narrowing (normal flow capacity).[17] The subsequent category depicts slightly reduced coronary flows; lower than in patients without epicardial narrowing, but of adequate magnitude to prevent myocardial ischemia (mildly reduced flow capacity). Moderately reduced flows lie within the range of flows reported to be related to inducible myocardial ischemia, and can produce some manifestations of myocardial ischemia (moderately reduced flow capacity).[18] Finally, severely reduced flows lie below the lower flow threshold reported for myocardial ischemia (severely reduced flow capacity).

The above-mentioned flow ranges have been well documented for invasively derived CFR, but not for hAPV. Therefore, categorization was based on literature-derived CFR ranges, and hAPV values matched according to the corresponding percentiles, as

follows. Normal CFC was defined as a CFR≥2.8, as encountered in patients with risk factors for IHD without epicardial narrowing,[17] with its corresponding hAPV of ≥49.0 cm/s. Mildly reduced CFC was defined as a CFVR<2.8, but >2.1, which reflects the upper limit of reported CFR cut-off values for inducible ischemia,[18] and the corresponding hAPV of <49.0 cm/s, 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,[18] and the corresponding hAPV of ≤33.0 cm/s 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[18] and analogous to the ischemic CFR threshold on non-invasive imaging,[19] and the corresponding hAPV of ≤26.0 cm/s.

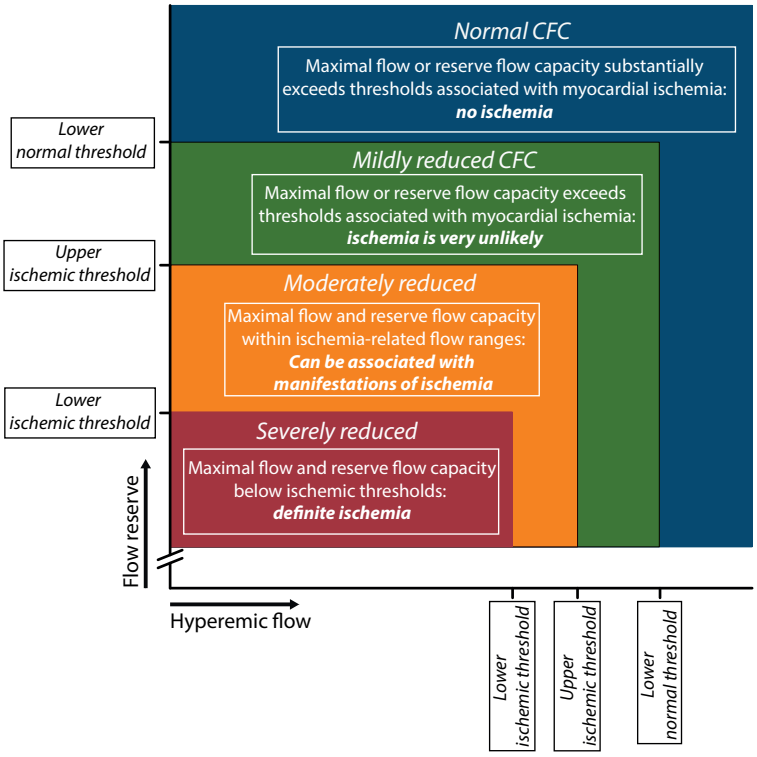


Figure 1 | Invasive coronary flow capacity map. Since coronary flow reserve (CFR) equals hyperemic to baseline average peak flow velocity (hAPV), a two-dimensional map of CFR versus hAPV comprehensively describes the invasive flow characteristics of the coronary vasculature under investigation. Within this concept, four clinically meaningful categories are defined (coded with different colours in the graph) based on well-validated invasive CFR cut-off values and the according hAPV percentiles. See text for further details.

Statistical analysis

Data were analyzed on per-patient basis for clinical characteristics, and on per-vessel basis for all other calculations. Normality and homogeneity of the variances were tested using Shapiro-Wilk and Levene tests. Continuous variables are presented as mean±standard deviation or median [1st , 3rd quartile (Q1, Q3)], and were compared with Student's t test or Mann-Whitney U test. Categorical variables are presented as counts and percentages, and were compared with Chi square or Fisher´s exact test. Analyses of linear trends across CFC categories were performed with polynomial contrasts. In the presence of multiple coronary stenoses, one was randomly marked as index and used for clinical outcome analyses, which were restricted to patients in whom revascularization was deferred. First, the prognostic value of CFR and hyperemic flow for long-term MACE were assessed using separate Cox regression analyses, adjusted for the effect of relevant clinical and angiographic characteristics. Optimal models were identified using Akaike's information criterion, where candidate co-variates were: clinical characteristics (Table 1), percent diameter stenosis, and the interrogated vessel (left anterior descending (LAD), left circumflex (LCx), or right (RCA) coronary artery). Results are presented as standardized hazard ratios (sHR), and their 95% confidence intervals (95%CI), which were estimated from these models by exponentiating the β-coefficient multiplied by the SD [exp(β × SD)]. Second, the incremental prognostic value of hyperemic flow to CFR was assessed in a multivariable Cox regression model, including both CFR and hyperemic flow as well as adjustments for relevant characteristics as defined previously. As a sensitivity analysis, the additive value of hyperemic flow to CFR was evaluated with the continuous net reclassification index (NRI), integral discrimination improvement (IDI) and relative IDI (rIDI) (Supplemental Methods). Third, after stratification into CFC categories, event rates over time were estimated using the Kaplan-Meier (KM) method, and linear trends were tested with log rank tests. Finally, adjusted Cox proportional hazard analyses were used to assess the impact of CFC on long-term MACE. A p-value <0.05 (two-sided) was considered statistically significant. The STATA 13.1 (StataCorp, College Station, Texas) software package was used for calculations.

RESULTS

Patient population

A total of 228 patients with 299 coronary stenoses were included. Baseline characteristics are depicted in Table 2. Revascularization was deferred in 159 patients, and follow-up was obtained in 154 patients (97%) with 183 stenoses. In patients with multiple stenoses, one was chosen at random for MACE analyses, which consequently included 154 patients with 154 stenoses (Supplemental Table 1). Median follow-up in

these patients was 11.9 years (Q1, Q3: 10.0, 13.4 years). The distribution of FFR values in this deferred study population resembled that of reported clinical populations undergoing FFR-measurements (Supplementary Figure 1).

Table 2 | Baseline characteristics

Number of patients	228
Demographics	
Age, yrs	60±11
Male sex	157 (69)
Coronary risk factors	
Hypertension	85 (37)
Hyperlipidemia	135 (59)
Positive family history	101 (44)
Cigarette smoking	68 (30)
Diabetes mellitus	33 (14)
Prior myocardial infarction	83 (36)
Prior coronary intervention	45 (20)
Medication at hospital admission	
Beta-blocker	166 (73)
Nitrates	137 (60)
Calcium antagonists	141 (62)
ACE-inhibitors	46 (20)
Lipid-lowering drugs	133 (58)
Aspirin	204 (89)

ACE: Angiotensin-converting enzyme

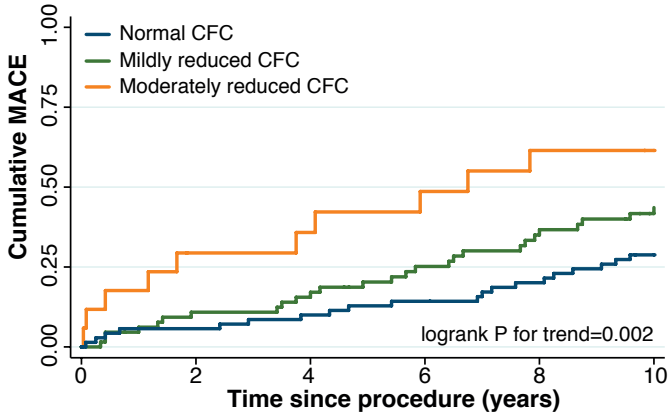
Improvement in risk stratification by integrating CFR and hyperemic flow

In separate adjusted Cox proportional hazards models (adjusted for angiotensin-inhibitor use, diabetes, diameter stenosis, and interrogated vessel), both CFR and hAPV were significantly associated with long-term MACE (CFR sHR: 0.5, 95%CI: 0.4–0.8, p<0.001; hAPV sHR: 0.7, 95%CI: 0.5 – 0.9, p=0.02). Adding hAPV to the CFR adjusted Cox model yielded a significant model improvement (Likelihood-ratio test p=0.01), and both CFR and hAPV remained independent predictors for long-term MACE (CFR sHR: 0.5, 95%CI: 0.4–0.7, p<0.001; hAPV sHR: 0.7, 95% CI: 0.5 – 0.9, p=0.01).

The sensitivity analyses using NRI, IDI and rIDI supported these findings, showing a significant improvement in the prediction of MACE by adding hAPV to CFR (Supplementary Table 2). In contrast, FFR, HSR or MPS did not improve prediction of MACE over CFR alone (Supplementary Table 2).

Clinical outcome after deferral of revascularization

Figure 2 shows the KM curves of MACE across CFC categories. The severely reduced CFC category was omitted because only two patients within this category were deferred, and both suffered a MACE within the first year of follow-up. MACE increased significantly with advancing impairment of CFC at all time-points (logrank for trend p=0.002; Figure 2).



No. at risk:						
Normal CFC	70	66	63	60	55	47
Mildly reduced CFC	65	57	54	46	39	31
Moderately reduced CFC	17	11	10	8	6	5

Figure 2 | Kaplan Meier curves showing the occurrence of major adverse cardiac events (MACE) in patients with normal, mildly reduced and moderately reduced coronary flow capacity in the interrogated coronary artery. The severely reduced coronary flow capacity category was omitted since revascularization was deferred in only 2 patients within this category, whom both suffered an event within the first year of follow-up.

Adjusted Cox regression analysis identified CFC as an independent predictor for long-term MACE. Compared with normal CFC, a mildly and moderately reduced CFC were associated with a 2.1-fold (95% CI: 1.1 – 4.0, p=0.017), and a 7.1-fold (95% CI: 2.9 – 17.1, p<0.001) increase in MACE, respectively. Using the same cut-off values, CFR alone showed a more modest discrimination: mildly reduced vs. normal CFR (HR 1.6 (95% CI: 0.8 – 3.5), p=0.20), and moderately reduced CFR vs. normal CFR (HR 3.8 (1.7 – 8.3), p=0.001)).

Comparison with contemporary diagnostic tests in IHD

The distribution of all 299 vessels across CFC categories is shown in Figure 3. A total of 121 vessels (40.5%) had normal CFC, 99 vessels (33.1%) mildly reduced CFC, 30 vessels (10.0%) moderately reduced CFC, and 49 (16.4%) severely reduced CFC (Table 3).

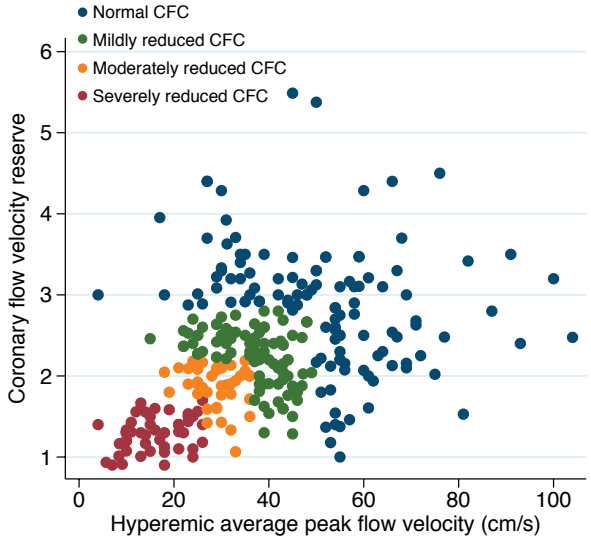


Figure 3 | Scatterplot of invasive flow data across the coronary flow capacity concept.

The frequency of abnormal values of FFR, CFR, HSR, and MPS across the CFC categories is shown in Table 3, and is visualized in Figure 4. Identification of severely reduced CFC was good for all tests, particularly for FFR≤0.80 (90%) and HSR>0.80 mm Hg/cm/s (92%). With increasing CFC, however, discordance with CFC increased substantially (Table 3; Figure 4), particularly for FFR.

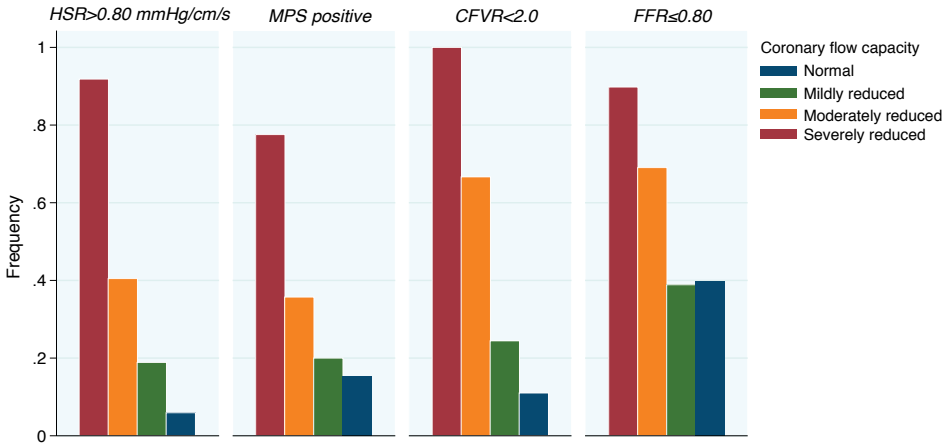


Figure 4 | Bar chart indicating the frequency of abnormal test results of fractional flow reserve (FFR), coronary flow reserve (CFR), hyperemic stenosis resistance index (HSR), and myocardial perfusion scintigraphy (MPS) across the coronary flow capacity concept.

Table 3 | Angiographic and hemodynamic characteristics according to coronary flow capacity groups

	Coronary Flow Capacity				
	Normal	Minimally to mildly reduced	Moderately reduced	Severely reduced	
Number of stenoses	121	99	30	49	P-value for linear trend
Angiographic parameters					
Interrogated vessel					
LAD	71 (59)	43 (43)	13 (43)	19 (39)	0.03
LCX	15 (12)	33 (33)	12 (40)	11 (22)	0.08
RCA	35 (29)	23 (23)	5 (17)	19 (39)	0.45
Measurement location					
Proximal vessel	30 (25)	19 (19)	9 (30)	12 (24)	0.67
Middle Vessel	66 (55)	53 (54)	15 (50)	23 (47)	0.34
Distal vessel or side branch	25 (21)	27 (27)	6 (20)	14 (29)	0.49
Diameter Stenosis, %	52 [45, 57]	54 [48, 61]	53 [48, 62]	66 [53, 72]	<0.001
Reference diameter, mm	3.0 [2.5, 3.4]	2.9 [2.6, 3.3]	2.8 [2.3, 3.0]	2.8 [2.3, 3.3]	0.12
Minimal lumen diameter, mm	1.4 [1.2, 1.7]	1.2 [1.0, 1.6]	1.3 [1.0, 1.4]	0.9 [0.7, 1.1]	<0.001
Hemodynamic parameters					
APV (Basal), cm/s	18 [12, 27]	17 [13, 20]	14 [13, 17]	12 [8, 16]	<0.001
APV (Hyperemia), cm/s	53 [39, 60]	37 [31, 42]	29 [25, 30]	15 [10, 21]	<0.001
Aortic pressure (Basal), mm Hg	99±13	99±12	96±8	98±16	0.66
Aortic pressure (Hyperemia), mm Hg	95±13	96±12	89±8	95±17	0.51
Distal pressure (Basal), mm Hg	95 [84, 100]	93 [85, 102]	86 [78, 92]	65 [55, 79]	<0.001
Distal pressure (Hyperemia), mm Hg	78 [70, 88]	79 [68, 91]	72 [61, 78]	47 [39, 62]	<0.001
Pressure drop (Basal), mm Hg	5 [2, 8]	5 [2, 9]	9 [6, 11]	33 [20, 42]	<0.001
Pressure drop (Hyperemia), mm Hg	16 [10, 22]	16 [10, 26]	22 [15, 26]	47 [31, 57]	<0.001
Heart rate (Basal), BPM	68±11	69±11	70±11	68±10	0.81

Table 3 | Angiographic and hemodynamic characteristics according to coronary flow capacity groups (continued)

	Coronary Flow Capacity				
Heart rate (Hyperemia), BPM	69±11	69±11	73±10	69±10	0.44
Derived indices					
CFR	2.9 [2.4, 3.3]	2.3 [2.0, 2.5]	1.9 [1.8, 2.0]	1.3 [1.1, 1.4]	<0.001
CFR≤2.0	13 (11)	28 (28)	22 (73)	49 (100)	<0.001
FFR	0.84 [0.77, 0.90]	0.84 [0.74, 0.91]	0.77 [0.71, 0.81]	0.49 [0.40, 0.64]	<0.001
FFR≤0.80	48 (40)	43 (43)	20 (67)	44 (90)	<0.001
HSR, mm Hg/cm/s	0.30 [0.19, 0.53]	0.46 [0.26, 0.77]	0.78 [0.60, 0.94]	3.00 [1.80, 4.38]	<0.001
HSR>0.80 mm Hg/cm/s	7 (6)	21 (21)	13 (43)	45 (92)	<0.001
Inducible ischemia on MPS	18 (15)	22 (22)	11 (37)	38 (78)	<0.001

LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; APV: average peak velocity; BPM: beats per minute; CFR: coronary flow reserve; FFR: fractional flow reserve; HSR: hyperemic stenosis resistance index; MPS: myocardial perfusion scintigraphy. Pressure drop equals aortic pressure minus distal coronary pressure.

Figure 5 shows the distribution of FFR across the CFC categories (overall p<0.001). FFR was not statistically different between the normal and mildly reduced CFC groups (median FFR: 0.84 [Q1, Q3: 0.77-0.90] vs 0.84 [Q1, Q3: 0.74-0.91]; P=0.99), but 40% and 43% of vessels within these categories had an FFR≤0.80, despite only mildly reduced or normal flow characteristics. With a further reduction in CFC, FFR decreased significantly to a median of 0.77 [Q1, Q3: 0.71-0.81] in the moderately reduced, and to 0.49 [Q1, Q3: 0.40-0.64] in the severely reduced CFC category, where 75% of stenoses had an FFR<0.65 (Table 3). HSR increased significantly with decreasing CFC (Table 3; P<0.001), and showed a lower discordance with CFC than FFR (6% and 11% for normal or mildly reduced CFC, respectively). Finally, MPS reversible perfusion deficits were present in 78% of severely reduced CFC vessels, whilst discordance in higher CFC categories was limited to 15% and 22% for normal or mildly reduced CFC, respectively.

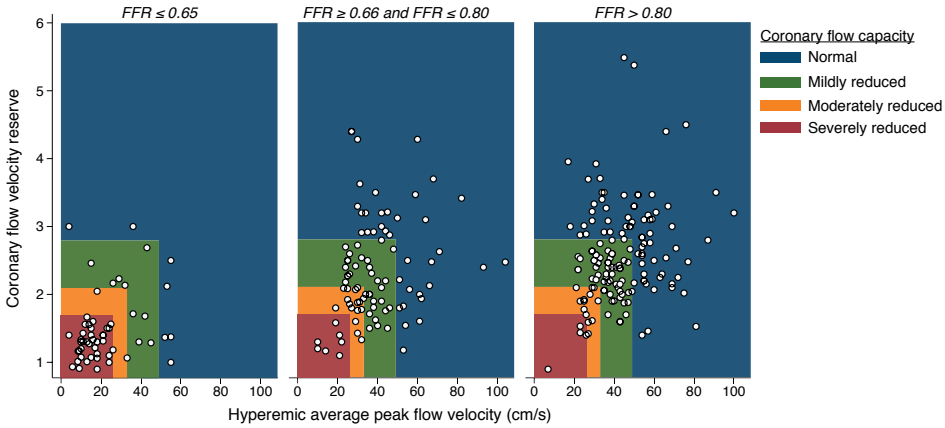


Figure 5 | Scatterplots of fractional flow reserve (FFR) across the coronary flow capacity map.

Notably, 13 out of 15 vessels associated with moderately (9 out of 10 vessels) or severely reduced CFC (4 out of 5 vessels) that were not identified by FFR≤0.80, were characterized by high HMR (3.24 mm Hg/cm/s [2.69 – 3.37 mm Hg/cm/s]), and low HSR (0.53 mm Hg/cm/s [0.46 – 0.60 mm Hg/cm/s]), suggestive of a dominant non-obstructive origin of flow impairment. The other two stenoses were characterized by a positive HSR (>0.80 mm Hg/cm/s) and a very high HMR (>3.5 mm Hg/cm/s), suggestive of concomitant obstructive and non-obstructive origins of flow impairment.

DISCUSSION

The physiological complementarity of CFR and hyperemic flow, integrated within the CFC concept, translates into meaningful incremental risk discrimination for adverse

clinical outcomes compared with CFR alone, which is not attainable by other contemporary diagnostic tests in IHD. CFC provides a robust cross-modality physiological platform for the comprehensive diagnosis and risk-stratification of IHD, incorporating the consequences of both focal obstructive, diffuse, and microcirculatory causes of myocardial blood flow impairment.

Coronary flow capacity rationale: complementarity of CFR and hyperemic flow

Myocardial ischemia originates from impairment of myocardial perfusion resulting from both focal obstructive, diffuse, and microcirculatory causes, and occurs when the maximal achievable perfusion is insufficient to meet myocardial demand. The principle of CFR has been extensively applied to both invasive and non-invasive diagnostic techniques, including intracoronary Doppler- and thermodilution-derived flow, transthoracic echocardiography, PET and magnetic resonance imaging. Nonetheless, its sensitivity towards resting hemodynamics has been considered an important limitation in its use to diagnose myocardial flow limitation, despite repeated documentation of a substantial ability to stratify the risk for MACE.[2-4]

The rationale behind CFC relies on the fact that the combination of CFR with hyperemic flow comprehensively captures all relevant flow characteristics of the vasculature under investigation.[11] For example, as suggested by Johnson and Gould, in the setting of anxiety or increased myocardial workload, baseline flow may be high, whilst maximal flow is adequate. In this situation, CFR may be low while no signs or symptoms of ischemia occur. Conversely, in patients on beta blockade therapy, maximal flow may be reduced to ischemic levels, while basal flow can be low due to the beta blockade effects, resulting in a normal CFR preventing signs or symptoms of inducible ischemia. Hence, combining hyperemic flow with CFR conceivably provides a more comprehensive assessment and overcomes many limitations of using CFR alone to diagnose clinically pertinent impairment of myocardial flow.

We documented that the physiological complementarity of hyperemic flow and CFR, as the basis of the CFC concept, translates into an improved discrimination of patients at risk for MACE compared with CFR alone. In contrast, none of the contemporary tests for ischemia, including FFR, provided improvement in discrimination above CFR (Supplementary Table 2). It is likely that this advantage derives from the fact that CFC 1) assesses both focal obstructive, diffuse, and microcirculatory causes of IHD,[20] and 2) is less susceptible to the limitations of CFR linked to the baseline state.

Although CFC was initially derived from PET-studies, the present results expand this concept to invasive coronary flow assessment. The demonstrated improvement in MACE discrimination together with its previous validation in PET studies suggests that CFC is a potentially disruptive physiological concept, likely applicable to both invasive

and non-invasive IHD diagnostic modalities that measure flow, including intracoronary Doppler- and thermodilution-derived flow, transthoracic echocardiography, PET and magnetic resonance imaging.

Relationship between contemporary diagnostic tests for IHD and coronary flow capacity

The CFC concept is governed by the understanding that vascular beds perfused by vessels with severely reduced maximal flow and exhausted CFR will exhibit signs of ischemia and that the latter will be unlikely in myocardial territories perfused by vessels showing high maximal flow or high CFR.[11,19] On this basis, we sought to relate established indices for ischemia with CFC (Figure 4). We observed that FFR, HSR and MPS were very likely to be abnormal in vessels with severely reduced CFC, which corroborates the documented high sensitivity of FFR for the detection of inducible myocardial ischemia,[21] and the high accuracy of HSR to identify stenoses associated with perfusion abnormalities on non-invasive imaging.[14] On the other hand, many vessels perfusing vascular territories with normal or only mildly reduced CFC (with high values of either maximal flow or CFR) presented abnormal functional tests, particularly positive FFR values. However, since myocardial function dominantly depends on coronary flow and not on perfusion pressure— as myocardial contraction remains preserved with stable flow, even at very low perfusion pressures (FFR<0.50)[22]— the benefit of revascularization of such stenosis is less clear. [4,23] It is important to note that FFR values within the severely reduced CFC category were dramatically lower than in the other categories, as 75% of FFR values in this category were <0.65. This finding is in accordance with initial FFR validation and clinical outcome studies, since one of the first proposed FFR cut-offs was 0.66 (derived from electrical manifestations of ischemia),[24] and the clinical benefit of revascularizing FFR-positive stenoses in the FAME II trial was dominant in vessels with FFR<0.65.[25] Moreover, a recent patient-level meta-analysis on the prognostic value of FFR identified an optimal FFR treatment threshold of 0.67.[26] Our findings add to this evidence by suggesting that coronary flow characteristics associated with signs of severe ischemia and impaired clinical outcomes are dominantly associated with FFR values far below contemporary interventional thresholds.[11]. Since ischemia is a *continuum*, further studies should address if the currently adopted FFR threshold is the most optimal to trigger revascularization.

Implications for clinical practice

Accumulated evidence strongly supports a multi-level involvement of the coronary circulation in IHD, which urges reconsideration of contemporary stenosis-centered diagnostic strategies in this complex disease. Although the documented clinical benefit of FFR-guided revascularization illustrates important progress in the treatment and

risk-stratification of IHD, inadvertently, this clinical merit has led several reports to suggest FFR as a gold standard test for diagnosis of IHD, and to dismiss the prognostic pertinence of non-obstructive involvement in IHD. Although FFR is a simple and effective surrogate for focal obstructive flow impairment, IHD goes beyond the domain that can be interrogated by FFR. In this regard, the CFC concept provides a robust cross-modality physiological platform for IHD diagnosis and risk stratification purposes, which overcomes many of the limitations of using CFR and FFR alone. In addition, CFC seems to enrich the interpretation of contemporary diagnostic standards in IHD, like FFR.

LIMITATIONS

Although conceptually applicable to the spectrum of IHD, our conclusions refer to patients with a clinical indication for intracoronary interrogation of epicardial stenosis, which constituted the study population. Assessment of flow velocity is sensitive for technical failures. However, all measurements in this study were performed by operators with ample experience. In the absence of an established cut-off value or normal ranges for hAPV, the proposed cut-off values were derived from the percentiles of hAPV corresponding to literature-defined CFR cut-offs. Particularly the hAPV cut-off value for severely reduced CFC should be subject to confirmation, which may allow further optimization of the invasive CFC concept. Importantly, because nature normalizes coronary artery wall stress, coronary flow velocity is intrinsically normalized for myocardial mass in the arterial distribution.[27,28] This constitutes a theoretical concern, since some normal but anatomically reduced myocardial territories could therefore exhibit lower values of hAPV.[29] However, only 6 (3%) reference vessels in our study showed an hAPV within the severely reduced CFC region (Supplemental Figure 2), and none of these vessel had a reduced CFR (range 2.2 – 4.6). This strongly suggests that clinically relevant coronary branches, suitable for invasive physiological interrogation, can be adequately stratified by means of the proposed invasive CFC concept. The diagnostic accuracy of MPS for definite ischemia should be interpreted carefully, since a positive MPS requires the presence of perfusion deficit reversibility. It cannot be excluded that some of the MPS-CFC discordance occurred in the presence of persistent perfusion defects. 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 towards a possible patient recall bias, which may have resulted in underreporting of adverse events. Nonetheless, the long-term MACE rates reported in the present study are generally comparable with those reported in contemporary observational studies using FFR guidance.[30]

CONCLUSIONS

The CFC concept provides a comprehensive cross-modality platform for the diagnosis and risk-stratification of IHD, and allows to enrich the interpretation of contemporary diagnostic tests in IHD. CFC may thereby provide a robust and disruptive physiological framework in IHD, likely applicable to all invasive and non-invasive diagnostic modalities that measure flow.

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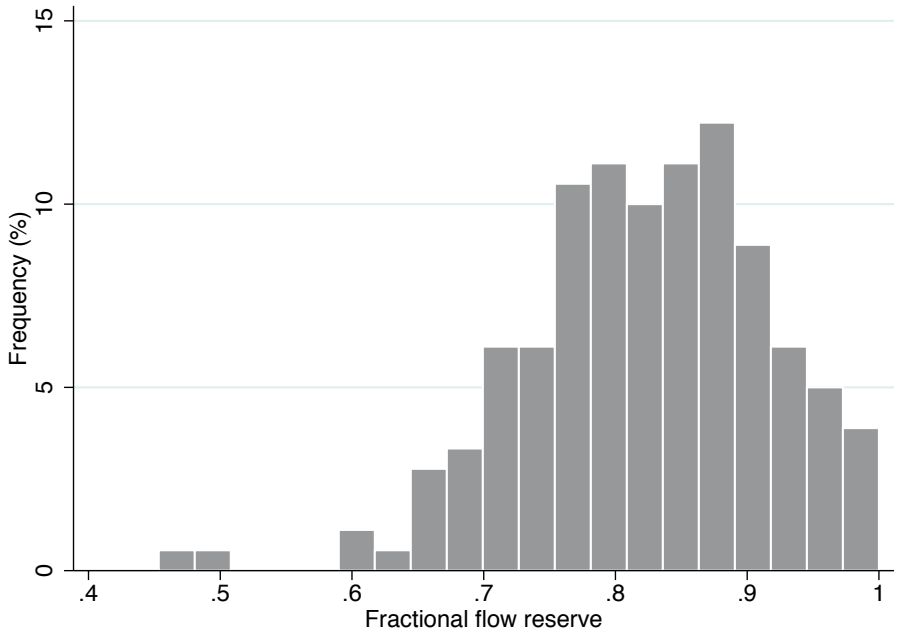
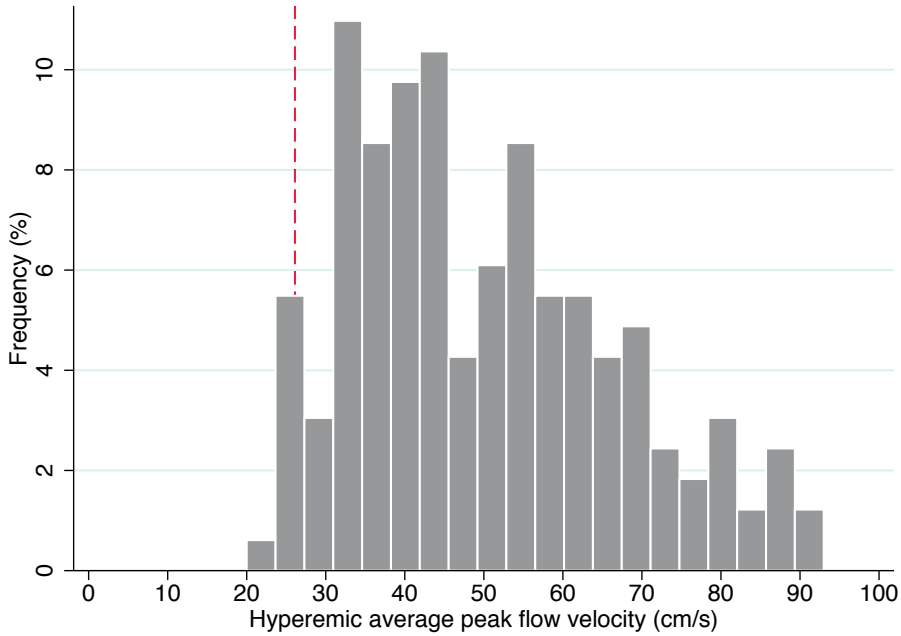


Supplemental Figure 1 | Distribution of FFR values across the deferred study population.



Supplemental Figure 2 | Distribution of hyperemic average peak flow velocity (hAPV) values within the studied reference coronary arteries. Dashed red line indicates the threshold for severely reduced hAPV (<26.1).

CHAPTER 16

Predicting the effect of myocardial revascularization on the coronary flow reserve from pre-interventional intracoronary pressure and flow measurements. A meta-analytic and individual validation study

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Submitted

ABSTRACT

Aims

Although the aim of percutaneous coronary intervention (PCI) is to restore coronary flow supply to the myocardium, no methods are currently available to estimate a priori the potential improvement in the coronary flow reserve (CFR) produced by PCI. Based on fractional flow reserve (FFR) theory, we hypothetized that the ratio of CFR to FFR measured prior to PCI (CFRp) can be use to predict post-PCI CFR. We sought to comprehensively test this use of FFR theory.

Methods and results

We first performed a metanalysis of studies measuring CFR and FFR before and after PCI. Subsequently, we compared CFRp with actually observed post-PCI CFR in individual stenosed coronary arteries. Seventeen studies including 654 patients were included in metanalyses. Additionally, CFR and FFR were measured in 75 stenosed coronaries before and after PCI. At study-level, mean CFRp was moderately associated with mean observed CFR post-PCI (analytic weights-$R2=0.40$, $p<0.001$). At vessel-level, concordance analyses revealed absence of constant ($A=0.17$, 95% CI: -0.56 to 0.63) and proportional ($B=0.99$, 95% CI: 0.78 to 1.32) differences, small systematic bias (+0.13), yet, imprecision (95% limits of agreement: -1.61 to 1.88) between the predicted and observed CFR post-PCI. However, from all available pre-PCI indices of coronary physiology, CFRp was the only independent predictor of observed CFR post-PCI.

Conclusions

A moderate concordance between the predicted and observed CFR post-PCI was observed in previous studies and in individual vessels. The clinical implications of CFRp are encouraging and should foster research on its use.

INTRODUCTION

Chronic ischemic heart disease (IHD) results from the complex interplay between focal stenosis, diffuse atherosclerosis (DA) and microcirculatory disease (MCD).[1] When the combined effect of these entities results in an exhaustion of the coronary flow reserve (CFR), blood supply is not able to satisfy demand, and myocardial ischemia develops.[2] By removing epicardial stenosis, percutaneous coronary intervention (PCI) aims to restore the CFR, and thereby to relieve ischemia.[3] However, available pre-PCI physiology indices do not inform on the specific contribution of the focal stenosis to the overall degree of CFR impairment. Therefore, it is currently not possible to estimate *a priori* the potential gain in CFR that will follow PCI—when only background DA and MCD should endure. A clinical tool capable to predict the potential gain in CFR that will follow PCI is highly desirable, as it would allow to predict the physiological result of PCI before it is performed, and could so tailor treatment.

The purpose of this work was to apply fractional flow reserve (FFR) theory to predict the restoration in the CFR produced by PCI (CFRp) from pre-PCI intracoronary pressure and flow measurements.[2,4] To comprehensively test this use of FFR theory, we first performed a metanalysis of available literature, to appraise the mean performance of CFRp across different populations, and then predicted and observed the restoration in the CFR produced by individual PCI, to assess the vessel-level performance of CFRp.

METHODS

Predicting post-PCI CFR from preinterventional physiology

CFR and FFR are complementary techniques that summarize coronary flow and pressure in the catheterization laboratory.[1,2] Their relationship is illustrated in Figure 1, where a severe coronary stenosis is used as example. CFR is defined as the ratio of hyperemic flow (Qh) to baseline flow (Qb), and in the absence of a stenosis, CFR reflects to what extent DA and MCD impair vasodilator reserve.[2] In the presence of a focal stenosis, however, CFR equals the ratio of hyperemic stenotic flow (Qs) to Qb. Therefore, CFR cannot distinguish the relative contribution of the stenosis to the overall degree of flow impairment. This question can be answered with the relative CFR, that equals the ratio of Qs to hyperemic flow in the absence of the stenosis (Qh). Since coronary pressure and flow are linearly and proportionally related during hyperemia, the hyperemic distal-to-aortic pressure ratio—the FFR—can be used as proxy of the relative CFR.[2,4] This hyperemic pressure and flow proportionality is the critical element that allows to predict the CFR in the absence of the stenosis from FFR and CFR values obtained in the presence of the stenosis (Figure 1, panel B). Since FFR is linearly and proportion-

ally related with the relative CFR,[2,4] the increase in CFR that will follow PCI should be linearly and proportionally related to the increase in FFR. If it is then assumed that PCI fully reestablishes epicardial conductance so that the driving pressure fully is restored (i.e., post-PCI FFR=1.00), and if wedge pressure is neglected from FFR calculation (as it is usual in clinical practice), the CFR post-PCI can be predicted from pre-PCI FFR and CFR values with the following equations:

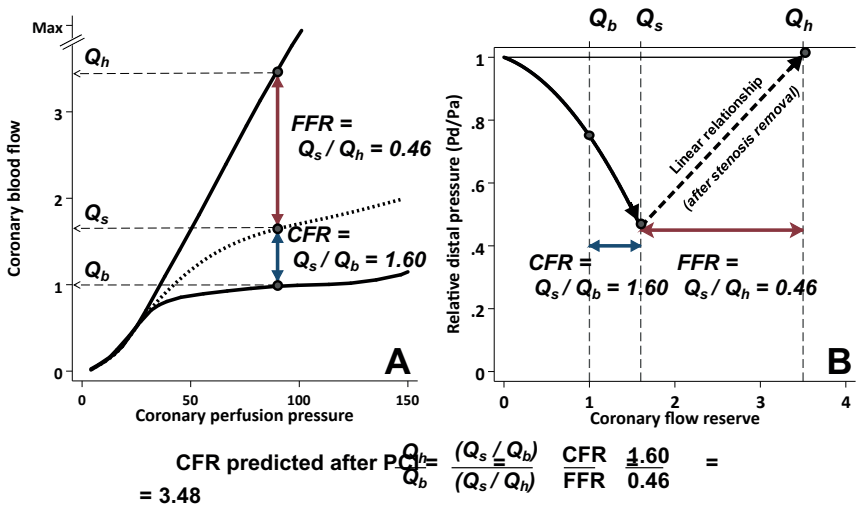

Figure 1 | Schematic coronary pressure and flow relationships in the presence and absence of epicardial stenosis. Panel A shows the relationship between perfusion pressure, baseline coronary flow (Qb), hyperemic stenotic flow (Qs), and hyperemic flow in the absence of the stenosis (Qh). A hypothetical severe coronary stenosis is plotted, with a fractional flow reserve (FFR) of 0.46 and a coronary flow reserve (CFR) of 1.60. Panel B shows the relationship between the relative pressure drop (Pd to Pa) produced by this stenosis with the relative increase in flow (CFR). Dashed lines represent the predicted increase in relative pressure and flow after the stenosis removal. Since FFR is linearly related to relative CFR, the increase in relative distal pressure following the stenosis removal should be linearly related to the increase in CFR. Consequently and relative to Qb pre-PCI, the X intercept of the relative distal pressure with the Y value of one (FFR=1.00) is the predicted CFR after PCI (in this case: 3.48).

1) In the presence of the stenosis (Figure 1):

$$FFR = \frac{Qs}{Qh} \tag{1}$$

or

$$FFR = \frac{Qs}{Qh} = \frac{Qs/Qb}{Qh/Qb} \tag{1.1}$$

and

$$CFR = \frac{Qs}{Qb} \tag{2}$$

2) If it is assumed that PCI removes the stenosis completely, so that:

$$Qs \cong Qh$$

3) CFR after complete stenosis removal should equal thus:

$$CFR\ after\ complete\ stenosis\ removal = \frac{Qh}{Qb} \tag{3}$$

4) FFR equation (1.1) can also be rearranged into the following form:

$$\frac{Qh}{Qb} = \frac{Qs/Qb}{Qs/Qh} \tag{4}$$

or

$$CFR\ predicted\ after\ PCI = \frac{Qh}{Qb} = \frac{Qs/Qb}{Qs/Qh} = \frac{CFR}{FFR} \tag{4.1}$$

Literature search used for meta-analytic validation

A search in the literature for studies written in English from 1993 to 2015 was performed in PubMed and Embase. Full details on this search are specified in the Data Supplement. Briefly, we included only studies that measured and reported both CFR (either by Doppler flow velocity or coronary thermodilution) and FFR before and after PCI to coronary stenosis in humans. From each study, summary statistics of CFR and FFR were recorded as well as sample size, technique to measure flow, hyperemic route and agent. If overall population values were not reported, subsamples data was then extracted. We excluded studies performed in chronic total occlusions and in the acute phase of myocardial infarction where simplified FFR theory does not apply.

Study population used for individual validation

The JUSTIFY-PCI database (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity), described in detail elsewhere,[3] was used for individual validation. Here, pressure and flow velocity intracoronary data was prospectively collected from patients scheduled for elective PCI, at the Academic Medical Centre, Amsterdam, the Netherlands, and Imperial College London, United Kingdom. PCI was performed at the operators discretion based on usual clinical care. Local ethical review boards approved the study protocols and all subjects gave written informed consent. Full details on the study population, coronary catheterization procedure, haemodynamic recordings and data analyses are provided in the Supplement.

Statistical analysis

For metanalysis, the average mean increase (post-PCI – pre-PCI) in FFR and CFR produced by PCI was calculated in each study. If overall study data was not available, within-studies samples were then used as populations. Each mean difference was weighted according to the inverse of its variance, the average was taken as weighted

mean difference, and individual weighted mean differences were then pooled in fixed and random effects metanalysis with the user-written command *mar* in STATA 12.1 (StataCorp, College Station, Texas). From these, only random effects are reported because heterogeneity (I^2>50%) was important (Supplemental Tables 1 and 2). In each study, the average mean CFRp was calculated as the ratio of the study mean CFR to mean FFR prior to PCI. To assess the relationship between CFRp and the observed post-PCI CFR throughout studies, linear regression models were performed using analytic weights (aw) with sample size as weight variable and clustered (subpopulations-within-studies) robust standard errors. Clustered regressions were compared by testing for equivalence in their slopes. For vessel-level analyses, data was analyzed on per-patient basis for clinical characteristics and on per-vessel basis for the rest of calculations. Continuous variables are presented as mean ± standard deviation or median [quartile 1 and 3 (Q1,3)] and categorical variables as counts and percentages. Normality and homogeneity of the variances were tested using Shapiro-Wilk and Levene tests, respectively. Continuous variables were compared with unpaired or paired t tests or Mann-Whitney U tests, and categorical variables with Chi square or Fisher´s exact tests, as appropriate. Correlation coefficients (Pearson´s r, Spearman´s ρ) between physiology indices were calculated. Continuous agreement was assessed with parametric (Bland-Altman) and robust (Passing-Bablok) methods as well as with Lin´s concordance correlation coefficient. The association between the observed CFR post-PCI and all pre-PCI physiology indices was evaluated with univariable lineal regressions, and a multivariable forward stepwise lineal regression analysis (criterion for inclusion p<.10, exclusion p≥0.20) was constructed to identify potential independent predictors of observed CFR post-PCI. Differences were considered significant at p<0.05 (two-sided). The STATA 12.1 software was used for all calculations.

RESULTS

Average mean effect of PCI on FFR and CFR

The search strategy is provided in Supplemental Figure 1. In total, 17 studies (26 subpopulations) including 654 patients were identified and included in quantitative synthesis. [3,5–19] General characteristics of patients included in these studies are reported in Table 1. Population-weighted mean pre-PCI FFR and CFR values were 0.65±0.07 and 1.78±0.29, respectively. Both FFR (0.91±0.04) and CFR (2.69±0.49) increased significantly after PCI (p<0.001 for both) (Supplemental Figure 2). Supplemental Tables 1 and 2 summarize the metanalyses of the effect of PCI on FFR and CFR. Their summary plots are shown in Figure 2. The pooled-average mean increase in FFR and CFR produced by PCI was 0.26 (95% CI: 0.23 to 0.28) and 0.90 (95% CI: 0.72 to 1.08), respectively.

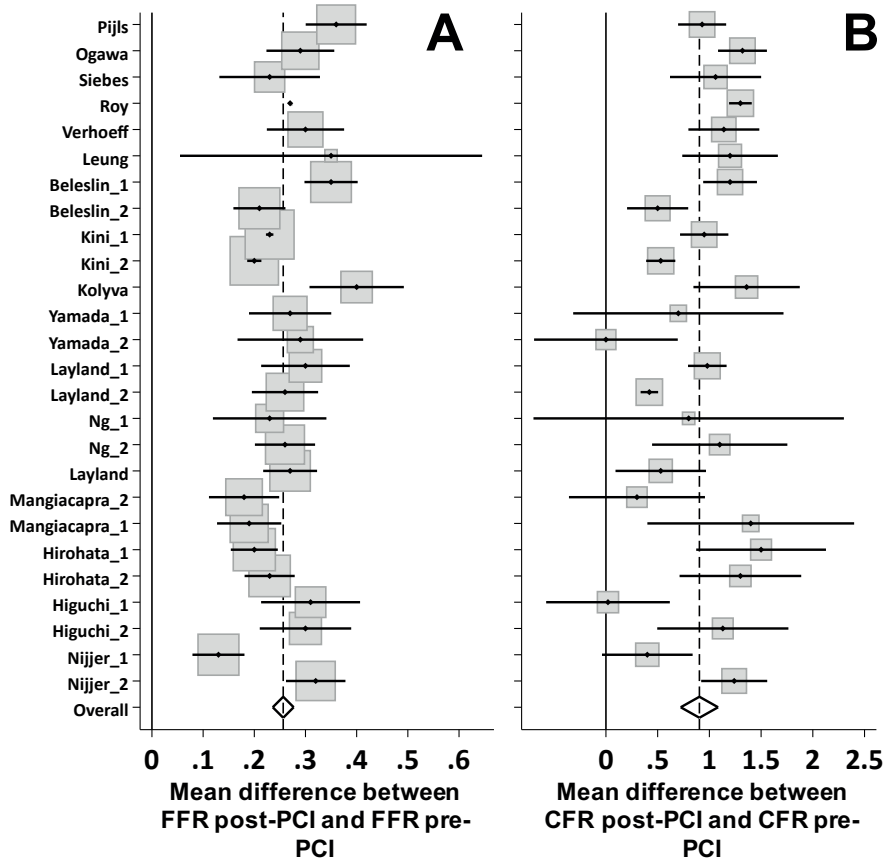

Figure 2 | Average mean effect of PCI on FFR and CFR. Random effect metanalyses of the mean difference between post-PCI and pre-PCI FFR (A) and CFR (B). Full data is provided in Supplemental Tables 1 and 2. Studies are ordered according to year of publication.

Meta-analytic validation: study-level performance of CFRp

Figure 3 shows the relationship between the mean predicted (CFRp) and mean observed CFR post-PCI for each study. Throughout studies, mean CFRp was moderately associated with the mean observed CFR post-PCI (aw- r=0.654, p<0.001, aw- R^2=0.40, p<0.001). However, this association varied widely (Figure 4), being numerically stronger in studies in whom intracoronary hyperemia was used, Doppler technology was employed, and more severe stenosis were assessed (mean pre-PCI FFR≤0.64, the average FFR mean of total studies), as compared to those in whom intravenous hyperemia was used (difference in slopes, p=0.386), Thermodilution technology was employed (difference in slopes, p=0.365), and less severe stenosis were assessed (difference in slopes, p=0.365), respectively.

Table 1 | Summary characteristics of studies included in metanalyses

Author	Year	Sub-population ID	N	Patients included	Doppler or Thermodilution
Pijls (8)	2002	1	33	Patients referred for physiological assessment	D and T*
Ogawa (9)	2004	2	7	Children with Kawasaki disease in convalescent state and coronary stenosis	D
Siebes (10)	2004	3	15	Patients with stable angina scheduled for elective PCI	D
Roy (11)	2005	4	32	Patients with unstable or stable angina	D
Verhoeff (12)	2005	5	24	Patients with stable angina scheduled for elective PCI	D
Leung (13)	2006	6	18	Patients with stable angina scheduled for elective PCI	D
Beleslin (14)	2008	7	33	Patients with chronic myocardial infarction and improvement in myocardial function at follow-up by echocardiography	T
		8	11	Patients with chronic myocardial infarction without improvement in myocardial function at follow-up by echocardiography	T
Kini (15)	2008	9	36	Patients without diabetes undergoing PCI	D
		10	36	Diabetic patients undergoing PCI	D
Kolyva (16)	2008	11	10	Patiens scheduled for elective PCI	D
Yamada (32)	2010	12	21	Patients with angina admitted for PCI without TCFA by VH-IVUS	T
		13	9	Patients with angina admitted for PCI with TCFA by VH-IVUS	T
Layland (17)	2012	14	21	Patients with stable angina scheduled for elective PCI that did not developed periprocedural myocardial infarction	T
		15	33	Patients with stable angina scheduled for elective PCI that developed periprocedural myocardial infarction	T
Ng (18)	2012	16	10	Patients with stable angina and single vessel disease scheduled for elective PCI that developed periprocedural myocardial infarction	T
		17	40	Patients with stable angina and single vessel disease scheduled for elective PCI that did notdeveloped periprocedural myocardial infarction	T
Layland (19)	2013	18	55	Patients with stable angina scheduled for elective PCI	T
Mangiacapra (20)	2013	19	20	Patients with stable angina scheduled for elective PCI randomized to IV enalaprilat before PCI	T
		20	20	Patients with stable angina scheduled for elective PCI randomized to placebo before PCI	T

Hyperemic agent, dose	Route of hyperemia	PCI technique	Pre-intervention			Post-intervention		
			DS,%	FFR	CFR	DS,%	FFR	CFR
IV adenosine (140 µg/kg/min) or IC papaverine (20 mg)	IV or IC	POBA or stent	68±0.16	0.53±0.16	1.47±0.52	11±5	0.89±0.07	2.40±0.44
IC infusion of papaverine (0.3 mg/kg in LM and 0.2 mg/Kg in RCA)	IC	POBA	>90	0.62±0.04	1.09±0.21	<50	0.91±0.08	2.410.24
IC adenosine (20 to 40 µg)	IC	stent	52.2±8.6	0.62±0.16	1.80±0.64	2.5±8.9	0.85±0.11	2.86±0.59
IC papaverine (6 to 12 mg)	IC	POBA	90±1	0.62	2.30±0.10	61±2	0.89	3.60±0.30
IC boluses of adenosine (20 to 40 µg)	IC	stent	60.0±10.3	0.59±0.16	1.70±0.57	7.8±11.6	0.89±0.10	2.84±0.64
IC adenosine (24 µg in LM, 18 µg in RCA)	IC	stent	88±9	0.57±0.19	1.80±0.60	2±7	0.92±0.61	3.0±0.80
IC papaverine (15 mg for LM and 10 mg for RCA)	IC	stent	62±8	0.56±0.14	1.40±0.30	18±10	0.91±0.06	2.60±0.70
IC papaverine (15 mg for LM and 10 mg for RCA)	IC	stent	63±8	0.70±0.07	1.50±0.30	17±8	0.91±0.05	2.0±0.40
IC adenosine (32 µg in LM, 18 µg in RCA)	IC	stent	74±4	0.76±0.02	1.49±0.25	<30	0.99±0.01	2.44±0.67
IC adenosine (32 µg in LM, 18 µg in RCA)	IC	stent	76±5	0.77±0.03	1.36±0.31	<30	0.97±0.03	1.89±0.30
IC adenosine (20 to 40 µg)	IC	stent	62.9±13.2	0.53±0.14**	1.48±0.46	0±11.7	0.93±0.05	2.84±0.69
IV adenosine (150 µg/kg/min)	IV	PCI	58.7±10.7	0.67±0.17	1.70±0.90	-	0.94±0.08	2.40±2.20
IV adenosine (150 µg/kg/min)	IV	PCI	58.3±16.8	0.61±0.17	1.50±0.70	-	0.90±0.08	1.50±0.80
IV adenosine (140 µg/kg/min)	IV	stent	-	0.62±0.19	1.99±0.26	-	0.92±0.07	2.97±0.35
IV adenosine (140 µg/kg/min)	IV	stent	-	0.67±0.18	1.93±0.19	-	0.93±0.06	2.35±0.16
IV adenosine (140 µg/kg/min)	IV	stent	58.2±12.8	0.61±0.16	2.10±1.50	-	0.84±0.08	2.90±1.90
IV adenosine (140 µg/kg/min)	IV	stent	55.4±15.7	0.58±0.18	2.10±1.10	-	0.84±0.06	3.20±1.80
IV adenosine (140 µg/kg/min)	IV	stent	71.5±10.9	0.65±0.19	1.97±1.14	-	0.92±0.06	2.50±1.20
IV adenosine (140 µg/kg/min)	IV	stent	65±11	0.70±0.13	2.20±1.40	-	0.89±0.06	3.60±1.80
IV adenosine (140 µg/kg/min)	IV	stent	64±13	0.71±0.14	2.40±0.90	-	0.89±0.07	2.70±1.20

Table 1 | Summary characteristics of studies included in metanalyses (continued)

Author	Year	Sub-population ID	N	Patients included	Doppler or Thermodilution
Hirohata (21)	2014	21	33	Patients with stable angina scheduled for elective PCI in the LAD randomized to IV nicorandril before PCI	T
		22	29	Patients with stable angina scheduled for elective PCI in the LAD randomized to placebo before PCI	T
Higuchi (22)	2014	23	12	Patients with stable angina scheduled for elective PCI that developed periprocedural myocardial infarction	T
		24	21	Patients with stable angina scheduled for elective PCI that did not developed periprocedural myocardial infarction	T
Nijjer (4)	2015	25	43	Patiens scheduled for elective PCI	D
		26	32	Patiens scheduled for elective PCI	D
Total			654		
Population-weigthed means			30.8 ± 11.8		

FFR: fractional flow reserve; CFR: coronary flow reserve; SD: standard deviation; IV: intravenous; IC: intracoronary; T: thermodilution; D: Doppler; LM: left main; RCA: right coronary artery; PCI: percutaneous coronary intervention; TCFA: thin-cap fibroatheroma; VH_IVUS: virtual histology intravascular ultrasound
*Only D measurements were included in synthesis
**Obtained from reference 1

Hyperemic agent, dose	Route of hyperemia	PCI technique	Pre-intervention			Post-intervention		
			DS,%	FFR	CFR	DS,%	FFR	CFR
IV adenosine (140 µg/kg/min) or IC papaverine (15 mg)	IV or IC	stent	-	0.71±0.09	1.70±0.70	-	0.91±0.10	3.20±1.70
IV adenosine (140 µg/kg/min) or IC papaverine (15 mg)	IV or IC	stent	-	0.70±0.09	1.80±0.60	-	0.93±0.10	3.10±1.50
IV papaverine (12 mg for LM and 8 mg for RCA)	IV	stent	79±9	0.61±0.16	1.67±0.80	3±5	0.92±0.06	1.69±0.69
IV papaverine (12 mg for LM and 8 mg for RCA)	IV	stent	81±9	0.64±0.20	1.79±0.73	4±5	0.94±0.06	2.92±1.29
IV adenosine (140 µg/kg/min)	IV	stent		.074±0.15	1.82±0.98		.087±0.08	2.22±1.09
IC adenosine (60 µg)	IC	stent		0.59±0.16	1.66±0.49		0.91±0.05	2.90±0.78
				0.65±0.07	1.78±0.29		0.91±0.04	2.69±0.49

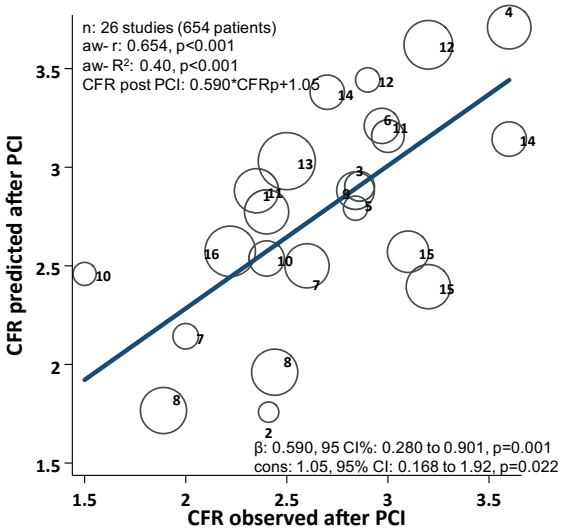

Figure 3 | Relationship between the mean predicted and observed post-PCI CFR across pooled studies. Each circle represents a study included in metanalyses, and its diameter is proportional to the sample size. The regression line summarizes the mean predicted and mean observed post-PCI CFR relationship across pooled studies.

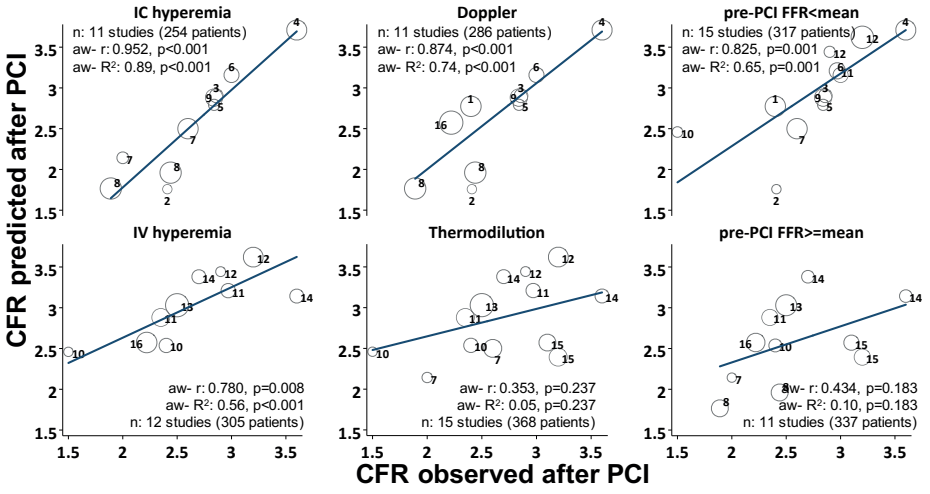

Figure 4 | Sub-analyses of the relationship between the mean predicted and observed CFR post-PCI across studies. Pooled studies were stratified according to route of hyperaemia (intracoronary or intravenous), technology to measure flow (Doppler or thermodilution) and pre-PCI stenosis severity as defined by the FFR (pre-PCI FFR below or above the mean of total studies, which was 0.64). Three studies (1, 21 and 22 from Table 1) were excluded in the left upper and lower figures, because intravenous and intracoronary hyperaemia were both used.

Individual validation: vessel-level performance of CFRp

Clinical, angiographic, and physiological characteristics of the study population where FFR and CFR assessment was performed before and after PCI are shown in Table 2. In total, 75 stenosed coronary arteries from 67 patients were investigated. Overall, coronary stenoses were of intermediate severity (diameter stenosis: 61.4 ± 13.7%). Median pre-PCI FFR and CFR values were 0.70 (Q1-3, 0.52 to 0.82) and 1.60 (Q1-3, 0.19 to 2.20), respectively, and both increased significantly ($p<0.001$) to 0.90 (Q1-3, 0.85 to 0.94) and 2.45 (Q1-3, 1.79 to 3.04) after PCI (Supplemental Figure 3).

Table 2 | Summary characteristics of study population

	FFR and CFR assessment before and after PCI
Patients	**n=67**
Age	62.4±9.3
Male	50 (74.6)
Hypertension	36 (53.7)
Hyperlipidemia	56 (83.6)
Current or former smoker	31 (46.3)
Diabetes	20 (28.2)
Chronic kidney disease	4 (6.0)
Previous myocardial infarction	8 (11.9)
Stable angina	64 (95.5)
Unstable angina	3 (4.5)
Multivessel disease	25 (37.3)
	Vessels wth stenosis undergoing PCI
Vessels	**n=75**
Left anterior descending artery	44 (58.7)
Circumflex	13 (17.3)
Right coronary artery	18 (24.0)
Stenosis severity by QCA, %	60 (52.3-69.4)
Intravenous adenosine	43 (57.3)
Intracoronary adenosine	32 (42.7)
Intracoronary physiology indices	
CFR	1.58 (1.19-2.20)
FFR	0.70 (0.52-0.82)
HSR	1.04 (0.44-2.25)
BSR	0.66 (0.27-1.77)
Pd/Pa	0.90 (0.68-9.95)
iFR	0.84 (0.58-0.93)
CFR-predicted	2.49 (1.79-3.19)

CFR: coronary flow reserve; FFR: fractional flow reserve; QCA: quantitative coronary angiography; HSR: hyperemic stenosis resistance; BSR: baseline stenosis resistance; Pd/Pa: baseline distal to aortic pressure ratio; iFR: instantaneous wave free ratio.

Figure 5 provides the scatterplot and the continuous agreement between the predicted (CFRp) and observed CFR post-PCI in individual vessels. Overall, CFRp was moderately correlated with the observed CFR post-PCI (ρ=0.562, 95% CI: 0.384 to 0.670, p<0.001), with a coefficient of determination (R^2) of 0.38 (p<0.001), a linear slope of 0.62 (95% CI: 0.44 to 0.81, p<0.001), and a linear intercept of 0.86 (95% CI: 0.34 to 1.38, p=0.001). A moderate concordance between CFRp and the observed post-PCI CFR was demonstrated by a Lin´s correlation coefficient of 0.614. Panel A of Figure 5 shows the Passing-Bablok regression line, that revealed absence of constant (A=0.17, 95% CI: -0.56 to 0.63) and proportional (B=0.99, 95% CI: 0.78 to 1.32) differences between these two indices. Their Bland-Altman plot (Figure 5, panel B) demonstrated no heteroscedasticity, no proportional error and only a small systematic bias (+0.13); yet, significant imprecision on individual basis, as the 95% limits of agreement were wide (-1.61 to 1.88). However and as shown in Table 3, from all the available pre-PCI indices of coronary physiology, CFRp was the only independent predictor of observed CFR post-PCI.

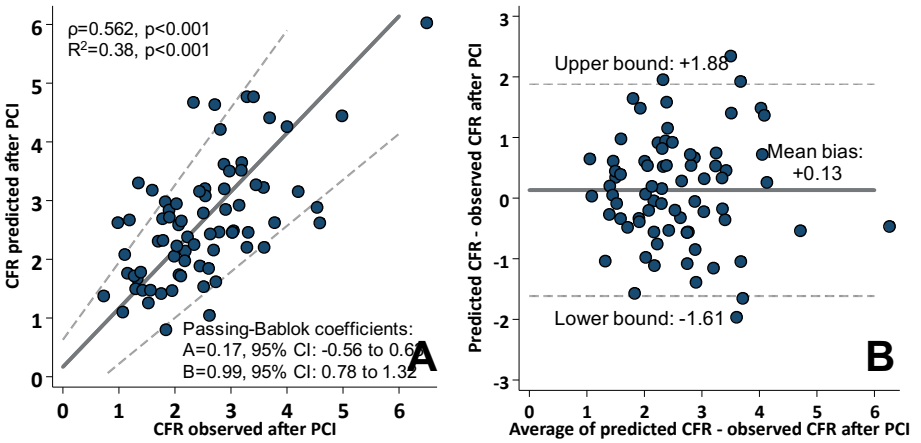

Figure 5 | Scatterplot and continuous agreement between the predicted and observed CFR post-PCI. Panel A provides the scatterplot of the predicted (CFRp) and observed CFR post-PCI relationship. The line is the Passing-Bablok regression, with its 95% confidence intervals. Panel B shows the Bland Altman plot of differences against means, with the 95% limits of agreement.

Table 3 | Univariable and multivariable predictors of observed CFR post-PCI n=75

	Univariable								Multivariable
Pre-PCI physiology indices	**Association with CFR post-PCI**					**β-coefficient**			**Forward stepwise selected***
	Spearman ρ	**P-value**	**Pearson r**	**P-value**	**R2**	β	**95% CI**	**P-value**	
CFR	0.429	<0.001	0.556	<0.001	0.30	0.707	0.460 to 0.953	<0.001	no
FFR	-0.175	0.133	-0.073	0.534	0.00	-0.436	-1.827 to 0.955	0.534	no
HSR	0.133	0.254	0.042	0.718	0.00	0.026	-0.116 to 0.168	0.718	no
BSR	0.314	0.006	0.216	0.063	0.03	0.115	-0.006 to 0.237	0.063	no
Pd/Pa	-0.048	0.682	0.029	0.804	0.00	0.179	-1.255 to 1.612	0.804	no
iFR	-0.010	0.936	0.069	0.555	0.00	0.301	-0.713 to 1.315	0.555	no
CFR predicted	0.562	<0.001	0.620	<0.001	0.38	0.622	0.438 to 0.806	<0.001	yes

PCI: percutaneous coronary intervention; CFR: coronary flow reserve; FFR: fractional flow reserve; HSR: hyperemic stenosis resistance; BSR: baseline stenosis resistance; Pd/Pa: baseline distal to aortic pressure ratio; iFR: instantaneous wave free ratio
*Inclusion criterion: p<0.10; exclusion criterion: p≥0.20

Assessment of CFRp imprecision

The relative error of CFRp (CFRp – CFR post-PCI /CFR post-PCI) was not significantly explained by any pre-PCI haemodynamic parameter (all p>0.05, Supplemental Table 3), and only marginally explained by post-PCI hyperaemic flow velocity (R^2=0.07, p=0.023), microvascular resistance (R^2=0.10, p=0.003) and residual FFR (1— FFR post-PCI) (R^2=0.07, p=0.020); suggesting thus that CFRp imprecision was partly due to variations in the hyperemic intracoronary flow and microcirculatory resistance response and due to residual epicardial resistance after PCI.

DISCUSSION

The main finding of our study is that, prior to the performance of PCI, the potential gain in CFR produced by the intervention can be predicted from intracoronary pressure and flow measurements. The applicability of the calculations used for this purpose, derived from FFR theory, was tested first in metanalyses of available studies, and subsequently with measurements made in the catheterization laboratory. A moderate concordance between the predicted and observed CFR post-PCI was observed, both across studies and across individual coronary vessels. Most importantly, from all the available pre-PCI physiology indices, CFRp was the only independent predictor of the truly observed post-PCI CFR. Altogether, our findings provides support to the clinical use of CFRp and expand with simplicity the information derived from intracoronary physiology measurements.

Assessment of ischaemic heart disease with CFR and FFR

The relevance of predicting prior to PCI the potential gain in CFR after the intervention stems from the fact that myocardial ischaemia may result from both obstructive and non-obstructive causes.[20] FFR provides valuable information on whether a given focal stenosis plays a dominant role in limiting myocardial flow supply, but not on whether concomitant non-obstructive IHD, partly caused by DCA and MCD, constitutes the predominant flow-limiting problem in the interrogated myocardial territory.[2,20] Large observational registries have established that DA (defined by angiography) and MCD (defined by abnormal CFR) are associated with a noteworthy and quantifiable risk for cardiovascular morbidity and mortality;[21,22] and either by invasive or non invasive means, CFR has demonstrated to be a robust risk stratification tool.[21,23] Indeed, a normal CFR has been constantly associated with a low risk of cardiovascular events, and conversely, an exhausted CFR has demonstrated to be a powerful predictor of strong clinical endpoints including death.[2,21,23] Since the capacity of CFR to stratify the risk for adverse events seems to extend beyond the presence or absence of stress-induced

ischaemia —i.e., the ultimate objective of FFR— little doubts exist now on the incremental information that CFR provides to FFR assessment.[21]

Use of FFR theory to predict post-PCI CFR

FFR and CFR were both initially intended to estimate coronary stenosis severity. However and shortly after their introduction, investigators realized constant between-indices discordance when defining the latter.[1,2] Since CFR provides the ratio of Qs to Qb, and FFR the ratio of Qs to Qh, it should be acknowledged that by definition CFR and FFR explore different but interdependent regions of the stenotic pressure and flow relationship. Therefore, FFR and CFR provide complementary rather than competing information, which includes baseline flow, maximum stenotic flow and maximum flow in the absence of the stenosis. A simple rearrangement of their clinical equations (formula 4, CFR/FFR=CFRp) hence allows to predict the theoretical CFR in the absence of the stenosis from FFR and CFR values obtained in the presence of the stenosis (Figure 1). It should be highlighted that the simplified calculation of CFRp used in our work implies that post-PCI stenotic flow (Qs) equals the maximum non-stenotic flow (Qh), wedge pressure equals zero, and the hemodynamic conditions remain constant.

Limitations of the simplified calculation of CFRp

Our study establishes the clinical feasibility of CFRp and demonstrates a moderate concordance between the predicted and observed CFR post-PCI both across studies and across individual vessels. Moreover and from all the available pre-PCI physiology indices, CFRp was the only independent predictor of the CFR post-PCI. However, CFRp was relatively imprecise, which most likely reflects real biological variability and not a failure of theory. This is because robust concordance analyses failed to identify significant constant and proportional errors and the systemic bias was very small. Sources of imprecision can be many. Indeed, 8 of the 17 (47%) studies included in metanalyses documented periprocedural myonecrosis in variable proportions.[12,14–19] This myocardial damage between the measurements can affect the prediction of the CFR, by modifying flow post-PCI.[12,14] Since the prevalence of periprocedural myonecrosis in stable PCI ranges from 3 to 24%,[24] it should be anticipated that in a significant proportion of cases CFRp "fails" to accurately predict CFR post-PCI due to real modifications in the circulatory function and not due to oversights of theory. An additional source of imprecision comes from residual epicardial resistance as demonstrated by the abnormal FFR post-PCI. The simplified CFRp formula assumes that epicardial conductance is completely restored, which was not the case, neither in the metanalyses (population weighted FFR post-PCI: 0.91±0.04) nor in our individual vessel population (median FFR post-PCI: 0.90, Q1-3, 0.85 to 0.94). These findings reflect an inherent limitation of PCI and not a failure of theory. The fact that Bland-Altman analyses failed to demonstrate a significant sys-

tematic bias (which should be expected shall abnormal epicardial conductance be the predominant cause of bias) suggest a complex interaction between diverse biological factors that affects the predicted and observed post-PCI CFR interrelation in different directions. Next, the CFRp formula used in our work neglects the relative contribution of collateral flow to myocardial flow. This simplification is evidently required to predict post-PCI CFR at the diagnostic stage, but might lead to bias. As a matter of fact, theory suggest that for the same post-PCI FFR value, increasing wedge pressures will lead to increasing post-PCI CFR values, because of a rightward shift of the pressure and flow relationship. Finally, our work assumed that the restoration of coronary perfusion pressure has no effect on microvascular coronary resistance. As coronary resistance vessels are pressure-distensible, and since vessel resistance is related to vessel diameter, it is possible that microcirculatory resistance decreases upon restoration of perfusion pressure.[3,23,25] This may lead to a more substantial restoration of vasodilator reserve after PCI than that expected from pre-procedural FFR and CFR assessment. Further studies are needed to establish the clinical impact of pressure restoration and wedge pressure omission in the calculation of CFRp.

Conceptual application of CFRp

CFRp represents the maximum CFR that can be theoretically achieved in a particular myocardial territory if epicardial conductance is fully restablished. Therefore, CFRp allows to predict the relative contribution of the focal stenosis to the overall degree of exhaustion in the vasodilator reserve and the residual limitation to flow due to DA and MCD that should theoretically persist after an "ideal" PCI. This information cannot be derived neither from FFR or CFR alone nor from their standard combined use alone. The incorporation of CFRp into the pressure and flow diagnostic rationale seems hence incremental. As explained in detail in the Supplement (including Supplemental Figures 4 and 5), CFRp would allow to identify vessels in whom the CFR is mostly exhausted by a focal stenosis, where PCI could potentially relief ischemia by increasing post-PCI CFR to non-isquemic values, and vessels in whom the CFR is mostly exhausted by DAN and MCD, where even if PCI is able to fully restablish epicardial conductance, ischemia will not be relieved, because the CFR post-PCI will still remain theoretically exhausted. Whether if the latter subgroup of vessels identified by CFRp might persist at high risk after the intervention, be more responsible of recurrent post-PCI angina or might receive a higher benefit from surgical revascularization are open questions.

LIMITATIONS

First, all studies included in quantitative synthesis consisted of a small sample size. Moreover, their PCI technique ranged from plain balloon angioplasty to the latest drug eluting stents, and technologies to measure flow, hyperaemic route and agents were heterogeneous. The JUSTIFY PCI database used for individual validation was also of modest sample size, albeit the largest available in the literature. Here, hyperaemia was not standardized, still, the used adenosine doses exceed the ones originally validated for human hyperaemia.[26] The use of intravascular ultrasound (IVUS) to optimize PCI was not reported in any of the studies of the metanalyses nor used in the JUSTIFY PCI cohort. Consistent data demonstrates how minimum lumen increases with IVUS-guidance; [27] yet, its effect on post-PCI FFR and CFR is unclear. Finally, the simplified estimation of CFRp has physiological limitations as discussed above.

CONCLUSIONS

Prior to the performance of PCI, the potential gain in CFR produced by the intervention can be predicted from intracoronary pressure and flow measurements. A moderate concordance between the predicted and the observed CFR post-PCI was observed, both in previous studies and in individual vessels. The clinical implications of CFRp are stimulating and should foster research on its clinical use.

SUPPLEMENTAL MATERIAL

Literature search used for meta-analytic validation

A search in the literature for studies written in English from 1993 to 2015 (last updated in june 2015) was performed in PubMed and Embase. This search followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations 1. We used the following medical subject headings and search terms: fractional flow reserve, coronary flow reserve, coronary flow velocity reserve, coronary velocity reserve, coronary reserve, vasodilatory reserve and myocardial reserve, in combination with the exploded term "coronary artery disease." Titles and abstracts were examined, and potentially eligible studies were scrutinized in full text. The reference lists of recognized articles and the "related articles" link in PubMed was also reviewed to identify additional studies. In case of overlapping, we retained only the largest study. From all eligible studies, we included only articles that measured and reported both CFR (either by Doppler velocity or thermodilution) and FFR before and after PCI to

coronary stenoses in humans. From each study, summary statistics of CFR and FFR were recorded as well as sample size, technique to measure flow, hyperemic route and agent. If overall population values were not reported, subsamples data was then extracted. We excluded studies performed in chronic total occlusions and in the acute phase of myocardial infarction where simplified FFR theory do not apply.

Study population used for individual validation

The JUSTIFY-PCI database (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity), described in detail elsewhere 2, was used. Here, pressure and flow velocity data was prospectively collected from patients scheduled for elective PCI, at the Academic Medical Centre, Amsterdam, the Netherlands, and Imperial College London, United Kingdom. PCI was performed at the operators' discretion based on usual clinical care, including angiographic and noninvasive findings. The local ethical review boards approved the study protocols, and all subjects gave written informed consent. Patients with significant valvular disease or previous coronary artery bypass grafts were not included in this study. After diagnostic coronary angiograms via the femoral artery and intracoronary administration of nitrates (300µg), combined pressure and Doppler-flow velocity wires (Combowire XT; Volcano Corporation, San Diego, CA) were advanced, pressure-equalized and progressed distal to the target stenosis, where the flow velocity envelope tracking was optimized. Hyperemia was induced with adenosine, through a femoral vein in 43 stenosis (140 µg/kg/min) and intracoronary boluses in 32 stenoses (60 µg). The same adenosine dose was used before and after the intervention. After PCI, all stents were optimized with balloon post-dilation at high pressures where angiographically indicated. Post-PCI pressure and flow velocity measurements were performed after stent optimization at the same coronary location as preangioplasty using the same adenosine dose. At the end of each recording the pressure sensor was returned to the catheter tip to check for pressure drift. If drift was identified the measurements were then repeated. An adequate flow velocity envelope was obtained in all patients permitting adequate calculation of flow velocity-based indices. The ECG, pressures, and flow velocity signals were directly extracted from the digital archive of the device console (ComboMap; Volcano Corporation). Data was analyzed off-line, using a custom software package designed with Matlab, where the following physiology indices were calculated: CFR= hyperemic flow velocity / baseline flow velocity; FFR= hyperemic distal pressure (Pd) / hyperemic aortic pressure (Pa); baseline distal-to-aortic pressure ratio= baseline Pd / baseline Pa; hyperemic stenosis resistance= (hyperemic Pa – hyperemic Pd) / hyperemic flow velocity; baseline stenosis resistance= (baseline Pa – baseline Pd) / baseline flow velocity, and instantaneous wave free ratio= resting Pd during wave-free period / resting Pa during wave-free period 2.

Supplemental Results

Supplemental Tables 1 and 2 provide the metanalysis of the average mean increase in FFR (Supplemental Table 1) and CFR (Supplemental Table 2) that followed PCI in the included studies. Fixed and random effects models are provided as well as their heterogeneity measures. Supplemental Table 3 shows the relationship between the physiology variables and the relative error of the predicted (CFRp) as compared to the observed CFR post-PCI in the individual vessel population. The relative error of CFRp was calculated as: (CFRp – post-PCI CFR) / post-PCI CFR. Finally, supplemental Table 4 provides descriptive statistics of the data of the IDEAL (Iberian Dutch Collaborators Study)[35], that was used for supplemental Figures.

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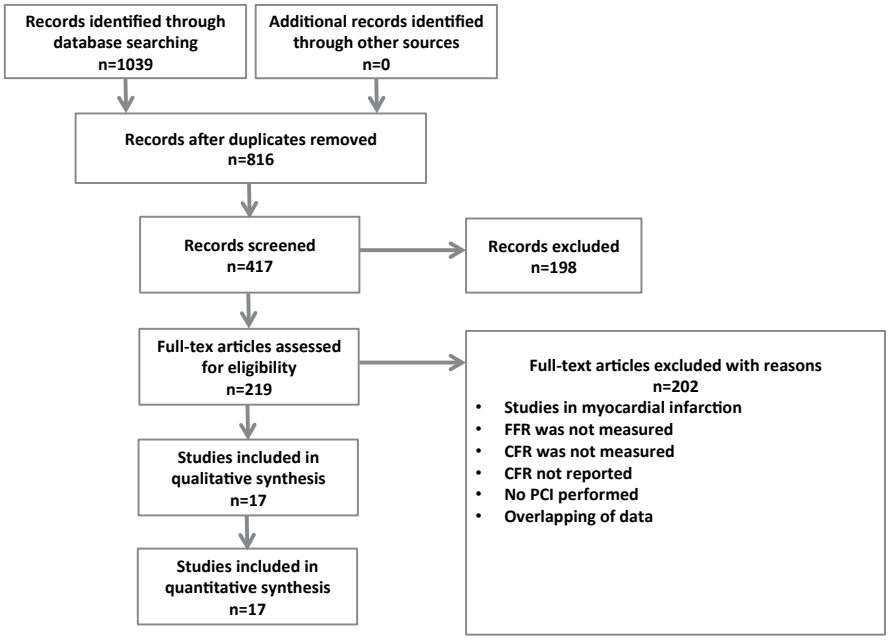
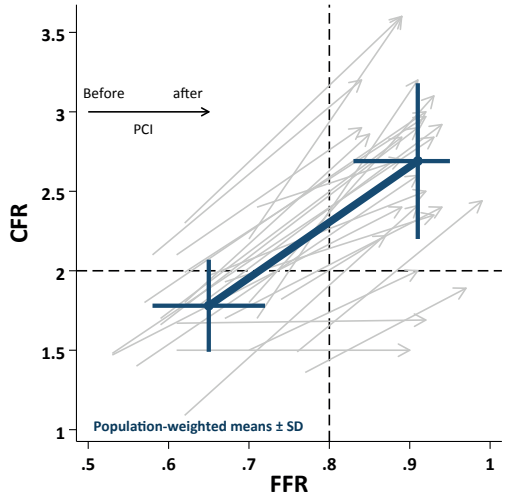
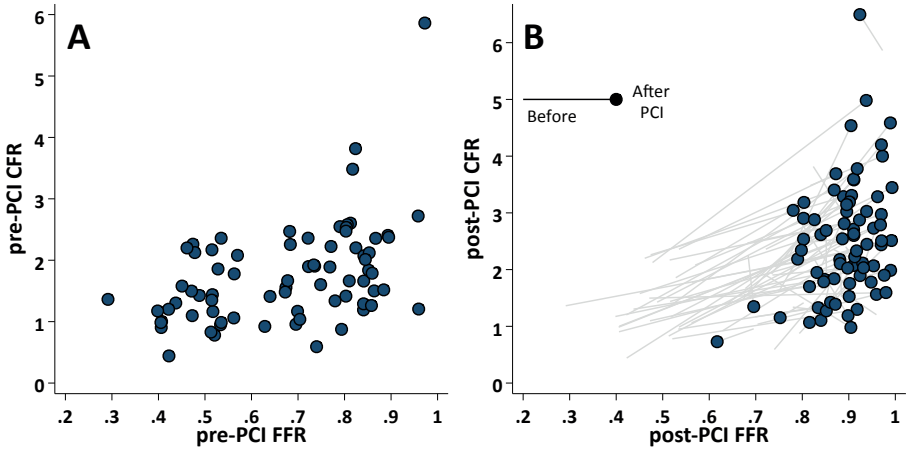


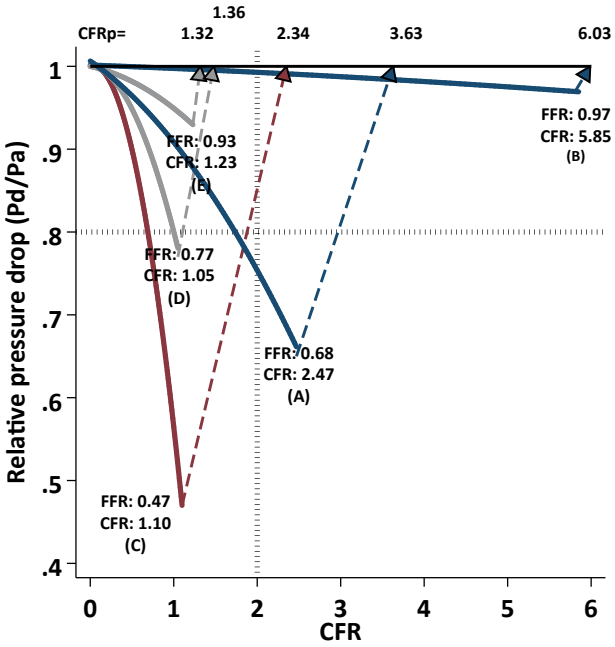
Supplemental Figure 1 | Search strategy used for the meta-analysis. Search strategy used for the metanalyses as proposed by PRISMA criteria 1.



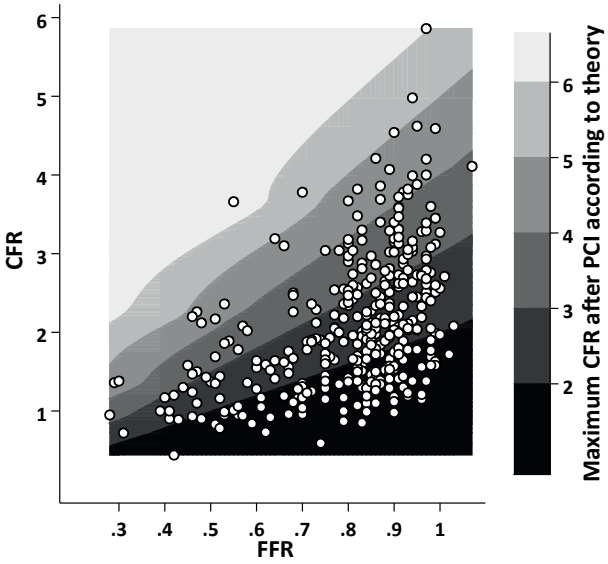
Supplemental Figure 2 | Summary CFR and FFR before and after PCI reported in identified studies. Ths figure illustrates the average CFR and FFR observed in each study before and after PCI. Each line represent a study included in the metanalysis, starts at the study mean pre-PCI CFR and FFR values, and ends at the study mean post-PCI CFR and FFR values. Lines in blue represent the population-weighted mean pre-PCI and post-PCI CFR and FFR values with their respective standard deviations. Dashed lines are drawn at the CFR cut-off value of 2 and at the FFR cut-off value of 0.80.



Supplemental Figure 3 | CFR and FFR values observed in individual vessels before and after the PCI. This figure shows the CFR and FFR relationship before (Panel A) and after (Panel B) PCI allowing thus to appraise the effect of PCI in both variables at the vessel-level. In Panel B, each grey line starts at the pre-PCI CFR and FFR values and ends at the post-PCI CFR and FFR value represented with the blue dot.



Supplemental Figure 4 | Meaningful examples of the CFRp concept. This figure sought to illustrate the clinically meaningful possible scenarios derived from the clinical use of the CFRp concept. Pre-PCI CFR and FFR values were obtained from real vessels from the Iberian-Dutch-English (IDEAL) collaborators 3 database, and their predicted CFR was calculated. In vessel A (pre-PCI FFR of 0.68 and CFR of 2.47) the intervention would be able to increase CFR to values above 3.5. However, pre-PCI CFR is preserved, and the benefits of revascularization might thus be small 4. Vessel B states for an unobstructed coronary artery with normal pre-PCI FFR and CFR values. Vessel C from the same figure (pre-PCI FFR of 0.47 and CFR of 1.10) illustrates a case of a FFR-positive stenosis superimposed on little DA and MCD, because CFR could theoretically increase to non-ischemic values after an ideal intervention. Vessel D exemplifies also a FFR-positive stenosis (pre-PCI FFR of 0.77 and CFR of 1.05), but in this case, superimposed on significant DA and MCD. This is because even if the intervention is able to re-establish completely epicardial conductance (i.e., post-PCI FFR=1), ischemia would not be relieved in the subtended myocardial bed according to theory, as demonstrated by a CFRp of 1.36. Finally, vessel E states for a coronary artery where pre-PCI FFR is almost normal (0.93) but the CFR is highly exhausted (1.23). Here, PCI will not increase flow significantly (CFRp=1.36) suggesting thus that the focal stenosis plays a minor role in the myocardial flow impairment.



Supplemental Figure 5 | Graphical distribution of the CFRp concept across the observed CFR and FFR relationship. A contourplot based on thin-plate-spline interpolation was used to display as third variable the distribution of CFRp across the pre-PCI CFR and FFR relationship in the stenosed vessels investigated within the IDEAL collaborators study3. The CFRp unitary boundaries provides hence a visual estimation of the distribution of DA and MCD across the CFR and FFR relationship, which seems to concur with the theoretical model predictions proposed by Johnson et al.5. The darkest area of this figure (lowest, right-shifted area) state for the region of the pre-PCI CFR and FFR relationship where DA and MCD are so severe that even a fully restablishment of epicardial conductance will not be, theoretically, able to relieve ischaemia, because post-PCI CFR will still remain exhausted (<2). Further studies are needed to establish the long term prognosis of this FFR-positive and FFR-negative vessel subgroups.

Supplemental Table 1 | Average mean increase in FFR after PCI across studies

			Confidence intervals			Relative inverse of variances weights	
Study	Year	Mean-difference	Lower	Upper	Confidence limit	Fixed	Random
Pijls	2002	0.3600	0.3004	0.4196	95	1.0%	4.4%
Kolyva	2008	0.4000	0.3079	0.4921	95	0.4%	2.9%
Beleslin_1	2008	0.3500	0.2980	0.4020	95	1.3%	4.9%
Leung	2006	0.3500	0.0548	0.6452	95	0.0%	0.4%
Ng_2	2012	0.2600	0.2012	0.3188	95	1.0%	4.5%
Verhoeff	2005	0.3000	0.2245	0.3755	95	0.6%	3.6%
Nijjer_2	2015	0.3200	0.2619	0.3781	95	1.0%	4.5%
Higuchi_1	2014	0.3100	0.2133	0.4067	95	0.4%	2.7%
Ng_1	2012	0.2300	0.1191	0.3409	95	0.3%	2.3%
Yamada_2	2010	0.2900	0.1673	0.4127	95	0.2%	2.0%
Layland_1	2012	0.3000	0.2134	0.3866	95	0.5%	3.1%
Ogawa	2004	0.2900	0.2237	0.3563	95	0.8%	4.1%
Siebes	2004	0.2300	0.1317	0.3283	95	0.4%	2.7%
Roy	2005	0.2700	-	-	-	-	-
Higuchi_2	2014	0.3000	0.2107	0.3893	95	0.4%	3.0%
Layland	2013	0.2700	0.2173	0.3227	95	1.2%	4.8%
Layland_2	2012	0.2600	0.1953	0.3247	95	0.8%	4.2%
Yamada_1	2010	0.2700	0.1896	0.3504	95	0.5%	3.4%
Mangiacapra_1	2013	0.1900	0.1273	0.2527	95	0.9%	4.3%
Beleslin_2	2008	0.2100	0.1592	0.2608	95	1.3%	4.9%
Hirohata_2	2014	0.2300	0.1810	0.2790	95	1.4%	5.1%
Hirohata_1	2014	0.2000	0.1541	0.2459	95	1.6%	5.2%
Mangiacapra_2	2013	0.1800	0.1114	0.2486	95	0.7%	4.0%
Nijjer_1	2015	0.1300	0.0792	0.1808	95	1.3%	4.9%
Kini_1	2008	0.2300	0.2227	0.2373	95	64.1%	7.1%
Kini_2	2008	0.2000	0.1861	0.2139	95	17.8%	6.9%
				Total		100%	100%
				Total weights (rounded)		112259	9186

			95% CI		P
Fixed effects model		**Estimation**	**Lower**	**Upper**	
	Weighted mean difference	0.2295	0.2236	0.2353	<0.001
	Standard error	0.0030			
	Heterogeneity measures				
	I2 parameter	79.2106	701473	85.52	
	Homogeneity Chi-square	120.2534			<0.001
	Tau2	0.0015			
Random effects model		**Estimation**	**Lower**	**Upper**	
	Weighted mean difference	0.2265	0.2360	0.2769	<0.001
	Standard error	0.0104			
	Heterogeneity measures				
	I2 parameter	30.156	71.1413	85.52	
	Homogeneity Chi-square	35.7942			0.0747

Supplemental Table 2 | Average mean increase in CFR after PCI across studies (continued)

			Confidence intervals			Relative inverse of variances weights	
Study	**Year**	**Mean-difference**	**Lower**	**Upper**	**Confidence limit**	**Fixed**	**Random**
Pijls	2002	0.9300	0.6976	11,624	95	4.2%	4.8%
Kolyva	2008	13,600	0.8460	18,740	95	0.9%	3.7%
Beleslin_1	2008	12,000	0.9402	14,598	95	3.3%	4.7%
Leung	2006	12,000	0.7380	16,620	95	1.1%	3.9%
Ng_2	2012	11,000	0.4463	17,537	95	0.5%	3.1%
Verhoeff	2005	11,400	0.7971	14,829	95	1.9%	4.4%
Nijjer_2	2015	12,400	0.9208	15,592	95	2.2%	4.5%
Higuchi_1	2014	0.0200	-0.5777	0.6177	95	0.6%	3.3%
Ng_1	2012	0.8000	-0.7004	23,004	95	0.1%	1.1%
Yamada_2	2010	0.0000	-0.6945	0.6945	95	0.5%	3.0%
Layland_1	2012	0.9800	0.7935	11,665	95	6.5%	5.0%
Ogawa	2004	13,200	10,838	15,562	95	4.0%	4.8%
Siebes	2004	10,600	0.6195	15,005	95	1.2%	4.0%
Roy	2005	13,000	11,904	14,096	95	18.7%	5.1%
Higuchi_2	2014	11,300	0.4961	17,639	95	0.6%	3.2%
Layland	2013	0.5300	0.0926	0.9674	95	1.2%	4.0%
Layland_2	2012	0.4200	0.3353	0.5047	95	31.3%	5.2%
Yamada_1	2010	0.7000	-0.3166	17,166	95	0.2%	2.0%
Mangiacapra_1	2013	14,000	0.4006	23,994	95	0.2%	2.0%
Beleslin_2	2008	0.5000	0.2045	0.7955	95	2.6%	4.6%
Hirohata_2	2014	13,000	0.7120	18,880	95	0.7%	3.4%
Hirohata_1	2014	15,000	0.8727	21,273	95	0.6%	3.2%
Mangiacapra_2	2013	0.3000	-0.3574	0.9574	95	0.5%	3.1%
Nijjer_1	2015	0.4000	-0.0381	0.8381	95	1.2%	4.0%
Kini_1	2008	0.9500	0.7164	11,836	95	4.1%	4.8%
Kini_2	2008	0.5300	0.3891	0.6709	95	11.3%	5.1%
					Total	100%	100%
				Total weights (rounded)		1709	118

			95% CI		P
Fixed effects model		**Estimation**	**Lower**	**Upper**	
	Weighted mean difference	0.8148	0.7674	0.8622	<0.001
	Standard error	0.0242			
	Heterogeneity measures				
	I2 parameter	90.3182	87.0477	92.7629	
	Homogeneity Chi-square	258.2163			<0.001
	Tau2	0.16216			
Random effects model		**Estimation**	**Lower**	**Upper**	
	Weighted mean difference	0.9036	0.7230	10,843	<0.001
	Standard error	0.0922			
	Heterogeneity measures				
	I2 parameter	0.9036	0.7230	1.0843	
	Homogeneity Chi-square	19.9961			0.7470

Supplemental Table 3 | Explanatory variables of the relative error* between the predicted and observed CFR post-PCI

Hemodynamic parameter	Coefficient of determination (R2)	P value
	R	
Pre-PCI		
Baseline Pa, mmHg	0.00	0.779
Baseline Pd, mmHg	0.00	0.874
Hyperemic Pa, mmHg	0.00	0.408
Hyperemic Pd, mmHg	0.01	0.370
Heart rate, pre	0.02	0.280
Rate pressure product	0.02	0.286
Baseline flow velocity, cm/s	0.03	0.168
Hyperemic flow velocity, cm/s	0.00	0.924
Baseline microvascular resistance, mm Hg/cm/s	0.00	0.622
Hyperemic microvascular resistance, mm Hg/cm/s	0.05	0.068
post-PCI		
Baseline Pa, mmHg	0.00	0.962
Baseline Pd, mmHg	0.01	0.463
Hyperemic Pa, mmHg	0.01	0.367
Hyperemic Pd, mmHg	0.04	0.093
Heart rate, post	0.00	0.940
Rate pressure product	0.00	0.847
Baseline flow velocity, cm/s	0.04	0.105
Hyperemic flow velocity, cm/s	0.07	0.023
Baseline microvascular resistance, mm Hg/cm/s	0.03	0.136
Hyperemic microvascular resistance, mm Hg/cm/s	0.10	0.003
1-FFR post-PCI (Residual FFR)	0.07	0.020

*(CFRp-CFR post-PCI) /CFR post-PCI

Supplemental Table 4 | Summary characteristics of patients included in the IDEAL collaborators study

	FFR and CFR assessment before and after PCI	FFR and CFR diagnostic assessment	
Patients	**n=67**	**n=234**	
Age	62.4±9.3	61.6±9.9	
Male	50 (74.6)	159 (68.0)	
Hypertension	36 (53.7)	121 (51.7)	
Hyperlipidemia	56 (83.6)	116 (49.6)	
Current or former smoker	31 (46.3)	97 (41.5)	
Diabetes	20 (28.2)	48 (20.5)	
Chronic kidney disease	4 (6.0)	1 (0.4)	
Previous myocardial infarction	8 (11.9)	26 (11.1)	
Stable angina	64 (95.5)	224 (95.7)	
Unstable angina	3 (4.5)	10 (4.3)	
Multivessel disease	25 (37.3)	36 (15.4)	
	Vessels wth stenosis undergoing PCI	**Vessels with stenosis not undergoing PCI**	**Vessels without stenosis**
Vessels	**n=75**	**n=291**	**n=201**
Left anterior descending artery	44 (58.7)	163 (56.0)	70 (34.8)
Circumflex	13 (17.3)	76 (26.1)	83 (41.3)
Right coronary artery	18 (24.0)	52 (17.9)	48 (23.9)
Stenosis severity by QCA, %	60 (52.3-69.4)	44.0 (24.0-60.0)	NA
Intravenous adenosine	43 (57.3)	153 (52.6)	38 (18.9)
Intracoronary adenosine	32 (42.7)	138 (47.4)	163 (81.1)
Intracoronary physiology indices			
CFR	1.58 (1.19-2.20)	2.05 (1.55-2.74)	2.50 (2.10-3.15)
FFR	0.70 (0.52-0.82)	0.87 (0.80-0.93)	0.97 (0.95-0.99)
HSR	1.04 (0.44-2.25)	0.3 (0.13-0.60)	0.07 (0.02-0.14)
BSR	0.66 (0.27-1.77)	0.24 (0.08-0.48)	0.07 (0.01-0.17)
Pd/Pa	0.90 (0.68-9.95)	0.96 (0.92-0.99)	0.99 (0.97-1.00)
iFR	0.84 (0.58-0.93)	0.94 (0.88-0.98)	0.98 (0.96-1.00)
CFR-predicted	2.49 (1.79-3.19)	2.51 (1.91-3.16)	2.62 (2.17-3.30)

All values n (%), mean ± standard deviation or median (quartile 1 and 3)
CFR: coronary flow reserve; FFR: fractional flow reserve; QCA: quantitative coronary angiography; HSR: hyperemic stenosis resistance; BSR: baseline stenosis resistance; Pd/Pa: baseline distal to aortic pressure ratio; iFR: instantaneous wave free ratio; NA: not applies

Part E

Discussion: facing the complexity of ischaemic heart disease with invasive pressure and flow measurements

CHAPTER 17

Combined use of intracoronary pressure and flow to assess ischemic heart disease

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Book chapter in Coronary Stenosis, Imaging and Physiology

ABSTRACT

Previous chapters have emphasized the value of different techniques to assess epicardial stenosis severity. However, it has to be stressed that Impairment of myocardial blood supply in ischemic heart disease (IHD) results from both obstructive and non-obstructive coronary involvement. Fractional flow reserve (FFR) provides valuable information on whether focal stenosis play a dominant role in limiting myocardial flow supply, but not on whether concomitant non-obstructive IHD, partially caused by diffuse coronary artery disease and microvascular disease, constitutes the dominant problem in the interrogated myocardial territory. In this chapter, we envisage coronary flow reserve (CFR), FFR and microcirculatory resistance indices as complementary rather than competing techniques, and discuss emerging data on their combined use. Overall, this chapter focuses on a more comprehensive, yet required, intracoronary assessment of IHD, which may improve prognostic characterization and guide therapeutic strategies aiming to both obstructive and non-obstructive coronary disease.

HISTORICAL INTRODUCTION

In seminal experimental work published in 1974, Gould et al. described the haemodynamic consequences of progressive focal reductions in coronary artery diameter on baseline and hyperaemic coronary flow.[1,2] It was observed that stenosis ≥50% impaired hyperaemic coronary flow, and luminal reductions ≥85% limited baseline coronary flow. These experimental findings were rapidly translated and incorporated into clinical cardiology practice, and little after the terms "ischaemia-generating stenosis" and "obstructive coronary artery disease (CAD)" appeared. A *sine qua non* relationship between obstructive CAD, myocardial ischaemia and adverse cardiovascular events progressively matured and became the reigning paradigm, and epicardial stenosis were thought to *cause*[3] ischaemic heart disease (IHD). As a consequence—and in a logical attempt to fulfill causality criteria of disease[3]— the mechanical resolution of such epicardial stenoses (either by surgical[4] or percutaneous[5] approaches) became the ultimate objective of IHD therapy.

Paralleling the development of this "stenosis-centred" theory of IHD, Likoff et al. described a group of 15 women with angina, ischaemic electrocardiographic responses to physical exercise, and normal coronary angiograms in 1967.[6] This stimulated the discussion as to whether these patients had an organic illness resulting in myocardial ischaemia or were primarily suffering from a phychosomatic disease. Later on, the term "syndrome X" was used by Kemp in an editorial to denote the uncertainty of the etiology of the study patient´s angina.[7] Subsequent efforts by Cannon and colleagues helped to established that impaired coronary microcirculatory vasodilator responsiveness limited hyperaemic coronary flow in some patients with unobstructed coronary arteries,[8] and the term "microvascular angina" was latterly introduced by the same author in 1988 as descriptor of the syndrome.[9] Many reports then documented impaired hyperaemic flow response and signs of myocardial ischaemia in patients with angina and non-obstructed CAD, but in contrast to obstructive CAD, left ventricular wall motion appeared to be preserved.[10,11] This finding substantiated successive speculation on the benign course of microvascular angina and microcirculatory dysfunction (MCD), and indeed early reports suggested that the outcomes of patients with this entity were similar to those of subjects without angina and obstructive CAD.[12] Altogether, this data shadowed partly the importance of non-obstructive components in the genesis of IHD, and boosted the embracement of the "stenosis-centred" paradigm. As will be discussed in the next sections, however, this has changed.[13]

A final aspect that deserves a historical perspective is the relative contribution of diffuse coronary atherosclerosis (DCA) to the genesis of myocardial ischaemia and the overall risk of IHD. More than 40 years ago, postmortem studies reported the diffuse nature of coronary atherosclerosis.[14,15] Soon it was clear that DCA not only was often

present when coronary angiography revealed only mild stenosis,[16,17] but also that it largely complicated the quantification of focal CAD.[18–20] However, the fact that initial human studies[21,22] suggested that maximal myocardial flow only decreased when focal stenosis were >50% (supporting previous experimental animal data)[1] expanded the perception that DCA without focal components had no influence on myocardial blood flow and therefore was not associated nor a cause of ischaemia. It was from a different standpoint that DCA achieved progressive attention. Namely, the description in 1989 by Muller et al. of either "severe fixed stenosis" or even only "luminal irregularities" with a higher propensity to rupture and cause acute myocardial infarctions (AMI), as vulnerable plaques.[23] Nearly 10 years later, Gould et al. demonstrated that in patients with only mild arteriographic disease, DCA produces actually a gradual base-to-apex, longitudinal perfusion gradient, compatible with fluid dynamic theory;[24] and with the graded, continuous pressure fall along the arterial length observed subsequently in humans by De Bruyne.[25]

Several fundamental strains arise from the complex interaction between focal stenosis, MCD and DCA in the genesis and prognosis of IHD. This chapter focuses first on the reasons to pursue a more comprehensive assessment of IHD and then on how does combined intracoronary pressure and flow measurements can help achieve the former task.

ISCHAEMIC HEART DISEASE: BEYOND CORONARY STENOSES

Decades of information have established that atherosclerosis underlies IHD in the majority of cases, and indeed compelling evidence coming from different lines support the important role of flow-limiting stenosis in the development of IHD.[26,27] However, the connection between symptoms, obstructive atherosclerosis and myocardial ischaemia is so deeply rooted, that even physicians doubt that patients may present with symptoms and signs of myocardial ischaemia in the absence of epicardial stenosis. Cumulative evidence suggests, nonetheless, that such causative relationship between obstructive CAD and IHD represents a simplistic view of the leading cause of death worldwide (Table 1).[28] Indeed, several studies have shown that many patients with objective evidence of myocardial ischaemia do not have obstructive CAD, and conversely, many patients with obstructive CAD neither experience anginal symptoms nor develop objective signs of ischaemia.[13] These conditions are not anecdotic, since large observational registries have established that more than half of women and around one-third of men with stable angina undergoing coronary angiography are found to have non-obstructive CAD.[29–32] MCD seems to accounts for at least one-third of the cases of non-obstructive CAD,[33] and both endothelium-dependent[34] and endothelium-

independent[35] coronary microvascular disease appear to predict major adverse cardiovascular events (MACE). Furthermore, the quality of life of patients with non-obstructive CAD is significantly affected, as >40% are admitted for recurrent angina, and up to 30% undergo repeated coronary catheterizations. This evidently means high healthcare costs, similar to those of obstructive CAD.[36]

Table 1 | Proposed classification for stable ischaemic heart disease syndromes

Type	Location of defect	Potential mechanisms
Vascular		
Coronary	Macrovessels	Flow-limiting atherosclerosis (focal and diffuse disease), Endothelial dysfunction, spasm, muscle bridge, aberrant origin, dissection
	Microvessels	Microvascular disease, endothelial dysfunction, spasm, inflammation, microemboli, capillary insufficiency
Other vessels	Capacitance vessels	Increased stiffness
Non-vascular		
Cardiomyocyte	Transcellular	Oxygen transport, energy substrate
	Intracellular	Oxygen transport, energy substrate
	Mitochondria	Mitochondrial dysfunction/adaptation
Adventitia	Adipocytes	?
Matrix	Mast cells	?
Miscellaneous		?

Modifed from Pepine et al. This classification underscores the importance of non-obstructive causes of myocardial ischaemia, in addition to obstructive atherosclerosis

In addition to MCD —and at a difference from initial observational registries performed more than 20 years ago[12,37]— updated long term follow-up studies have clearly documented that patients with angina an DCA are at high risk for MACE. A large observational registry from Denmark (n=11,223, median follow up: 4.6 years) observed an adjusted hazard ratio for MACE (defined as cardiovascular death, AMI, stroke, heart failure and all-cause mortality) with angina and normal coronary arteries of 1.52 [95% confidence intervals (CI) 1.27-1.83], and for diffuse non-obstructive CAD of 1.85 (95% CI: 1.51-2.21), as compared to 5,705 reference participants from the Copenhagen City Heart Study.[31] Additionally, a recent report from the Veterans Affair Clinical Assessment program that included all Veterans Affair patients (n=33,674) undergoing elective coronary angiography for stable IHD symptoms, observed that the unadjusted 1-year AMI rate progressively increased with increasing CAD extent, ranging from 0.11% among patients with no apparent CAD, to 2.47% in patients with 3 vessel or left main obstructive CAD.[32] Notably, even 1 vessel-only DCA (without obstructive CAD) was associated with a significant increase in Kaplan-Meier estimates of 1 year mortality (2.02, 95% CI: 1.60-2.7) that significantly increased (2.72, 95% CI: 1.90-3.90) in patients

with 3-vessel lone-DCA. Therefore and overall, the results of this large studies support the concept that DCA is not 'insignificant' but rather is associated with a noteworthy and quantifiable risk for cardiovascular morbidity and mortality. Finally, a full description of the underlying mechanisms, diagnosis and treatment of non-obstructive CAD is beyond the scope of the present chapter. The interested reader is thus referred to in-depth reviews listed in the references.[13,26,38,39]

FRACTIONAL FLOW RESERVE, EPICARDIAL STENOSIS AND MYOCARDIAL ISCHAEMIA

Among several physiology indices (Figure 1), fractional flow reserve (FFR) has become the standard method to assess IHD in the catheterization laboratory following the demonstration that physiological rather than anatomical selection of stenosis candidates for revascularization results in better patients outcomes.[41] Although the principles and applications of FFR have been discussed and illustrated by clinical cases in previous sections of this book, it is conventient for the purpose of this chapter, to emphasise that FFR is an index of epicardial stenosis severity that uses the hyperaemic trans-stenotic pressure drop as surrogate of myocardial flow impairment.[40] FFR is reproducible, and because of convincing evidence, it is now recommended by clinical practice guidelines to identify haemodynamically relevant coronary stenosis when evidence of ischaemia is not else available (Class 1, Level A).[42] Nonetheless, FFR is a lone pressure-based index, and although coronary pressure and flow are closely related due to fluid dynamic and homeostatic interactions, flow is primarily more important than pressure for the preservation of myocardial function.[27,43]

Likewise, as discussed in other sections of this book, coronary flow reserve (CFR) is the physiology index that summarizes coronary flow. For a given arterial distribution—with or without epicardial stenosis, DCA or MCD—CFR is defined as the ratio of hyperemic to baseline flow.[2] CFR thus reflects the capacity of both the epicardial vessel and corresponding downstream myocardial bed to increase flow in order to satisfy myocardial demand. Relative CFR, on the other side, equals the ratio of hyperaemic flow in the diseased vessel to hyperaemic flow in the absence of disease, in either the same or adjacent arterial distribution.[27] Following these definitions, it should be highlighted that FFR was developed as a proxy measure of relative CFR (and not as a proxy measure of CFR), and that it was for discrete, focal epicardial stenosis that FFR demonstrated in both experimental[44] and human[45] studies to be indeed highly correlated with relative CFR. Hence, FFR was designed specifically to address the relative contribution of epicardial stenosis to the overall myocardial flow impairment.[46] A critical point to take in mind for FFR interpretation, however, is that, in clinical populations, the relation-

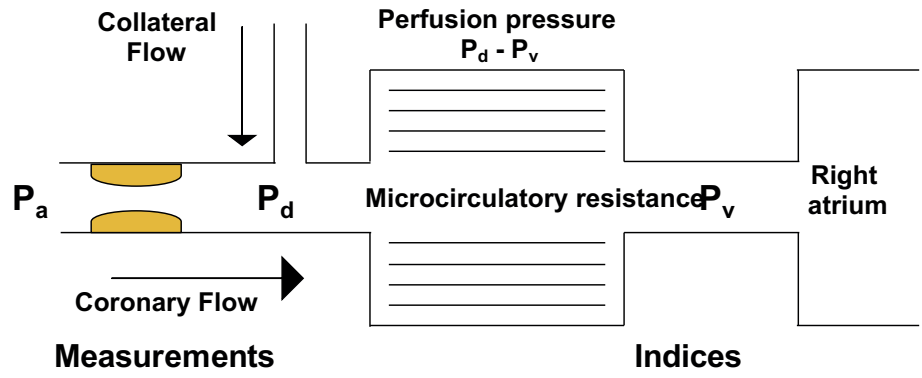

Figure 1 | Available physiology wires allow to measure intracoronary pressure and flow with two different technologies: Doppler-tipped guidewires, that estimate coronary flow velocity,[66] and thermal-sensitive guidewires, that based on the coronary thermodilution method estimate mean transit time, an index of absolute coronary flow.[67] When these pressure and flow measurements are obtained during baseline and hyperemia, several physiology indices can be obtained, by relating Ohm´s law to fluids flow.[53] These indices provide non-exclusive information of the status of the epicardial vessel and the coronary microcirculation of the downstream myocardial bed. FFR: fractional flow reserve; Pd/Pa: baseline distal to aortic pressure ratio; iFR: instantaneous wave free ratio; IMR: index of microcirculatory resistance; HMR: hyperaemic microcirculatory resistance; BSR: basleine stenosis resistance; HSR: hyperaemic stenosis resistance; CFR: coronary flow reserve; CFVR: coronary flow velocity reserve.

ship between the impairment in myocardial flow produced by the focal stenosis and myocardial ischaemia in itself is not a fixed one, because of the presence of variable degrees of DCA and MCD[27,47] This is, even if a stenosis is contributing "significantly" to myocardial flow impairment (i.e., FFR≤0.80), the maximum achievable flow might suffice and ischaemia will be avoided and, contrarily, even if a stenosis is not contributing "significantly" to myocardial flow impairment (i.e., FFR>0.80), the maximum achievable flow might not suffice, and ischaemia will be present. In other words, FFR represents the maximum achievable flow in the presence of an stenosis, expressed as a fraction of the maximum achievable flow in the absence of the stenosis; however, whether that maximum achievable flow will avoid or not ischaemia in the presence or

absence of the stenosis cannot be known from FFR alone.[27,40,47] Hence and above its proven clinical value as a tool to guide revascularization as compared to angiography, FFR is not intended to address comprehensively the relative contributions of DCA and MCD to the overall degree of myocardial flow impairment in IHD. This might help to explain why patients with FFR>0.80 in randomised clinical trials were not free from long-term events [21% MACE rate at 5 years in the DEFER[48] (Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis) study] and why does a significant percentage of patients persisted with angina at long term: 20% and 33% respectively, at 2 and 5 years of follow-up in FAME[49] (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and DEFER.[48] Conversely, the 1) low MACE rate observed in patients with preserved CFR —even in the presence of inducible ischaemia[50] or FFR values ≤0.80[51] — and the relatively 2) low hard MACE rate observed in patients with FFR≤0.80 on optimal medical therapy observed in the FAME 2 trial,[52] support the need for a more comprehensive IHD diagnostic strategy that, in addition to obstructive CAD, take also into consideration DCA and MCD.

COMBINED USE OF CORONARY FLOW RESERVE AND FRACTIONAL FLOW RESERVE IN THE ASSESSMENT OF ISCHAEMIC HEART DISEASE

FFR and CFR were both initially intended to estimate coronary stenosis severity and, during their initial phases, were extensively validated against non-invasive tests of inducible myocardial ischaemia (Figure 2). FFR<0.75 and CFR<2 were found as optimal cut-off values, with diagnostic accuracies for both of approximately 80%, as compared to non-invasive tests.[53] Since CFR and FFR were both initially suggested for the same purpose, their close agreement was also expected. However, investigators soon realized that in a significant proportion of cases (30-60%), CFR and FFR were discordant when defining coronary stenosis severity.[47,54,55] Meuwissen et al. were the first to describe the prominent role of the minimum achievable microvascular resistance (MR) in modulating the relationship between FFR and CFR.[54] In this study, the authors investigated 150 intermediate coronary stenosis with intracoronary pressure and Doppler-derived flow velocity, and observed that MR was significantly higher (2.42±0.77 $mmHg \times cm^{-1} \times s^{-1}$) and lower (1.91±0.70 $mmHg \times cm^{-1} \times s^{-1}$) in vessels with FFR≥0.75/CFR<2 and FFR<0.75/CFR≥2, respectively. Later on, a new interpretation of the FFR and CFR relationship (Figure 3) was proposed by Johnson et al.,[55] on the grounds of published studies and original positron emission tomography (PET) findings. The worst CFR and stress relative uptake form 1,500 cardiac PET cases was compared with an assemble of all combined invasive FFR and CFR measurements reported in the literature, and both datasets were then contrasted with a fluid dynamic model of the coronary circulation that predicted

the FFR and CFR relationship for variable degrees of diffuse and focal narrowings. The main findings of this elegant study were: 1) invasively (r=0.34, p<0.001) and non-invasively (r=0.36, p<0.001) FFR and CFR are modestly but significantly linearly related; 2) most patients undergoing FFR and CFR assessment have diffusely reduced CFR consistent with DCA or MCD; 3) the fluid dynamic model suggested that the distribution of values in the four quadrants of the FFR/CFR relationship obeys to the relative contributions of focal stenosis, DCA and MCD; and most importantly 4) that the FFR and CFR discordance therefore reflects clinically relevant pathophysiology and not methodological concerns.

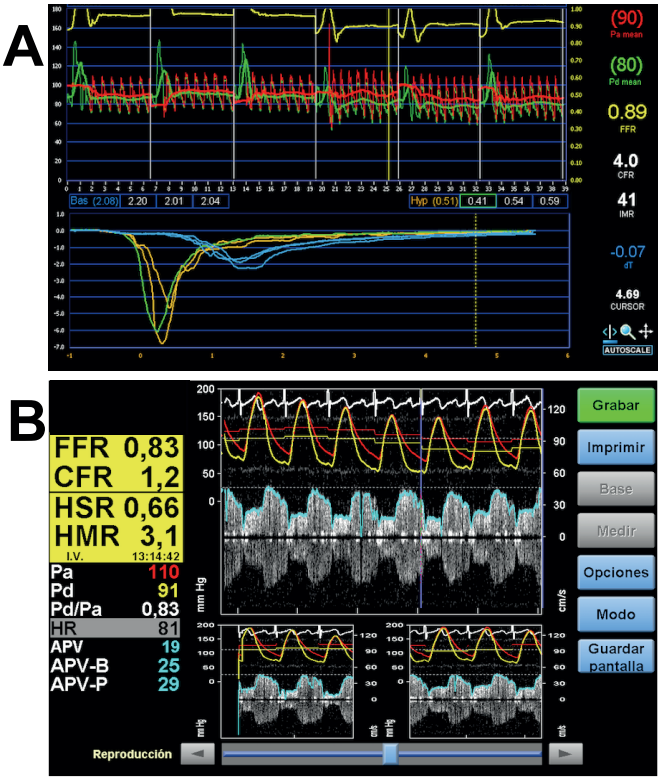

Figure 2 | Examples of combined intracoronary pressure and flow measurements obtained with both available technologies in vessels with intermediate stenosis. Panel A illustrates a case where coronary flow was investigated with the coronary thermodilution method[67] with a PressureWire™ Certus™ (St. Jude Medical, St. Paul, Minnesota). In this case, fractional flow reserve (FFR) and coronary flow reserve (CFR) are normal, although microvascular resistance (index of microcirculatory resistance, IMR) was above the 75th percentile for the study population. Panel B illustrates a case where coronary flow velocity was investigated with the Doppler method with a ComboWire® XT Guide Wire (Volcano Corporation, San Diego CA). Herein, FFR is above 0.80. However, CFR is highly exhausted, and microvascular resistance is high (above the 75th percentile), suggestive of both myocardial ischaemia and microvascular disease.

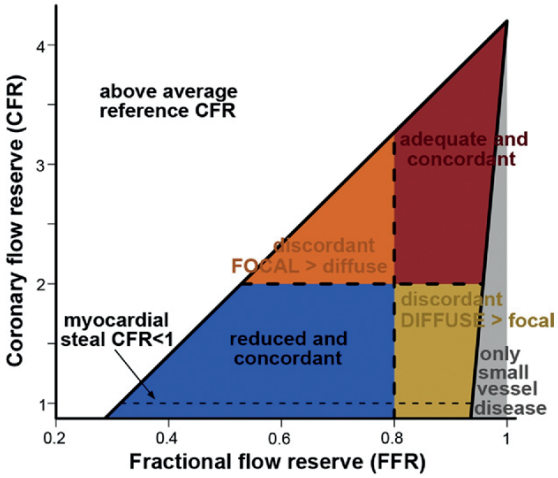

Figure 3 | Conceptual plot of the CFR and FFR relationship. For details read text. Legend as provided in Figure 2. Reproduced with permission from Johnson et al.[55]

UPDATED CONCEPTUAL INTERPRETATION OF THE CORONARY FLOW RESERVE AND FRACTIONAL FLOW RESERVE RELATIONSHIP

Figure 4 and 5 summarize 467 vessels with intermediate stenosis evaluated with pressure and flow sensors at our Institutions: 299 with Doppler-derived flow velocity and 166 with Thermodilution-derived flow. These figures will be used to illustrate the observed pressure and flow relationship across the FFR and CFR categories as proposed by Johnson et al.[55] In the absence of significant DCA or MCD, CFR should categorically match FFR. Therefore and under these conditions, a severe flow-limiting stenosis will exhaust flow supply (CFR<2) because the autoregulatory mechanisms cannot compensate for the abnormal epicardial resistance (FFR≤0.80). Here, FFR and CFR would be both reduced and concordant, and the stenosis will be indeed causing ischaemia (blue dots and blue pressure-drop line in Figures 4 and 5, respectively). Conversely, a physiologically mild stenosis in the absence of significant DCA and MCD will allow a normal flow supply (CFR>2), and will not generate a significant trans-stenotic pressure drop (FFR>0.80). Here, CFR and FFR would be both adequate and concordant, and ischaemia will be unlikely (red dots in Figures 4 and red pressure-drop line line in Figure 5). In the discordant group with FFR≤0.80 and CFR≥2 (orange dots in Figure 4 and orange pressurep-drop line in Figure 5), however, the expected substrate is a focal stenosis without DCA and functionally preserved microcirculation. A CFR>2.0 would therefore reflect that DCA and MCD are minimal, and that the flow supply suffices and avoids ischaemia, even if FFR≤0.80 (orange pressure-drop line in Figure 5). Finally, the discordant group with FFR>0.80 and CFR<2, would be explained by predominant DCA

(yellow dots in Figure 4 and yellow pressure-drop line in Figure 5) or MCD, and if the hyperaemic pressure drop is very minor (<5 mmHg), the exhausted CFR would be most likely due to predominant MCD (gray dots in Figure 4 and gray pressure-drop line in Figure 5). In this final quadrant of the CFR and FFR relationship, the flow supply is significantly impaired (CFR<2) and ischaemia is very likely, even if the relative contribution of the focal stenosis to the overall flow impairment is only minor (FFR>0.80) (yellow and gray pressure-drop lines in Figure 5).

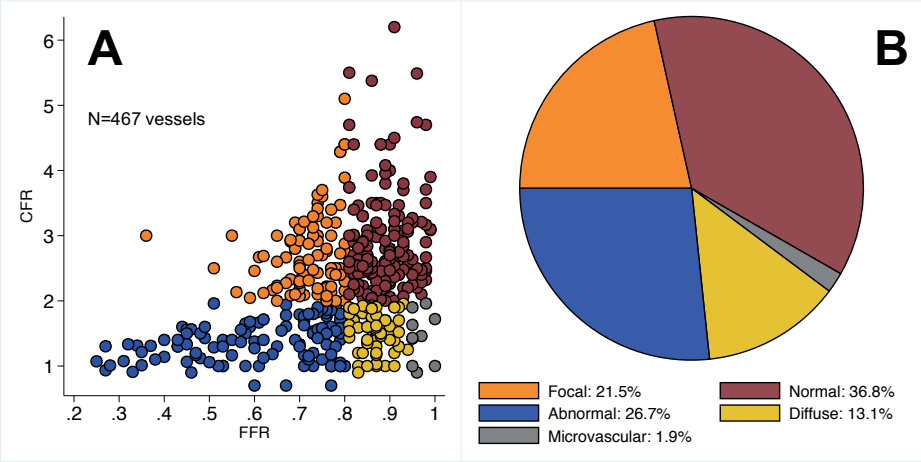

Figure 4 | CFR and FFR relationship across 467 vessels (299 investigated with Doppler-derived flow and 166 with Thermodilution-derived flow) with intermediate stenosis evaluated with pressure and flow sensors, at Hospital Clinico San Carlos, Madrid, Spain, and AMC Heart Centre, Academic Medical Centre-University of Amsterdam, Amsterdam, The Netherlands. Panel A shows the scatterplot of the CFR and FFR relationship. Vessels in blue and red were concordantly abnormal (CFR<2 and FFR≤0.80) and concordantly normal (CFR≥2 and FFR>0.80), respectively. Vessels in orange exhibited CFR≥2 and FFR<0.80, suggestive of predominantly focal disease. The yellow region contains vessels with CFR<2 and FFR>0.80 suggestive of predominantly diffuse epicardial or microcirculatory disease. Finally, within this region, vessels in gray exhibited only a minor hyperaemic pressure drop (<5mmHg) suggestive of predominant microcirculatory disease. Panel B shows a pie graph illustrating the prevalence (%) of vessels within each of this CFR and FFR regions.

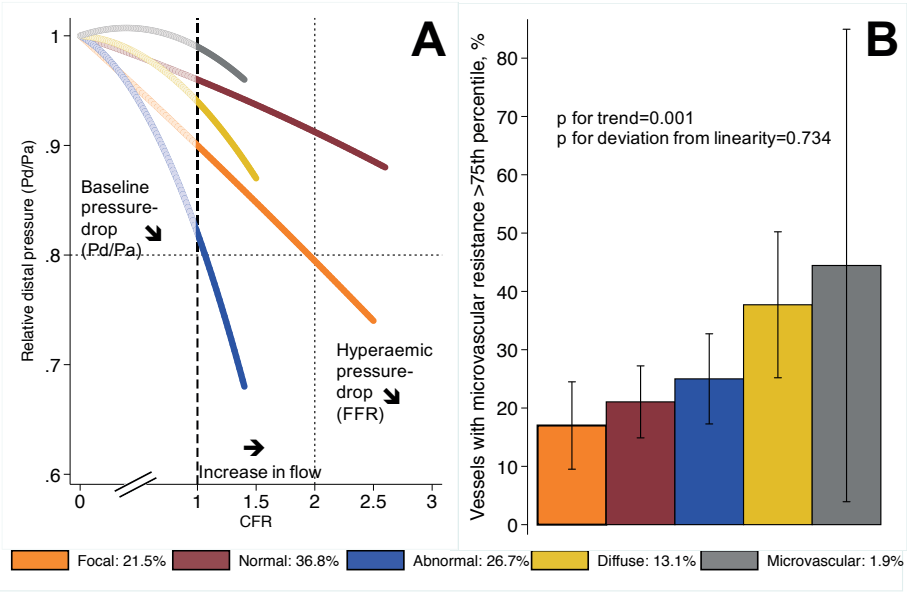

Figure 5 | This figure was produced from the same data described in Figure 4. Panel A shows the observed relative pressure-drop (distal to aortic pressure drop, Pd/Pa) from baseline (dotted vertical line) to hyperaemia (end of each color line) across the CFR and FFR classification quadrants. Each lines provides a quadratic fit that starts at an hypothetical zero flow and zero pressure-drop, crosses the vertical dotted line at the median baseline Pd/Pa value observed in each category, ends in the X-axis at the median CFR value, and ends in the Y-axis at the median FFR vaue observed in each category. Vessels within the focal group exhibited a preserved flow supply (CFR≥2) in spite of a significant pressure drop (FFR≤0.80). Contrarily, vessels within the predominantly diffuse and microvascular categories exhibited an exhausted flow supply (CFR<2) in spite of developing only mild pressure drops (FFR>0.80). Panel B shows the prevalence of vessels with high microcirculatory resistance (above the 75th percentile for each Doppler and thermodilution database) across the CFR and FFR regions. Please note how these vessels were more likely to be present in the predominantly diffuse and microvascular disease regions, and contrarily, less likely to be present in the focal quadrant. Herein, vertical lines represent error bars.

The reinterpretation of the CFR and FFR relationship proposed by Johnson et al.[55] was put to test by our groups,[47,51] and was complemented by a detailed evaluation of invasive MR as a quantitative measure of the microcirculatory functional status. Echavarría-Pinto et al (Figure 6). investigated 91 coronary arteries with intermediate epicardial stenoses with FFR and thermodilution-derived flow, during baseline and hyperemia. The index of MR (IMR)[56] and the angiographic Gensini score[57] were also measured to obtain additional insights on the functional status of the coronary microcirculation, and on the angiographic extent of DCA, respectively. Coronary arteries were then categorized into FFR (cut-off: 0.80) and CFR (cut-off: 2) classification quadrants, and the main findings were the following: 1) more than half (59%) of the coronary arteries with FFR>0.80 presented data suggestive of abnormal haemodynamics associ-

ated with IHD (CFR<2 in 52%; high IMR in 33%); 2) vessels with FFR>0.80 presented higher IMR [adjusted mean of IMR: 27.6 (95% CI: 23.4 to 31.8)] than vessels with FFR≤0.80 [adjusted mean of IMR: 17.3 (95% CI: 13.0 to 21.7), p=0.001]; 3) vessels with FFR>0.80 and CFR<2 (n=28, 39%), had a wide IMR dispersion (7-72.7 U) suggestive of DCA and/or microvascular disease; 4) vessels with FFR≤0.80 and CFR>2 presented the lowest iMR values, suggesting a preserved microcirculation and finally; 5) vessels meeting the "predominant microvascular disease" (FFR>0.80, CFR<2 and pressure loss <5mmHg) definition exhibited the highest IMR values providing thus supporting to the model of Johnson et a.[55] Panel B of Figure 5 shows the percentage of vessels within the highest quartile of microcirculatory resistance across the CFR and FFR relationship in the above-mentioned 467 vessels. These larger analysis provides further support to this model. With a similar perspective, van de Hoef et al., explored also the FFR and CFR relationship with intracoronary pressure and Doppler-derived flow velocity in a larger (n=157) population.[51] Herein, the two groups in which FFR and CFR were discordant were characterized by divergent values of baseline and hyperaemic microcirculatory resistance and vasodilatory capacity reserve, emphasizing the important role that plays the coronary microcirculation in delineating the FFR and CFR relationship. Furthermore, hyperaemic stenosis resistance (the most specific index of coronary stenosis severity, see Chapter by Maria Siebes)[58] was also significantly different across the FFR and CFR quadrants, being lower and higher in the FFR>0.80/CFR≥2 and FFR<0.80/CFR≥2 groups, respectively. Overall, these studies underscore the value of combined pressure and flow measurements (Figure 7), and serve as a preamble to a more comprehensive, yet required, intracoronary assessment of IHD.

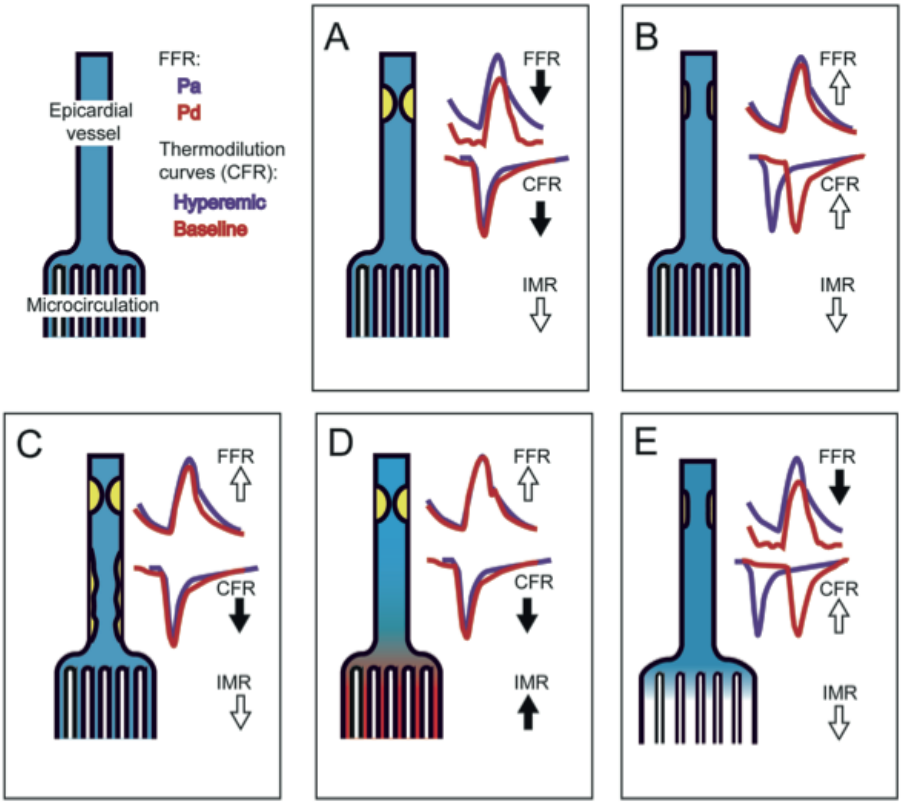

Figure 6 | Schematic representation of the possible haemodynamic patterns derived from the CFR and FFR relationship after the incorporation of invasive microvascular resistance (IMR). Panel A shows a vessel with concordantly abnormal FFR and CFR values, with a low IMR, suggestive of a severe, flow-limiting stenosis without superimposed DCA or microvascular disease. Panel B: vessel with concordantly normal FFR and CFR values without associated DCA or microvascular disease. Panel C: Despite the normal FFR, an exhausted CFR with low IMR might suggest ischaemia and DCA as predominant affection. Panel D shows also a vessel with a normal FFR and an exhausted CFR. At a difference with the vessel shown in panel C, the high microcirculatory resistance may account for the discrepancy between FFR and CFR. Finally, panel E illustrates a vessel with an abnormal FFR that has preserved CFR. Herein, microcirculatory disease and DCA should be absent and ischaemia is highly unlikely, even if FFR is low. Reproduced with permission from Echavarria-Pinto et al.[47]

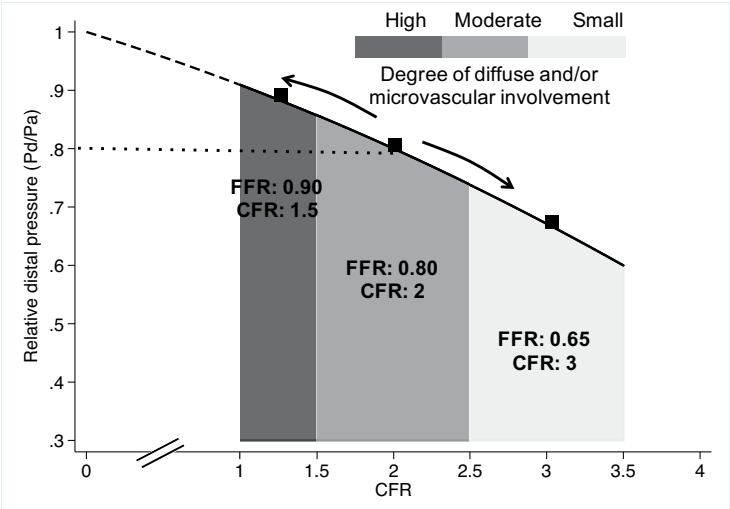

Figure 7 | Schematic influence of diffuse and/or microvascular disease on the FFR and CFR relationship for a given theoretical stenosis commonly observed in clinical populations (FFR=0.80, CFR=2, middle of the Figure). In the absence of diffuse and or microvascular disease, maximal hyperaemic flow and CFR will increase, whilst FFR will decrease (right side of the Figure). Contrariwise, if diffuse and/or microcirculatory disease worsen for the same given stenosis, maximal hypearemic flow and CFR will decrease, and FFR will increase (left side of the Figure).

PROGNOSTIC IMPLICATIONS OF CORONARY FLOW RESERVE: THE IMPORTANCE OF FLOW

In the past 20 years, a large number of studies using both invasive and non-invasive techniques have produced a large wealth of data leading to a better understanding of the important role of coronary physiology in identifying patients that will receive most benefit from revascularization and that are at higher risk of MACE. FFR has greatly contributed to these. But in a parallel way, powerful outcome data is also supporting CFR as a meaningful prognostic tool (Table 2).

Table 2 | Prognostic value of coronary flow reserve in stable ischaemic heart disease settings

First author	Year	n	Clinical population	CFR cut-off	Endpoint	Follow-up	Events,%	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
CFR from transthoracic echocardiography									
Nemes	2008	397	Stable angina	1.73	Cardiovascular mortality	3.4	5.8	-	2.9, p<0.02
Sicari	2009	394	Stable angina, non-obstructive CAD and normal wall motion by echo	2	Death and non-fatal ACS	4.3	7.8	16.7 (6.7-40.2)	16.4 (6.7-40.2)
Cortigiani	2012	4313	Known or suspected CAD	2	All-cause mortality	1.6	3.4	6.7 (4.74-9.47)	3.31 (2.29-4.78)
Kawata	2013	111	Asymptomatic patients with type 2 diabetes	2.5	All-cause mortality, non-fatal ACS and coronary revascularization	6.6	18.0	4.89 (2.02-12.5)	3.95 (1.6-10.3)
Gaibazzi	2013	718	Stable angina	2	All-cause mortality and non-fatal ACS	1.3	7.0	3.58 (1.99-6.45)	2.25 (1.21-4.17)
Nakanishi	2013	139	Suspected or known CAD and chronic kidney disease	CFR (continue)	MACE	3.3	18.7	0.32 (0.13-0.83)	0.21 (0.06-0.68)
Lowenstein	2014	651	Suspected or known CAD with normal wall motion by echo	2	Cardiovascular mortality, ACS and late revascularization	2.9	7.4	-	4.2 (2.4-7.4)
CFR from positron emission tomography									
Herzog	2009	256	Suspected or known CAD	2	MACE	5.5	31.1	2.14 (1.35-3.37)	1.6 (1.00-2.57)
Murthy	2011	2783	Suspected or known CAD	CFR tertiles	All-cause mortality	1.4	10.3	-	5.6 (2.5-12.4)
Ziadi	2011	704	Suspected or known CAD	2	Cardiac mortality and MI	1.1	4.0	-	3.3 (1.1-9.5)
Fukushima	2011	275	Suspected or known CAD	2.11	Cardiac mortality and MI	1	15	-	2.93 (1.3-5.1)
Taqueti	2015	329	Patients referred for invasive angiorgaphy within 90 days after PET	CFR per -1 Unit	MACE	3.1	19.4	2.17 (1.34-3.52)	2.02 (1.20-3.40)
CFR from intracoronary Doppler									
van de Hoef	2013	178	Stable angina and intermediate epicardial stenosis	CFR≥2 and FFR>0.80 vs CFR<2 and FFR>0.80	MACE	5	-	8.8 (4.1-19.1)*	-

CFR: coronary flow reserve; CI: confidence intervals; CAD: coronary artery disease; ACS: acute coronary syndrome; MACE: mayor adverse cardiovascular events; FFR: fractional flow reserve

*Relative risk at 5 years

CFR interrogates the coronary circulation as a whole, and summarizes most of the mechanisms leading to myocardial ischaemia. Therefore, a normal CFR highly excludes the possibility of an abnormal myocardial blood flow supply, and as discussed above, suggests both: a 1) preserved microcirculatory function and 2) the absence of physiologically relevant focal or diffuse coronary narrowings. An exhausted CFR, on the other side, reflects an impaired myocardial flow supply, either due to focal atherosclerosis, DCA or MCD. This theoretical framework hence suggests that independently from the ischaemia generating-mechanism, CFR can identify abnormal myocardial flow supply, and therefore stratify the risk for ischaemia-related MACE. Accumulating evidence is now supporting this chain of postulates. Indeed, Herzog et al. observed that patients with abnormal PET-derived CFR (n=32) had significantly higher annual MACE (6.25% vs. 1.4%, p<0.05) and cardiac death rates (3.1% vs. 0.5%, p<0.05) as compared to patients with normal CFR (n=71). Moreover and even in patients with abnormal perfusion (a surrogate of inducible ischaemia or FFR<0.75), CFR allowed further stratification of cardiac risk throughout the follow-up of 10 years.[59] In a much larger population (n=2783) investigated also with PET, Murthy et al. observed that patients with CFR <1.5 had an univariate 16-fold increased risk in mortality as compared to patients with CFR>2, and CFR significantly improved risk stratification among patients with visually normal PET scans, highly suggestive of DCA or MCD.[60] This prognostic capacity seems to apply also to diabetic patients, as in a large study (n>2500), those diabetics without known CAD but with impaired CFR experienced a high rate of cardiac death, comparable to that for nondiabetic patients with known CAD (2.8% per year versus 2.0% per year; p=0.33). Conversely, diabetics without known CAD and preserved CFR had a very low cardiac mortality, which was similar to patients without known CAD, diabetes and normal stress perfusion and systolic function (0.3% per year versus 0.5% year; p=0.65).[50] The largest available study comes from Cortigiani et al., that performed a prospective, multicentre, observational study where 4,313 patients with known (n=1,547) or suspected (n=2,766) IHD were evaluated with stress echocardiography and CFR evaluation in the left anterior descending artery.[61] Herein and as compared with patients with preserved flow supply (CFR>2), the 4-year mortality was notably higher in patients with CFR≤2, both considering the group with stress-induced ischaemia (39% vs. 7%; p<0.001) and the group without ischemia at stress echocardiography (12% vs. 3%; p <0.001) (Figure 8). Altogether, these robust data demonstrates that CFR not only is a powerful predictor of strong clinical endpoints, but also, that this capacity extends beyond the presence or absence of inducible ischaemia—the objective of FFR. Therefore, CFR offers a clear opportunity to improve risk stratification in IHD, and rises the possibility to further refine the selection of revascularization targets, as discussed below.

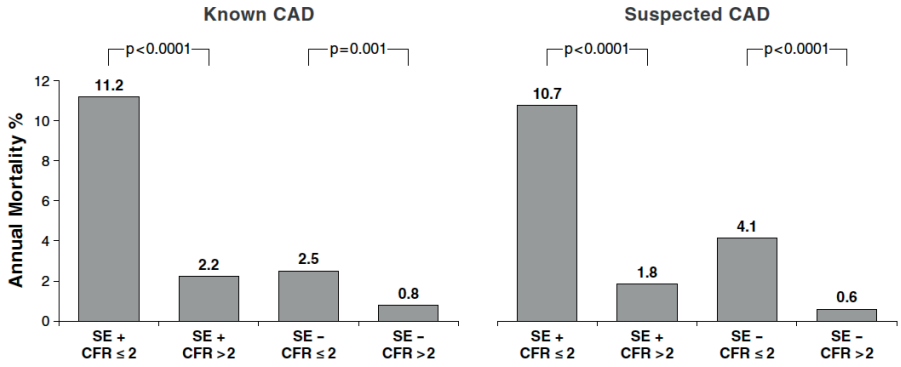

Figure 8 | Annual mortality rate according to CFR and the presence or absence of inducible ischaemia as assessed by transthoracic stress echocardiography. Stress ischaemia (SE) was defined as stress-induced new and/or worsening of prexisting wall motion abnormalities. In bot patients with known (n=1,547) or suspected (n=2,766) coronary artery disease (CAD), the highest mortality rate was observed in patients with exhausted CFR (≤2) and inducible ischaemia. Conversely, the lowest mortality was observed in patients with normal flow supply (CFR>2) and absence of inducible ischaemia. Notably, even in the presence of inducible ischaemia (a correlate of FFR≤0.80), patients with normal CFR (>2) exhibited a low mortality rate. Finally, patients with exhausted flow supply (CFR≤2) and absence of inducible ischaemia (a correlate of FFR>0.80) exhibited a higher annual mortality than the most normal patients. Reproduced with permission from Cortigiani et al.[61]

Preserved flow supply in vessels with FFR≤0.80: refinement in the selection of epicardial stenosis candidates for revascularization

Among the vessels with FFR≤0.80 (n=224) in Figure 9 –all current candidates for mechanical revascularization using FFR alone– 44.6% (n=100) have little or no ischemia and a likely good prognosis because of preserved myocardial flow supply, as demonstrated by a CFR>2. Therefore, many patients with a low FFR potentially are at low risk, and consequently receive minimal benefit from percutaneous or surgical revascularization, but remain exposed to procedural risks, failure of the devices, prolonged dual anti-platelet therapy, and hospital and patient costs. This hypothesis has been recently supported by the long follow-up (>10 years) observational study of Van de Hoef et al., where revascularization of stenosed vessels was deferred whenever intracoronary Doppler-derived CFR and FFR were not concordantly abnormal (using CFR<2.0 and FFR<0.75 as cut-offs).[51] When compared with patients with concordantly normal FFR and CFR values (which presented a 10% MACE cumulative rate at 5 years), an abnormal FFR with normal CFR was associated with a good and even equivalent clinical outcome (Figure 10), up to three years when using FFR<0.75, and throughout 10 years when using FFR≤0.80. Furthermore, even at 10 years, the relative risk for MACE among vessels with CFR>2 and FFR≤0.80 was not statistically different (40% vs 28%, relative risk of 1.4 (95% CI: 0.9 to 2.4), p=0.130) from that of vessels with concordantly normal FFR and CFR values. The study by van de Hoef et al. thus illustrates the advantages of combin-

ing CFR and FFR in daily clinical practice, and although corroboration from randomized trials should be awaited, this study vigorously suggests that non-revascularized vessels with preserved flow supply even if FFR≤0.80, exhibit a favorable outcome at long term.

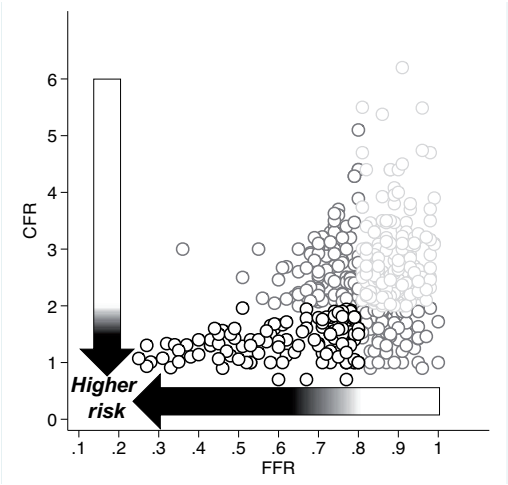

Figure 9 | This scatterplot provides an schematic figure of the continuum risk in both the X and Y axis of the CFR and FFR relationship. Whilst the lowest and higher risks are expected to be present on the concordantly normal (CFR≥2 and FFR>0.80) and concordantly abnormal (CFR<2 and FFR≤0.80) regions, respectively, discordant cases seem to exhibit intermediate risks. This offers an opportunity to achieve 1) further risk stratification and 2) improve the selection of stenosis candidates for revascularization as compared to a lone FFR strategy.

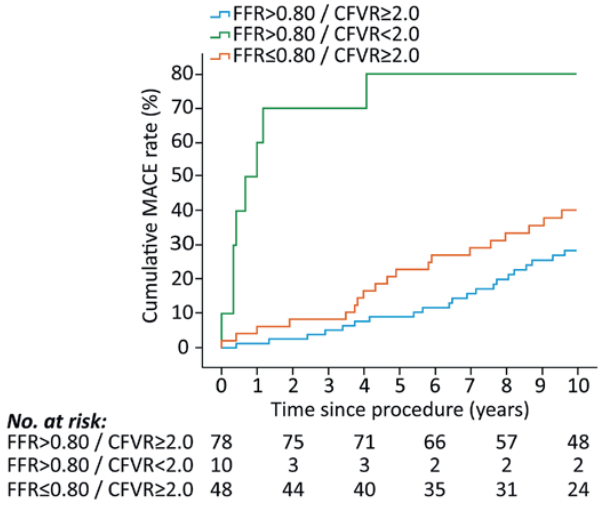

Figure 10 | Kaplan Meier estimates of long term mayor adverse cardiovascular events (MACE) [defined as the composite of cardiac death, acute myocardial infarction not clearly attributable to a non-target vessel, and clinically driven (urgent) revascularization of the target vessel by means of coronary artery bypass graft surgery and/or percutaneous coronary intervention] across deferred vessels where FFR and CFR were both normal or discordant. The highest MACE rate was observed in vessels with exhausted flow supply either due to predominantly DCA or MCD (FFR>0.80 and CFR<2). Contrariwise, vessels with a normal flow supply (CFR>2) were associated with a low MACE rate, even in those that developed positive FFR values (FFR<0.80). Reproduced with permission from van de Hoef et al.[51]

The open label, non-randomized, natural history DEFINE-FLOW study (Combined Pressure and Flow Measurements to Guide Treatment of Coronary Stenoses) (Clinical trials identifier: NCT02328820) is currently evaluating the prognostic value and therapeutic potential of combining CFR and FFR when evaluating coronary artery stenoses. Vessels with CFR>2 despite a reduced FFR will receive optimal medical therapy alone, and only stenosis with a simultaneous reduction in both CFR and FFR will be revascularized. The primary objective will be to determine the prognostic value of combined FFR and CFR measurements to predict the 24-month rate of MACE. And the secondary endpoints are: 1) to describe the test/retest repeatability of combined FFR and CFR measurements; 2) to explore individual components of MACE, including angina burden; 3) to determine the rate of MACE and angina burden during extended follow-up (up to 5 years); and 4) to document the procedural effort and success rate for combined pressure and Doppler flow velocity measurements. Results are expected in 2018.

Exhausted flow supply: concealed risk in vessels with FFR>0.80?

Among vessels with FFR>0.80 (n=241) in Figure 9, 29% (n=70) had an exhausted CFR. A mild focal stenosis superimposed on a background of severe DCA and/or MCD is the proposed substrate (Figure 3). The first question that rises is if DCA can impair significantly hyperaemic flow without a significant pressure loss, or positive FFR values. de Bruyne et al. already demonstrated that DCA produces a graded, continuous pressure fall along the arterial length, and indeed in many cases, such pressure drop will be significant, and DCA will cause FFR≤0.80.[25] However, fluid dynamic studies have also shown that in general, DCA is likely to induce low FFR values due to a lack of convective acceleration of blood flow.[62] Therefore, it is plausible for DCA to reduce CFR significantly, with only a small fall in pressure, as also demonstrated theoretically and empirically in a large (n=1,001) PET study by Gould et al.[24,27] The next question is whether this highly diseased and ischaemic vessels and territories respectively (FFR>0.80 and CFR≤2) will share the same prognosis as those with normal microcirculation and absence of DCA (FFR>0.80 and CFR>2). The registry group of the FAME 2 study sheds some light, by demonstrating that in deferred FFR>0.80 vessels, MACE occurs at a rate of 5% a year.[52] However, prognostic data from CFR studies have clearly documented that an exhausted CFR is associated with a significantly higher risk for adverse events: MACE: 6.25% per year, cardiac death: 3.1% per year in the study by Herzog;[59] mortality rised to 7.2% per year in patients with CFR<2 in the study by Cortigiani;[61] and in vessels with FFR>0.80 and CFR<2 van de Hoef et al. reported a remarkably high 5-year MACE rate of 80%.[51] Therefore, the risk of vessels with FFR>0.80 seems also dependable on the underlying CFR, and further risk stratification seems hence plausible.

MCD could also account for the FFR>0.80 and CFR<2 pattern. This is important as studies performed with Doppler derived and thermodilution-derived flow have

observed that MR is significantly higher in vessels with FFR>0.80.[47,51] Therefore, the presence of MCD almost invariably implies "non significant" FFR values, that could be wrongly interpreted as absence of significant disease. A recent study addressing this issue observed that, despite equivalent FFR values across microcirculatory resistance tertiles, the prevalence of inducible ischaemia by single positron emission tomography was significantly higher for vessels with high microcirculatory resistance, compared with those with either low or intermediate resistance values. Moreover, for a given hyperaemic stenosis resistance, FFR increased with increasing microcirculatory resistance (Figure 11).[63] Therefore, MCD not only modulates FFR values but also the development of ischaemia, a clear predictor of long term MACE.[27,40] Because of these, quantitative measurements of microcirculatory function are growingly used in clinical practice, and emerging data supports its value as adjuvant tools for risk stratification in IHD, particularly in the setting of acute coronary syndromes.

Finally, whether DCA or MCD mostly results in the FFR>0.80 and CFR<2 pattern, is an area of active research. The invasive calculation of microcirculatory resistance has been suggested as a tool to differentiate both components,[47] although further investigation on this hypothesis is required. In this regard, a recent study by Taqueti et al.[64] is incremental, by demonstrating that both CFR (assessed by PET) and CAD angiographic extent (assessed with the CAD angiographic prognostic index)[65] were independently associated with MACE (hazard ratio for unit decrease in CFR, 2.02; 95% CI: 1.20–3.40; p=0.008; hazard ratio for 10-U increase in CAD prognostic index, 1.17; 95% CI: 1.01–1.34; p=0.032) suggesting consequently that both DCA and MCD are independently associated with worse outcomes.

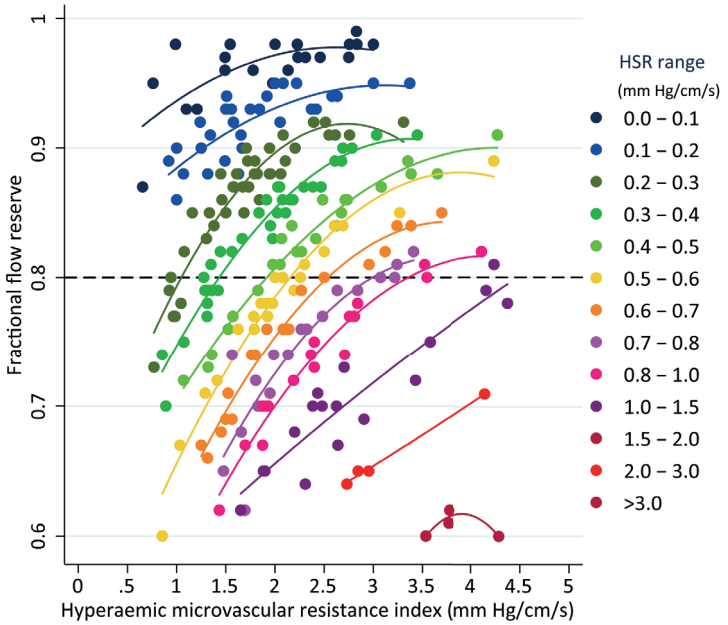

Figure 11 | Relationship between FFR and microcirculatory resistance calculated from Doppler flow velocity (hyperaemic microcirculatory resistance) for different values of epicardial stenosis, expressed by narrow ranges of hyperaemic stenosis resistance (HSR), the most specific index of stenosis severity. For a given epicardial stenosis severity, FFR increased with increasing HMR, reflecting the prominent role of microcirculatory disease in modulating the FFR values.

CONCLUSIONS

1. Myocardial flow impairment in IHD results from both obstructive and non-obstructive causes.
2. FFR provides valuable information on whether focal stenosis play a dominant role in limiting myocardial flow supply, but not on whether concomitant non-obstructive IHD, partially caused by diffuse coronary artery disease and microvascular disease, constitutes the dominant problem in the interrogated myocardial territory.
3. Emerging data suggests that non-obstructive causes of IHD have substantial prognostic implications
4. CFR FFR and microcirculatory resistance indices can be envisaged as complementary rather than competing techniques, and emerging data is supporting their combined use.
5. Further studies should address if a more comprehensive IHD invasive diagnostic approach that combine CFR, FFR and microcirculatory resistance may improve prognostic characterization and guide therapeutic strategies aiming for both obstructive and non-obstructive involvement.

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Summary and future perspectives

Samenvatting van het proefschrift

SUMMARY OF THE THESIS

This thesis sought to provide some novel insights on the complexity of the invasive assessment of ischaemic heart disease (IHD). Undoubtedly, focal coronary stenosis play a pivotal role in the genesis and prognosis of this entity. Furthermore, therapy guided by the functional assessment of such focal stenosis has shown to improve patient outcomes, as compared to therapy guided by their angiographic appearance alone.[1] However, wealth of consistent data currently show how does this stenosis-centred diagnostic and therapeutical approach, relying only on the fractional flow reserve (FFR), is not perfect, since many patients with non-physiologically significant epicardial stenosis still suffer from angina and cardiovascular events, and conversely, a significant proportion of patients with FFR-significant stenosis do well at medium term.[1,2] These leaves, consequently, room for further refinement. This thesis pursued to contribute to this refinement, and for these, followed a two-fold pathway. Firstly, it explored the diagnostic consequences of a simpler physiological approach, focused only on the pressure-lone assessment of focal stenosis under non-hyperaemic conditions. Secondly, it explored a more complex-yet comprehensive approach, that included, in addition to the FFR, the available indices to explore coronary microcirculation. In the following paragraphs, the salient findings of the different parts of the present thesis will be discussed in perspective.

Part A. Physiological assessment of coronary stenosis under non-hyperaemic and hyperaemic conditions

The introduction of coronary physiology as a tool to guide revascularization has clearly changed interventional cardiology practice. Not so long ago percutaneous coronary intervention was recommended for symptomatic patients with "significant coronary lesions", defined as >50% stenosis, with a class 1 level of evidence B.[3] Within this paradigm, fractional flow reserve (FFR) was born and matured as a diagnostic technique. However, this journey was not an easy one, and FFR was frequently challenged, with its additional complexity highligthed as one of the reasons for its low use. Nevertheless, this additional complexity slowly proved to be worth it, since FFR gradually demonstrated to be capable to identify those stenoses in which the risk and benefit ratio was more positive for the intervention, which ultimately has translated into an improvement in patient care.[4] *Chapters 2 and 3* of this thesis focuses on the FFR as a diagnostic technique, and on the wealth of data that supports its everyday use. Still and despite the large amount of consistent reassuring evidence now formally summarized in current clinical practice guidelines, FFR is underutilized worldwide.[5] One of the proposed reasons for this phenomena is the cost, additional time and cumbersomeness of achieving "true maximum and stable" hyperemia, largely proposed as an unequivocal

requirement to fulfil FFR theoretical framework. Within this rationale, and in an attempt to avoid pharmacological hyperaemia at all, several non-hyperamic physiology indices have been proposed, being the instantaneous wave free ratio (iFR) and the baseline distal to aortic pressure ratio (Pd/Pa) the most explored. *Chapter 4 and 5* of the thesis summarized the main findings of the ADVISE II Study (ADenosine Vasodilator Independent Stenosis Evaluation II). This was the first prospective and independent coronary physiology study analyzed at a core laboratory. ADVISE II focused on the diagnostic accuracy of iFR to correctly classify, outside of a pre-specified range of values, stenosis severity as defined by FFR. The study showed that the hybrid iFR-FFR approach was able to maintain a very high diagnostic accuracy against FFR, and was also able to avoid vasodilator agents in more than half of the patients. The same was observed for the baseline Pd/Pa, and the hybrid baseline Pd/Pa-FFR approach. One of the most important findings of ADVISE II is that, when FFR is used as a reference, a proportion of stenoses can be classified correctly without hyperaemic stress, existing a trade-off between higher diagnostic accuracy and adenosine spare. Moreover, the rigorous diagnostic methodology of ADVISE II study paved the way for the large ongoing outcome DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome) trials, powered to determine if the iFR-based selection of revascularization targets leads to a similar rate of mayor adverse cardiovascular events (MACE), as compared to FFR-guidance. *Chapter 6* of the thesis matured within a "pros vs. cons" scientific environment for the hyperaemia-free assessment of coronary stenosis.[6–8] However, in this chapter, we decided to avoid confrontation, and rather to show how does the combination of baseline and hyperaemic conditions provides incremental and not competing stenosis severity information. Finally, in Chapter 7 we offer some light on the safety of left main revascularization deferral based on FFR or intravascular ultrasound, which is a frequently faced problem in everyday interventional practice. Here, and in spite of the large amount of limitations of the study as outlined in the manuscript, we observed that both approaches (physiological and anatomical) lead to a similar rate of MACE at long term.

Part B. Systemic effects of adenosine and its impact on the physiological assessment of coronary stenosis

It can be argued that the introduction of the iFR was not only a scientific revolution but also a paradigm shift, because the fundamental basics and experimental practices of coronary physiology are currently under scrutiny and re-appraisal. This part of the thesis sought to contribute to this scrutiny, by assessing how does hyperaemia by itself can influence stenosis severity assessment. In *Chapter 8*, we observed that the systemic effect of adenosine is related to the microcirculatory response in the heart.

Moreover, the adenosine-induced hypotensive response was positively associated with coronary microcirculatory resistance and with lower FFR values. This was a surprising observation to us, because at first glance it was our thought that the driving pressure would be the main determinant of the trans-stenotic pressure drop, with higher aortic pressure leading to higher trans-stenotic pressure drops and lower FFR values.[9] Nevertheless, we observed the opposite, being larger hypotensive responses related lo lower FFR values, probably because of a lower microcirculatory resistance opposing to the trans-stenotic flow. *Chapter 9* explored from a different angle the influence of the fluctuations in aortic pressure and the development of the hyperaemic plateau on the FFR. Such analyses showed that the FFR value commonly used in clinical practice slightly differs from the original FFR framework, because in a significant proportion of cases, the minimum FFR value develops before the stabilization of hyperaemia, and not within the stable region. It can be suggested, hence, that the induction of pharmacological hyperaemia for coronary stenosis assessment somehow emulates the Hawthorne effect or the Heisenberg's uncertainty principle, where the diagnostic tool used by the observer to describe a phenomenon, ultimately contaminates the observation.

Part C. Influence of the coronary microcirculation on the invasive assessment of ischaemic heart disease

This section of the thesis addressed some clinical aspects of the invasive assessment of the microcirculatory function. This is important at a time when, in addition to obstructive involvement, microcirculatory dysfunction is increasingly acknowledged as determinant of clinical outcomes. The review provided in *Chapter 10* clearly show how does the coronary flow reserve (CFR) and microcirculatory resistance indices are related to worse ventricular function and long term survival in patients suffering from acute coronary syndromes. *Chapter 11* addressed the stable clinical setting, where it was observed that age is an important clinical characteristic related to coronary microcirculatory function. Advancing age was associated with a progressive impairment in coronary vasodilatory function and a progressive decrease in maximal coronary flow. Additionally, minimal microcirculatory resistance increased, which ultimately and altogether resulted in a progressive decrease in the CFR. These phenomena are important, because maximal flow determines the lowest FFR. Hence, ageing was associated with a contradictory increase in FFR values, that is not expected from the natural course of epicardial atherosclerosis, because atherosclerotic plaques slowly grow and obstruct conductance vessels. *Chapter 12* explored a theoretical concern for the clinical use of resistance indices to assess microcirculatory function, namely, the physiologically expected increase in estimated coronary resistance across the branching structure of the coronary tree. Our findings suggest an influence of the amount of myocardium subtended to a coronary stenosis on the index of microcirculatory resistance, however,

this influence seems to be rather modest. It is important to highlight that our findings only apply to thermodilution data, because in normal coronary arteries the decrease in flow velocity from proximal to distal segments is much smaller than the decrease in volumetric flow. As a consequence, the influence of this normal phenomenon in resistance indices derived from Doppler flow velocity should be smaller and is currently unknown.

Part D. Comprehensive invasive physiological assessment of ischaemic heart disease

Iimpairment of myocardial blood supply in ischemic heart disease results from both obstructive and non-obstructive coronary involvement. However, and as outlined above, its current diagnosis is largely stenosis-centred. FFR informs on whether treating epicardial stenoses may benefit the patient, but not on whether concomitant nonobstructive coronary disease, frequently caused by coronary microcirculatory dysfunction and diffuse disease, are present.[11] In *Chapter 13*, we sought to assess the contribution of coronary microcirculatory dysfunction and diffuse disease to ischemic heart disease by invasive means. For these, we investigated stenosed coronary arteries with FFR, CFR and the index of microcirculatory resistance. Interestingly, we observed that more than half of vessels with a normal FFR>0.80 presented disturbed hemodynamics, revealed by abnormal flow reserve or microcirculatory resistance. Moreover, and as theoretically expected, the presence of microcirculatory resistance almost invariably implied nonsignificant (>0.80) FFR values, that could be wrongly interpreted as absence of significant disease. Overall, the observations summarized in this Chapter serve as a preamble to a more comprehensive, yet required, intracoronary assessment of ischemic heart disease, which may improve prognostic characterization and guide therapeutic strategies aiming to both obstructive and non-obstructive coronary disease.

The final chapters of the thesis explored the diagnostic and prognostic value of two novel physiology indices. In *Chapter 15*, we translated to invasive physiology the coronary flow capacity concept that was originally described from positron emission tomography data. This concept soughs to overcome the limitations of the CFR, that are mainly attributable to its dependence on resting coronary hemodynamics. Coronary flow capacity summarizes two dimensions of the flow characteristics of the circulation: the CFR and the maximal achievable flow. This approach follows the assumption that myocardial ischaemia is unlikely when either CFR or maximal flow are above the normal thresholds. With increasing impairment of both of these flow characteristics, the likelihood of myocardial ischaemia and impaired clinical outcome should increase. Our work substantiated the possible prognostic role of this concept, since we observed that the combination of CFR with maximum achievable flow velocity improved the prediction of MACE over the CFR alone. Moreover, the likelihood of MACE increased significantly

with increasing impairment of the coronary flow capacity. Finally, a straightforward-yet unexplored-new index derived from the simple manipulation of the formulas of CFR and FFR was proposed in *Chapter 16*. Herein, the CFR predicted concept was proposed as a tool to investigate, prior to the performance of PCI, the potential gain in CFR produced by the intervention. The applicability of the calculations used for this purpose, derived from FFR theory, was tested first in metanalyses of available studies, and subsequently with measurements made in the catheterization laboratory. The salient finding of this study is a moderate concordance between the predicted and observed post-interventional CFR, both across studies and across individual coronary vessels. Most importantly, from all the available pre-interventional physiology indices, CFR predicted was the only independent predictor of the truly observed post-PCI CFR. Altogether, this Chapter provides support to the clinical use of the CFR predicted concept and expand with simplicity the information derived from intracoronary physiology measurements.

Future perspectives

The ultimate objective of any diagnostic test of ischaemic heart disease (IHD) is the identification of the heart elements that will lead to symptoms and MACE. Additionally, this "ideal" diagnostic test should be capable to direct therapy towards targets where the risk and benefit ratio is more positive for a particular intervention, including non-and pharmacological therapies, as well as interventional and surgical procedures. Available evidence strongly suggest that IHD-related MACEs arise from focal stenosis, diffuse atherosclerosis and microcirculatory dysfunction, among several other factors.[11,12] In this regard, and as outlined above, FFR provides very valuable information of the focal stenosis, but largely neglect the importance of other IHD levels. Since wealth of data suggest that diffuse disease and microcirculatory dysfunction are associated to MACE, it seems reasonable to suggest that the incremental information provided by the flow and resistance indices discussed in the thesis should provides incremental information on top of the FFR. If this additional diagnostic complexity ultimately improves symptoms or MACE in patients suffering from IHD, remains to be examined by future research.

Selection of revascularization targets

Cardiologists have struggle for decades in accurately identifying high risk coronary plaques. The DEFER and FAME studies showed that coronary plaques leading to significant hyperaemic trans-stenotic pressure drops are associated with higher rates of urgent revascularization, and that, conversely, coronary plaques that do not produce important hyperaemic pressure drops carry relatively low risk of strong MACE at follow up.[1,13] Importantly, it has been observed that, as compared to FFR, both iFR[14] and baseline Pd/Pa[15] are more closely related to the flow reserve of the downstream myocar-

dial bed (possibly as a consequence of the "hyperaemic Hawthorne effect" described above). This is a notable diagnostic characteristic, because the higher agreement of the non-hyperaemic indices with the flow reserve opens the possibility that a selection of revascularization targets based on baseline indices might more precisely direct stenting towards "flow-limiting" stenoses, which hypothetically could lead to a lower rate of MACE at follow-up, as compared to FFR. Currently, two large scale randomized trials, the DEFINE-FLAIR and iFR-SWEDEHEART trials, are investigating whether if an iFR-based selection of revascularization targets leads to a similar rate of MACE, as compared to the standard FFR-approach. An alternative diagnostic strategy based on combined pressure and flow data is being investigated in the DEFINE-FLOW study (Combined Pressure and Flow Measurements to Guide Treatment of Coronary Stenoses) (Clinical trials identifier: NCT02328820) that is currently evaluating the safety of revascularization deferral in vessels with low-FFR but preserved CFR, and will shed significant lights on the topic. Given the neutral results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D (Bypass Angioplasty Revasularization Investigation 2 Diabetes) trials,[16,17] a continued journey towards a further refinement in the selection of revascularization targets is critically important for the field.

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SAMENVATTING VAN HET PROEFSCHRIFT

Dit proefschrift tracht nieuwe inzichten te verschaffen in de complexiteit van invasieve diagnostiek van ischemische hartziekte. Met zekerheid speelt focale vernauwing van de kransslagaderen een belangrijke rol in de genese en prognose van deze aandoening. Behandeling van dergelijke focale vernauwingen op basis van de functionele ernst van de vernauwing, veelal bepaald met de fractional flow reserve (FFR), leidt objectief tot betere klinische uitkomsten dan behandeling van de vernauwing op basis van de visuele ernst op coronair angiografie.[1] Desalniettemin zijn er consistente aanwijzingen dat een dergelijke FFR-geleide strategie gericht op focale vernauwingen niet optimaal is. Een substantieel aantal patiënten met functioneel niet ernstige vernauwingen op basis van de FFR-meting hebben desalniettemin limiterende klachten van angina pectoris. Bovendien is er een significant deel patiënten met belangrijke focale vernauwingen op basis van de FFR-meting die hiervan op de middellange termijn geen nadelige gevolgen ondervinden als geen percutane coronaire interventie (PCI) wordt verricht.[1,2] Derhalve lijkt er ruimte te zijn voor verbetering in de diagnostiek van ischemische hartziekte. Dit proefschrift tracht op twee manieren bij te dragen aan verfijning van de diagnostiek van ischemische hartziekte. Allereerst werden de diagnostische consequenties van een vereenvoudigde fysiologie-gestuurde strategie onderzocht, met een focus op beoordeling van focale vernauwing van kransslagaderen middels intracoronaire drukmetingen zonder het gebruik van coronaire vasodilatatie. Ten tweede werd een meer complexe maar integrale fysiologische strategie onderzocht, welke behalve de FFR ook fysiologische parameters gebruikt die meer inzicht verschaffen in de coronaire microcirculatie. In de volgende paragraaf worden de bevindingen in deze onderdelen van het proefschrift in perspectief geplaatst.

Deel A. Fysiologische beoordeling van kransslagader vernauwingen met en zonder coronaire vasodilatatie

De introductie van coronaire fysiologie als een hulpmiddel voor besluitvorming omtrent revascularisatie van kransslagaderlijden heeft de klinische interventiecardiologie evident beïnvloedt. In het recente verleden werd revascularisatie in de klinische richtlijnen nog geadviseerd, met een klasse I level of evidence B classificatie, voor symptomatische patiënten met een visueel belangrijke vernauwing van de kransslagader op coronairangiografie, gedefinieerd als >50% vernauwing van de lumen diameter.[3] Binnen dit paradigma vond de introductie en validatie van FFR plaats. Gedurende deze ontwikkeling werd FFR echter vaak bekritiseerd, waarbij met name de relatieve complexiteit ten opzichte van angiografie-gestuurde interventie als belangrijke reden werd aangevoerd dat de adoptie van de techniek over de jaren beperkt bleef. Desalniettemin bleek deze additionele complexiteit zich uit te betalen, gezien het ontstaan

van consistent bewijs dat FFR de cardioloog in staat stelde juist die vernauwingen te identificeren waarbij de balans tussen risico en voordeel van PCI positief uitviel, met als gevolg een verbetering van de patiëntenzorg en klinische uitkomsten.[4] *Hoofdstuk 2 en 3* van dit proefschrift betreffen het gebruik van FFR als diagnostisch hulpmiddel en de veelvoud aan data die het nut van FFR en het dagelijks gebruik er van ondersteunen. Ondanks deze veelvoud aan ondersteunende data die de basis vormen van de brede klinische indicatie voor FFR die tegenwoordig wordt onderschreven in de klinische richtlijnen, is er sprake van drastisch ondergebruik van FFR wereldwijd.[5] Veel genoemde redenen voor dit ondergebruik zijn de kosten en additionele tijdsinvestering die benodigd zijn voor een FFR-meting, alsmede het problematische karakter van het behalen van "maximale en stabiele" coronaire hyperaemie, welk als noodzakelijk wordt gezien voor het verrichten van een betrouwbare FFR-meting. Binnen deze rationale, en in een poging om farmacologische vasodilatatie in zijn geheel te omzeilen, zijn diverse fysiologische parameters geïntroduceerd die geen vasodilatatie behoeven: de non-hyperaemische parameters. De meest onderzochte parameters die hier toe behoren zijn de instantaneous wave-free ratio (iFR), en de ratio tussen distale druk in de kransslagader tot aorta druk in rust-condities (Pd/Pa). *Hoofdstuk 4 en 5* van dit proefschrift vatten de belangrijkste bevindingen samen van de ADVISE II studie (ADenosine Vasodilator Independent Stenosis Evaluation II). Deze studie was de eerste prospectieve en onafhankelijke studie betreffende coronaire fysiologie waarbij gebruik werd gemaakt van een onafhankelijk analyse laboratorium. ADVISE II richtte zich op de diagnostische waarde van iFR om de ernst van kransslagader vernauwingen correct in te schatten ten opzichte van FFR als de referentiestandaard, met inachtneming van een grijze zone van iFR waarden rondom het afkappunt waarbij FFR per definitie werd bepaald. Deze zogenaamde iFR-FFR hybride strategie bleek in ADVISE II een zeer hoge diagnostische waarde te hebben, waarbij in meer dan de helft van de patiënten geen farmacologische vasodilatatie nodig zou zijn geweest. Hetzelfde werd gezien voor de Pd/Pa-FFR hybride strategie. Een van de belangrijkste bevindingen van ADVISE II was dat, wanneer FFR gebruikt wordt als referentie standaard, de functionele ernst van een belangrijk aandeel vernauwingen correct geclassificeerd kan worden zonder het gebruik van hyperaemie, waarbij er een wisselwerking bestaat tussen de absolute correcte classificatie van vernauwingen ten opzichte van FFR en de proportie patiënten waarbij geen hyperaemie nodig is. Bovendien opende de rigoreuze methodologie van ADVISE II de weg voor de grote klinische uitkomsten studies DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) en iFR-SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome), welke ontworpen zijn om te beoordelen of een iFR-gestuurde selectie van kransslagaderen voor revascularisatie tot gelijkwaardige klinische uitkomsten leidt in vergelijking met een FFR-gestuurde strategie. *Hoofdstuk 6* van het proefschrift is ontstaan terwijl er een hevig "pro –

contra" debat betreffende non-hyperaemische beoordeling van kransslagaderlijden gaande was.[6–8] In dit Hoofdstuk is echter gekozen te laten zien hoe de combinatie van non-hyperaemische en hyperemische parameters juist complementerende en niet conflicterende informatie geeft over de functionele ernst van kransslagaderlijden. Tenslotte geeft *Hoofdstuk 7* meer inzicht in de veiligheid van het uitstellen van revascularisatie van vernauwingen in de hoofdstam van de linker kransslagader op basis van FFR of intravasculaire echografie (IVUS), wat een veel voorkomend vraagstuk is in de klinische praktijk. Ondanks tekortkomingen van de studie, documenteerden we dat beide strategieën (fysiologie-gestuurd met FFR of anatomie-gestuurd met IVUS) op de lange termijn tot gelijkwaardige klinische uitkomsten leiden.

Deel B. Systemische effecten van adenosine en de gevolgen voor fysiologische beoordeling van kransslagader vernauwingen

Het kan gesteld worden dat de introductie van iFR niet alleen een wetenschappelijke revolutie was, maar tevens een verschuiving van een paradigma. Dit omdat de fundamentele en experimentele basis van coronaire fysiologie momenteel bekritiseerd worden en in belangrijke mate worden herbeoordeeld. Deel B vvasodilatatie door toediening van adenosine, het meest gebruikte medicament voor dit doel, de beoordeling van kransslagader vernauwingen beïnvloedt. *Hoofdstuk 8* documenteert dat de systemische effecten van adenosine zijn gerelateerd aan de respons van de microvasculatuur in het hart. Bovendien bleek een hypotensieve respons op het toedienen van adenosine geassocieerd met lagere microvasculaire weerstand en lagere FFR-waarden. Deze bevinding was verrassend, omdat onze hypothese dat de perfusie druk de belangrijkste determinant van het drukverval over de vernauwing was, waarbij hogere perfusie druk leidt tot een groter drukverval en derhalve tot lagere FFR-waarden, [9] niet juist bleek. Wij documenteerden het tegenovergestelde, waarbij ernstigere hypotensie bij toediening van adenosine leidde tot lagere FFR-waarden, meest waarschijnlijk door grotere bloedstroom door de vernauwing ten gevolge van een lagere microvasculaire weerstand. *Hoofdstuk 9* exploreerde de invloed van fluctuaties in aorta druk en het bereiken van een hyperaemische plateaufase op FFR-waarden vanuit een ander oogpunt. Deze analyses toonden aan dat de FFR-waarde die routinematig in de praktijk wordt gebruikt enigszins verschilt van het oorspronkelijk theoretisch model van FFR. In een groot deel van de patiënten ontstaat de laagste FFR-waarde namelijk voordat de hyperaemische respons stabiliseert, en niet binnen de stabiele hyperaemische plateaufase. Het kan derhalve worden gesteld dat het creëren van farmacologische hyperaemie voor beoordeling van de functionele ernst van kransslagaderlijden Hawthorne's effect of het onzekerheidsprincipe van Heisenberg reflecteert, waarbij het diagnostisch hulpmiddel gebruikt door de waarnemer de waarneming zelf uiteindelijk vertroebelt.

Deel C. Invloed van de coronaire microcirculatie op de invasieve beoordeling van ischemische hartziekte

Deel C van het proefschrift behandelt enkele klinische aspecten van de invasieve beoordeling van microvasculaire functie. Dit is van belang in een tijdperk waarin, buiten de bijdrage van focale vernauwingen, microvasculaire dysfunctie in toenemende mate wordt herkend als een belangrijke determinant van klinische uitkomsten in patiënten met ischemisch hartlijden. Het overzichtsartikel in *Hoofdstuk 10* geeft duidelijk weer hoe de coronaire flow reserve (CFR) en microvasculaire weerstand parameters gerelateerd zijn aan slechtere linker ventrikel functie en slechtere lange-termijns uitkomsten in patiënten met een acuut coronair syndroom. Hoofdstuk 11 beschrijft de situatie bij stabiel kransslagaderlijden, waar leeftijd een belangrijke klinische determinant van microvasculaire functie bleek te zijn. Hogere leeftijd was geassocieerd met een progressieve afname van de vasodilatoire capaciteit en met een progressieve afname in maximale coronaire bloedstroom. Bovendien was er een toename van microvasculaire weerstand met toename van de leeftijd, welk uiteindelijk resulteert in een progressieve afname van CFR met toenemen van de leeftijd. Deze fenomenen zijn belangrijk omdat maximale coronaire bloedstroom de uiteindelijke FFR-waarde bepaalt. Derhalve was een hogere leeftijd geassocieerd met een tegenstrijdig hogere FFR-waarde: een effect dat niet verwacht wordt op basis van het natuurlijk klinisch beloop van atherosclerose, omdat atherosclerotische plaques langzaam groeien met de tijd totdat ze uiteindelijk leiden tot obstructie van de epicardiale kransslagaderen. *Hoofdstuk 12* omvat de beoordeling van een theoretisch bezwaar van microvasculaire weerstand parameters. Theoretisch neemt de berekende weerstand in de microvasculatuur namelijk toe met iedere vertakking van de kransslagaderen, doordat een dergelijke vertakking direct gerelateerd is aan een afname van de achterliggende massa myocardweefsel. De bevindingen in dit hoofdstuk suggereren inderdaad dat de massa myocardweefsel distaal van een vernauwing in de kransslagader de berekende microvasculaire weerstand middels de "index of micrcirculatory resistance" (IMR) beïnvloedt, alhoewel de rol hiervan beperkt lijkt. Het is belangrijk te onderstrepen dat deze bevindingen alleen relevant zijn voor microvasculaire weerstand berekent met bloedstroom metingen waarvoor gebruik is gemaakt van de coronaire thermodilutie techniek. Dit is het geval omdat in normale kransslagaderen de afname in bloedstroomsnelheid, zoals verkregen wordt met intravasculaire Doppler metingen, met het vertakken van de kransslagaderen veel kleiner is dan de afname in absolute volumetrische bloedstroom, waarvan een afgeleide wordt verkregen met coronaire thermodilutie metingen. Als gevolg hiervan zal dit fysiologische fenomeen met waarschijnlijkheid minder effect hebben op microvasculaire weerstand parameters verkregen met Doppler bloedstroomsnelheid metingen; gegevens hierover ontbreken echter nog.

Deel D. Integrale invasieve fysiologische beoordeling van ischemische hartziekte

Beperking van de myocardiale bloedvoorziening in ischemische hartziekte ontstaat als gevolg van zowel obstructieve als niet-obstructieve aantasting van de coronaire circulatie. Desondanks is de huidige klinische praktijk zoals hierboven beschreven met name gericht op het identificeren en behandelen van focale vernauwingen. FFR geeft informatie over het verwachtte effect van revascularisatie van een focale vernauwing voor de patiënt, maar geeft geen informatie over gelijktijdige niet-obstructieve betrokkenheid van de coronaire circulatie in het ontstaan van ischemische hartziekte, welk bestaat uit microvasculaire dysfunctie en diffuse epicardiale atherosclerose.[11] In *Hoofdstuk 13* werd de bijdrage van microvasculaire dysfunctie en diffuse atherosclerose aan ischemische hartziekte onderzocht met behulp van invasieve diagnostiek. Hiertoe werden vernauwde kransslagaderen onderzocht met FFR, CFR, en IMR. In meer dan de helft van de kransslagaderen met een normale FFR-waarde (FFR>0.80) bleek er sprake van abnormale coronaire hemodynamica; ofwel een abnormale CFR, ofwel een abnormale microvasculaire weerstand weergegeven met IMR. Bovendien, en zoals theoretisch verwacht, was er in kransslagaderen met abnormaal hoge microvasculaire weerstand bijna uniform sprake van normale FFR-waarden (>0.80), welke derhalve verkeerd zouden kunnen worden geïnterpreteerd als aanwijzing voor de afwezigheid van relevant kransslagaderlijden. De observaties samengevat in dit Hoofdstuk dienen als een voorschot op een noodzakelijke integrale invasieve beoordeling van ischemische hartziekte, waarbij het evalueren van zowel obstructieve als non-obstructieve betrokkenheid mogelijk kan leiden tot verbetering van klinische uitkomsten in het kader van ischemische hartziekte. De laatste hoofdstukken van dit proefschrift exploreren de diagnostische en prognostische waarde van twee nieuwe fysiologische parameters. In Hoofdstuk 15 wordt de invasieve toepassing van coronaire flow capaciteit beschreven; een concept wat eerder werd geïntroduceerd vanuit positron emissie tomografie. Dit concept tracht voorbij te gaan aan de limitaties van CFR als fysiologische parameter, welke voornamelijk zijn gerelateerd aan de afhankelijkheid van CFR van coronaire hemodynamica in rustcondities. Coronaire flow capaciteit geeft omvattende informatie betreffende twee karakteristieken van de coronaire circulatie: CFR en de maximale bloedstroom. Dit concept is gebaseerd op de hypothese dat tekenen van myocardiale ischemie onwaarschijnlijk zijn wanneer ofwel CFR ofwel maximale bloedstroom normaal zijn. Met toenemende beperking van zowel CFR en maximale bloedstroom in de coronaire circulatie zouden volgens dit concept de kans op myocardiale ischemie en slechte klinische uitkomst toenemen. Dit hoofdstuk substantieert de diagnostische en prognostische rol van coronaire flow capaciteit; de combinatie van CFR met maximale bloedstroom was beter in staat slechte klinische uitkomsten te voorspellen in vergelijking met CFR als enige parameter. Bovendien bleek de frequentie van slechte uitkom-

sten toe te nemen met toenemende beperking van de coronaire flow capaciteit. In *Hoofdstuk 16* wordt tenslotte een eenvoudig, doch tot heden niet geëvalueerde, nieuwe parameter geïntroduceerd die gebaseerd is op een combinatie van de onderliggende formules van FFR en CFR. Dit concept, de voorspelde CFR, fungeert als een nieuw hulpmiddel om reeds voor het verrichten van revascularisatie te kunnen voorspellen wat het effect van revascularisatie op CFR zal zijn. De validiteit van de berekeningen die aan deze parameter ten grondslag liggen werd eerst getest in een meta-analyse van beschikbare studies waarin zowel FFR als CFR werd gemeten en werd vervolgens gevalideerd met metingen verkregen uit het hartkatheterisatie laboratorium. De belangrijkste bevinding in dit onderzoek is een redelijke concordantie tussen de voorspelde en direct gemeten post-procedurele CFR-waarde, zowel in de meta-analyse als in de direct verkregen metingen. Van alle voor revascularisatie beschikbare fysiologische parameters bleek de voorspelde CFR-waarde de enige onafhankelijke voorspeller van de daadwerkelijke post-procedurele CFR-waarde. Met deze bevindingen ondersteunt dit Hoofdstuk het gebruik van het concept voorspelde CFR om eenvoudig additionele informatie uit beschikbare intracoronaire fysiologische metingen te halen.

Toekomstperspectieven

Het uiteindelijke doel van iedere diagnostische test in het kader van ischemische hartziekte is de identificatie van die componenten die leiden tot klinische symptomen en het ontstaan van slechte klinische uitkomsten. Bovendien moet een dergelijke ideale diagnostische test in staat zijn om direct een indicatie te stellen voor behandeling van die componenten waarvan de balans tussen risico en voordeel positief is voor de gekozen interventie, onafhankelijk of deze bestaat uit medicamenteuze, percutane of chirurgische behandeling. Het beschikbare bewijs suggereert sterk dat slechte klinische uitkomsten gerelateerd aan ischemische hartziekte ontstaan door een combinatie van focale vernauwing van de kransslagaderen, microvasculaire dysfunctie en diffuse epicardiale atherosclerose.[11,12] In dit kader, en zoals eerder besproken, geeft FFR waardevolle informatie betreffende focale vernauwingen, maar negeert deze meting het belang van de andere componenten van ischemische hartziekte. Gezien het bestaan van substantieel bewijs voor een belangrijke prognostische waarde van microvasculaire dysfunctie en diffuse epicardiale atherosclerose voor het ontstaan van slechte klinische uitkomsten, lijkt het vanzelfsprekend dat de additionele informatie die verkregen kan worden uit de bloedstroom- en microvasculaire weerstandsmetingen besproken in dit proefschrift toegevoegde waarde moeten hebben boven op die verkregen via FFR. Of dergelijke meer complexe diagnostiek leidt tot verbetering van symptomen of klinische uitkomsten in patiënten met ischemische hartziekten dient verder te worden onderzocht.

Selectie van vernauwingen voor revascularisatie

Cardiologen worstelen al jaren om de juiste hoog-risico atherosclerotische veranderingen in de kransslagaderen te selecteren voor revascularisatie. De DEFER en FAME studies hebben laten zien dat die atherosclerotische plaques die tijdens coronaire vasodilatatie leiden tot een significant drukverval over de vernauwing zijn geassocieerd met een hogere frequentie van spoed-revascularisatie. Tegenovergesteld dragen plaques die niet leiden tot een belangrijk drukverval een relatief laag risico op slechte klinische uitkomsten.[1,13] Belangrijk is de observatie dat, in vergelijking met FFR, zowel iFR[14] als Pd/Pa[15] beter overeenkomen met de vasodilatoire reserve in het vasculaire bed, mogelijk vanwege het "Hawthorne effect" van coronaire vasodilatatie zoals boven beschreven. Dit is een belangrijke diagnostische karakteristiek, omdat de betere overeenkomst van niet-hyperaemische parameters met de vasodilatoire reserve de mogelijkheid genereert dat selectie van vernauwingen voor revascularisatie met dergelijke non-hyperaemische parameters invasieve behandeling met PCI beter richting die vernauwingen dirigeert die daadwerkelijk de bloedstroom in het bloedvat hinderen, waarmee mogelijk klinische uitkomsten kunnen worden verkregen die beter zijn dan die met FFR. Momenteel onderzoeken twee gerandomiseerd klinische studies, de DEFINE FLAIR en iFR-SWEDEHEART, of een iFR-gestuurde strategie tot gelijkwaardige klinische uitkomsten leidt in vergelijking met de standaard FFR-gestuurde strategie. Een alternatieve diagnostische strategie waarbij gebruik wordt gemaakt van gecombineerde intracoronaire druk- en bloedstroommetingen wordt momenteel geëvalueerd in de DEFINE-FLOW studie (Combined Pressure and Flow Measurements to Guide Treatment of Coronary Stenoses; Clinical trials identifier: NCT02328820). Deze studie onderzoekt de veiligheid van het uitstellen van revascularisatie in vernauwde kransslagaderen met abnormale FFR-waarden en normale CFR-waarden, en zal derhalve nieuwe inzichten geven in dit fenomeen. Gezien de neutrale resultaten van de COURAGE studie (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) en de BARI 2D studie (Bypass Angioplasty Revasularization Investigation 2 Diabetes),[16,17] is een verdere zoektocht naar optimalisatie van de selectie van vernauwingen voor revascularisatie van kritisch belang voor het veld.

Part F

Appendices

List of publications

Included in the thesis

Part A

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Curriculum vitae

Mauro Echavarría Pinto was born on the 14th of August 1980 in Santiago de Querétaro, Querétaro, México. After graduating from high school in 1998, he was admitted in the Autonomous University of Querétaro, México, to study medicine. He completed medical school in 2005, and then started a fellowship in internal medicine, at the National Institute of Health Sciences and Nutrition "Salvador Zubirán", followed by a fellowship in clinical cardiology, at the National Institute of Cardiology "Ignacio Chávez", both in México City, México. Throughout his medical training, Mauro earned several academic achievements, including the best medicine student of Class 2005, best cardiology fellow of Class 2011, and the first place in the National Cardiology Board Exams in 2011. After his core cardiology training, he pursued interventional cardiology skills at the Cardiovascular Institute, Hospital Universitario Clinico San Carlos, Madrid, Spain. In total, he spent almost 5 years in this Institution performing coronary and peripheral interventions. In 2014, he entered his PhD program at the Cardiology Department of the Academic Medical Center in Amsterdam, The Netherlands, under the supervision of promotors prof. dr. J.J. Piek and prof. dr. P.W. J.C. Serruys, and co-promotors prof. dr. J. Escaned and dr. H.M. García García. The research focused on the application of coronary physiology to the evaluation of ischaemic heart disease. Part of this research resulted in the thesis: 'Comprehensive assessment of ischaemic heart disease with invasive pressure and flow measurements'. In 2016, Mauro completed a MSc in clinical research, design and statistics of health sciences from the Autonomous University of Barcelona, Spain, and moved back to Santiago de Querétaro, Querétaro, México, where he currently works as an interventional cardiologist.

Portfolio

PhD student:	Mauro Echavarría Pinto
PhD period:	2014 –2017
Supervisors:	Prof. dr. J.J. Piek, and prof. dr. P.W. J.C. Serruys
Co-supervisors:	prof. dr. J. Escaned and dr. H.M. García García

Education

2014 – 2017	PhD. University of Amsterdam, Amsterdam, The Netherlands.
2012 – 2016	MSc in methodology of clinical research, design and statistics of health sciences. Autonomous University of Barcelona, Spain. (63 ECTS)
2011 – 2015	Fellowship in interventional cardiology. Cardiovascular Institute, Hospital Clinico San Carlos, Madrid Spain.
2011 – 2013	Master in interventional cardiology. Complutense University of Madrid, Spain.
2008 – 2011	Fellowship in cardiology. National Institute of Cardiology "Dr. Ignacio Chavez", Mexico. National Autonomous University of México.
2006 – 2008	Fellowship in internal medicine. National Institute of Medical Sciences and Nutrition "Dr. Salvador Zubiran", Mexico. National Autonomous University of México.
1998 – 2005	Degree in medicine. Faculty of Medicine, Autonomous University of Queretaro, México.

Honors

2013	First place "XX Scientific Award Hospital Clinico San Carlos". To the best original scientific publication published in 2013. Hospital Clínico San Carlos, Madrid, Spain.
2011	First place in the national board exam. Mexican Society for Certification in Cardiology, México.
2011	Best fellow of class 2011 ("SIBIC" Award). National Institute of Cardiology "Dr. Ignacio Chávez" Mexico City, Mexico.
2005	Best student of class 2005 ("Gonzalo Río Arronte Award"). Faculty of Medicine, Autonomous University of Querétaro, Mexico.
2005	"Honorary mention award". Faculty of Medicine, Autonomous University of Querétaro, México.
2005	Excellent Performance Award. National Center for the Evaluation of Higher Education in México.

Competitive scholarships

2013 - 2015	Clinical/Research scholarship. "Fundación de Investigación y Desarrollo Área Cardiovascular (FIC)". Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Spain.
2012 - 2013	Scholarship for postgraduate studies. Ministry of Health. Querétaro City, México.
2009 - 2011	Scholarship for postgraduate studies. National Council of Science and Technology (CONACYT), México.
2008 - 2010	Scholarship for postgraduate studies. "Promising Youth in Health, Nutrition and Environmental Investigation ". Carso Health Institute, México.

Positions of responsability

2010 - 2011	Second-resident in Chief. National Institute of Cardiology "Dr. Ignacio Chávez" Mexico city, México.
2009 - 2010	Team Leader. Coronary care unit. National Institute of Cardiology "Dr. Ignacio Chávez" México City, México.
2003 - 2004	Secretary of community outreach and social assistance. Faculty of Medicine, Autonomous University of Queretaro, México.

Scientific activity

2014-today	Associate Editor, "BMC Cardiovascular Disorders"
2015-today	Associate Editor, "Archivos de Cardiología de México"
Reviewer	Journal of the American Collegue of Cardiology, Eurointervention, International Journal of Cardiology, BMC Cardiovascular Disorders, International Journal of Cardiovascular Imaging.

Oral presentations

EuroPCR 2012, Paris, France
EuroPCR 2013, Paris, France
Transcatheter Cardiovascular Therapeutics 2014, Miami, US
Advances in Coronary Physiology 2014, Imperial College, London, UK.
Advances in Coronary Physiology 2015, Imperial College, London, UK.
EuroPCR 2015, Paris, France
EuroPCR 2015, Paris, France
EuroPCR 2015, Paris, France
Cardiovascular Research Technology 2015, Washington D.C.

Member of

European Association of Percutaneous Cardiovascular Interventions (EAPCI).
Working Group on Coronary Pathophysiology and Microcirculation (WGCPM) of the European Society of Cardiology.
Sociedad Mexicana de Cardiología (SMC).
Sociedad Mexicana de Cardiología Intervencionista (SOCIME).

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Hospital Universitario Clínico San Carlos, Madrid, España
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