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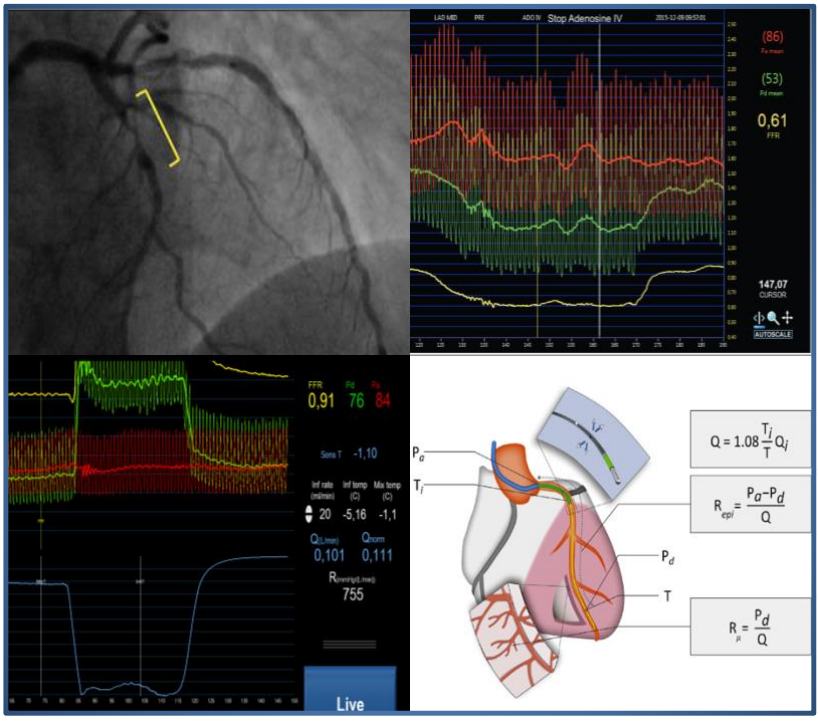

Towards a comprehensive understanding of coronary physiology: from the basics to applications in patients with comorbidities and current trends.

PhD thesis

Giuseppe Di Gioia, MD

Towards a comprehensive understanding of coronary physiology: from the basics to applications in patients with comorbidities and current trends.

PhD thesis

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"We live on an island surrounded by a sea of ignorance. As our island of knowledge grows, so does the shore of our ignorance"

John Archibald Wheeler

"What I've learnt from a traveller…There's a world to discover, but Home is Love"

Jacob Banks

To Antonia,

Myriam, and Camilla

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CHAPTER 1

General introduction and outline of the thesis

For decades, invasive coronary angiography has been the only available tool to define the presence and extent of obstructive coronary artery disease (CAD), and to guide revascularization[1]. However, coronary angiography produces 2-dimensional silhouette images of the 3-dimensional vascular lumen. Angiographic assessment is highly operator and view-dependent, and suffers from several artifacts, such as branch overlap, vessel foreshortening, or calcifications. Besides, the angiographic severity of coronary narrowings has been shown to be a poor predictor of the physiological behavior of epicardial coronary stenoses. In fact, the lack of information regarding the myocardial mass subtending the stenosis and the microvascular function may be responsible for a misjudgement even among expert operators, which may occur in up to 35% of the cases[2].

In the early 1990's, the scenario began to change as fractional flow-reserve (FFR) was introduced. FFR is a flow index, defined as the ratio of maximal hyperemic myocardial blood flow in the presence of a stenosis to the physiologic maximal hyperemic myocardial blood flow in the same territory but in the absence of any stenosis[3-5]. As such, its value is influenced and integrates hyperaemic flow, which itself depends on stenosis severity, myocardial mass, and its microvascular function. Since mass and microvascular function are not likely to change in a given patients before and after revascularization, FFR indicates to what extent hyperaemic myocardial flow will increase after percutaneous coronary intervention (PCI) (i.e. normalization of the epicardial resistance)[6,7]. FFR overcomes the visual-functional mismatch and stands alone in measuring ischemia in the catheterization laboratory with validated and durable clinical data supporting its use for predicting outcomes. Fifteen-year outcome data from the DEFER (Deferral vs. performance of percutaneous coronary intervention of functionally nonsignificant coronary stenosis)

study demonstrate that postponing PCI in vessels with an FFR >0.75 is safe and associated with a low rate of clinical endpoints[8], whereas the FAME-2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation-2) study, among others, showed that patients with an abnormal FFR (i.e., lesion-specific ischemia) benefit more from revascularization than continued optimal medical therapy[9-11]. The evidence supporting the use of FFR in clinical practice, especially in patients with chronic coronary syndrome, is so overwhelming that current European guidelines give it a Class IA recommendation for guiding revascularization when a non-invasive test of ischemia is not available[12,13].

Interestingly, over the last few years, operators have expanded their use of physiology to patients initially excluded from randomized controlled trials. For instance, after the widespread adoption of transcatheter aortic valve implantation (TAVI), the management of coronary disease in patient with severe aortic stenosis has shifted from exclusively surgical to a heart-team decision potentially favouring PCI and TAVI[14]. Since non-invasive detection of ischemia induced by epicardial coronary disease is particulary cumbersome in these patients, coronary physiology may prove very useful. However, the use of FFR has been questioned in these patients owing to safety concerns, and the supposed inability to reach maximum hyperemia after adenosine administration.

Anther potential subset of patients in whom coronary physiology might be of help in guiding revascularization is represented by patients with heart failure (HF). In fact, in patients with reduced left ventricular ejection fraction (LVEF) and CAD the indication to revascularization is often controversial. Myocardial stunning, hibernation, the presence and extent of myocardial scar and ischemia all play a role in the pathogenesis of left ventricular systolic dysfunction, and each of these aspects can be evaluated by different imaging modalities. Yet, non-invasive stress imaging in patients with coronary artery disease and HF with reduced LVEF has only a class IIb indication for guiding revascularization, de facto creating a clinical need for a decision-making test in these patients[15].

In this thesis, we report the very first studies reporting long-term clinical outcome of FFR-guided revascularization in patients with aortic stenosis, and in patients with reduced ejection fraction. Also, technical aspects regarding the reliability of coronary physiology assessment in these patients are investigated.

The success of FFR is partly explained by its ease of interpretation. Treatment decision-making is based on 1 FFR value, which provides a vessel-level metric as it is used as a surrogate of myocardial ischemia. However, FFR as a point estimate provides the sum of epicardial resistances generated by focal stenoses and diffuse atherosclerotic disease, but it does not allow to discern the individual contribution of these types of disease on flow impairment, nor it allows to predict the functional result of PCI[16]. The distribution of epicardial resistance can be evaluated using an FFR pullback maneuver[7]. This technique reveals the contribution of focal and/or diffuse CAD in terms of FFR drop along the coronary vessel. Recently, the experimental motorization of pressure pullbacks allowed the standardization of the pressure-length relationship. In this thesis, we report the first studies introducing the Pressure Pullback gradient index (PPG index), a new metric which varies between 0 and 1 and is directly proportional to the focality of epicardial disease. A PPG index close to 1 represents indeed a very focal disease. On the other hand, a low PPG is associated with diffuse disease, and is a predictor of poor functional PCI outcome.

Although the majority of patients with angina have some degree of epicardial coronary disease, it is now clear that microvascular dysfunction alone can cause ischemic symptoms in the absence of epicardial obstruction[17-19] and may contribute to persistent ischemia despite successful revascularization[20]. The microcirculation has historically been considered a mysterious “black box”, due to the lack of effective diagnostic tests. In 2003, William Fearon introduced the index of microvascular resistance (IMR), defined as distal coronary pressure divided by the inverse of the hyperemic mean transit time (a correlate to absolute flow), measured simultaneously with the coronary pressure wire[21-25] after the injection of a small

bolus of cold saline. The advantages of IMR include that is relatively easy to measure and can be performed simultaneously while measuring FFR without any extra equipment, is specific for the microvasculature and is independent from hemodynamic variability[26-28]. Still, it is not known whether therapeutic reduction of IMR (e.g. with an intracoronary vasodilator) confers clinical benefits. Nor is it known whether, in patient with stable CAD, treatment decisions based on an IMR threshold might have prognostic benefits (as has been shown to be the case with FFR). Also, during IMR assessment an intrinsic variability of resting mean transit time (Tmn_{rest}) of 7-10%, and Tmn_{hyp} of 4-8% has been reported.

IMR, however, is a surrogate of microvascular resistance but does not provide any information about the flow or the absolute resistance. At this regard, a recent development of a dedicated monorail infusion catheter (Rayflow™, Hexacath, Paris, France) has made possible the measurement of absolute coronary flow (Q) and microvascular resistance (R) in the cathlab, opening a new window to the coronary microcirculation. The present method relies on a simple basic principle. Three parameters should be known: the infusion rate of saline (in mL/min), the temperature of the saline when it enters the coronary tree (in degrees), and the temperature of the blood when saline and blood have been mixed in the distal part of the artery (in degrees). This rule of three allows the calculation of absolute Q[29]. The calculated flow is hyperemic flow because it has been shown that the infusion of saline at room temperature through the RayFlow catheter reliably uniformly induces maximal hyperemia[30]. A major advantage of this method is that—in contrast to Doppler or index of microcirculatory resistance—it is completely operator independent. The saline infusion can be continued until a true steady state is achieved (typically within 10–15 seconds), and during the entire measurement sequence, the operator does not touch the patient nor any catheter. In this thesis we present the first study reporting normal values of absolute coronary blood flow and microvascular resistance, and the demonstration that continuous

thermodilution also allows to compute resting absolute coronary flow, and thus coronary flow reserve.

Outline of the thesis

The thesis is divided in six parts:

Part I. Rediscovering the basics of coronary physiology. In the first part of the thesis we report two research projects aimed at confirming in humans some basics concepts of coronary physiology. In one paper (Chapter 2) the microcirculatory plateau of autoregulation, which is the ability of the heart to maintain resting coronary flow constant when perfusion pressure changes, was investigated in humans for the first time, whereas historical experiments were performed in dogs. In 26 stable patients with an isolated stenosis in the left anterior descending artery (LAD), [15O]H2O-positron emission tomography–derived blood flow and invasive distal coronary pressure were measured within 24 h. We found that a constant myocardial blood flow is present over a wide range of perfusion pressures (46 to 124 mm Hg). In another paper (Chapter 3) we demonstrated the linearity of the pressure-flow relationship during hyperemia in a patient immediately after PCI. This linearity, which constitutes the cornerstone of FFR, had been described in anesthetized open-chest dogs, but had never been demonstrated in humans.

Part II. Fractional flow reserve in clinical practice. In the second part of the thesis we report a cluster of research projects that focus on the importance of the FFR assessment of epicardial stenosis in patients with stable CAD. The studies hereby reported analyze procedural aspects of FFR measurement (Chapter 4 and 6), the prognostic value of FFR (Chapters 5 and 8), and the current use of coronary physiology in European cathlabs (Chapter 7).

Part III. Coronary physiology in patients with comorbidities. This section of the thesis is a collection of our research projects aimed at investigating the role of invasive functional assessment in patients with specific comorbidities, often

associated with coronary artery disease, that might potentially hamper invasive physiology-based assessment of coronary stenoses.

This part is further subdivided in three main topics: Aortic valve stenosis (Part IIIa); Heart Failure (Part IIIb); Diabetes mellitus (Part IIIc).

Part IV. Characterization of pattern of epicardial atherosclerosis. In this section, we report studies that represent a step forward in the characterization of the distribution of atherosclerosis in CAD. By means of motorized hyperemic pullbacks of a pressure wire, pullback curves were built and a new metric of the focality (or diffuseness) of the disease was introduced (Pullback pressure gradient index, PPG index).

Part V. Invasive assessment of coronary microcirculation. This part of the thesis is a collection of research projects aimed at evaluating coronary microvascular function by means of either bolus thermodilution (index of microvascular resistance, IMR), or continuous thermodilution (Absolute flow and resistance) methods. Chapters from 23 to 26 focus on the evaluation of specific antiplatelet drugs (clopidogrel or prasugrel) or devices (drug-eluting stents or bioresorbable vascular scaffold) on platelet reactivity, IMR, and periprocedural myocardial injury after PCI. Chapters from 27 and 28 respectively report normal values of thermodilution-derived absolute flow and resistance, and show the feasibility of resting coronary flow calculation by continuous thermodilution. Chapter 29 is a state of the art review on coronary thermodilution.

Part VI: Discussion and conclusions. The last section of the thesis is a broad discussion of the addressed topics with the conclusions.

Part I

Rediscovering the basics of coronary physiology

CHAPTER 2

Coronary Autoregulatory Plateau in Humans.

The ability of the heart to maintain resting coronary flow constant when perfusion pressure changes is generally referred to as “coronary autoregulation.” This mechanism is essential because even a modest reduction in resting flow (10% to 20%) is associated with significant contractile dysfunction. The range of pressures over which this autoregulation applies (i.e., the “autoregulatory plateau”) was initially described to be between 70 and 130 mm Hg in anesthetized dogs. Experiments in conscious dogs showed that the lower boundary of the autoregulatory plateau can be as low as 40 mm Hg. In patients with severe coronary stenoses, often presenting with distal coronary pressure lower than 70 mm Hg, it is not uncommon to observe a normal systolic wall motion of the myocardial territory perfused by the stenotic vessel. However, the lower limit of the autoregulatory range has not been described in humans. In 26 stable patients (age 56 $\pm$ 8 years, 82% men), with strictly normal ventricular wall motion (LVEF 64 $\pm$ 6%) and an isolated stenosis in the left anterior descending artery (LAD), [15O]H_2O-positron emission tomography–derived blood flow and invasive distal coronary pressure were measured within 24 h. Informed consent as approved by the local ethics committee for the use of personal data was obtained from each patient. Diameter stenosis by quantitative angiography ranged from 22% to 77%. Methods and patients’ characteristics have been detailed previously (2). Figure 1 displays the relationship between mean pressure at rest in the distal LAD and the corresponding resting myocardial perfusion in the territory of the LAD. A constant myocardial blood flow is present (range 0.73 to 1.94 ml $\cdot$ s^{-1} $\cdot$ g^{-1}) over a wide range of perfusion pressures (46 to 124 mm Hg) (regression equation: MBF = 0.00291* Pd + 1.032; slope = 0.00291 [95% confidence interval: -0.0034 to 0.00922]; R2 = 0.036; p = 0.36).

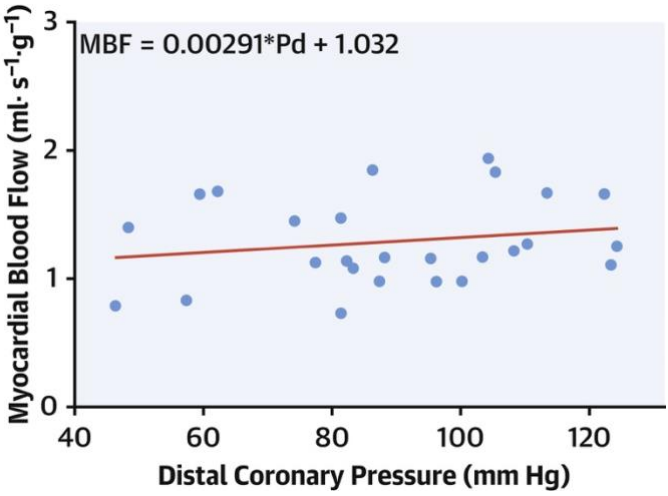


Figure 1. Myocardial blood flow (MBF) was assessed by 15O-labeled water positron emission tomography (PET) and distal coronary pressure (Pd) by a pressure wire. All 26 patients had an isolated stenosis in the proximal or mid-left anterior descending coronary artery and a normal regional left ventricular wall motion. A constant myocardial blood flow is present (range 0.73 to 1.94 ml · s^{-1} · g^{-1}) over a wide range of perfusion pressures (46 to 124 mm Hg) (regression equation: MBF = 0.00291* Pd + 1.032; slope = 0.00291 [95% confidence interval: -0.0034 to 0.00922]; R2 = 0.036; p = 0.36).

The present data indicate that down to mean driving pressures as low as 45 mm Hg, autoregulatory mechanisms are able to compensate for the increased epicardial resistance to maintain resting blood flow and contractile function. In our study very severe stenoses were not included, and we cannot exclude that the lower boundary of the autoregulation plateau in humans could be even lower than 45 mm Hg. Nevertheless, these findings are in line with the knowledge that collateral perfusion pressure of more than 30 to 40 mm Hg protects against systolic wall motion abnormalities. The clinical implication is that the severity of an epicardial narrowing predicts neither resting flow nor resting left ventricular wall motion, and, conversely, that a normal segmental wall motion (as assessed at echocardiography or at left ventricular angiography) is generally associated with a flow equal or larger to its normal resting value. The typical situation where this phenomenon is important is in patients admitted for an acute myocardial infarction and multivessel disease, especially when cardiogenic shock is present. Performing immediate percutaneous

coronary intervention (PCI) of a nonculprit lesion supplying a normally contracting segment offers no potential immediate benefit (i.e., resting myocardial perfusion and regional wall motion will not improve). In contrast, additional catheter manipulation and immediate multivessel PCI at the acute stage translated in higher death rates than PCI of the culprit lesion only as demonstrated in the CULPRIT-SHOCK (The Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial. Staged procedures for nonculprit stenoses might prevent a future event and will likely increase hyperemic flow, but are unlikely to improve resting flow or regional wall motion.

CHAPTER 3

Hyperemic Pressure-Flow Relationship in a Human

Fractional flow reserve (FFR) represents the ratio of hyperemic flow in the presence of an epicardial stenosis to hyperemic flow in the hypothetical absence of this stenosis. FFR can be calculated from hyperemic pressure measurements, provided the relationship between flow and pressure during hyperemia is linear. This linearity, which constitutes the cornerstone of the concept, has been described in anesthetized open-chest dogs, but has never been demonstrated in humans. The relationship between coronary flow and coronary driving pressure during maximal microvascular vasodilation was investigated in 1 patient immediately upon percutaneous coronary intervention (PCI).

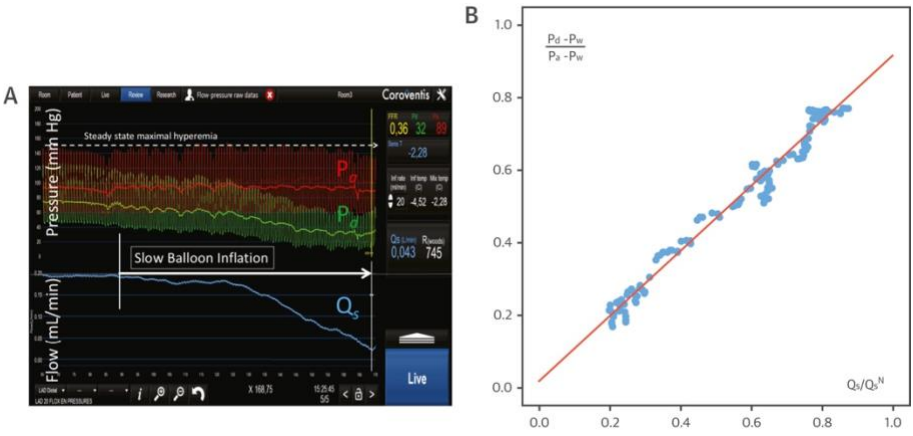


Figure 2. Simultaneous Recordings of Pa, Pd, and Qs in the Proximal LAD Across a Graded, Controlled Stenosis Induced by the Inflation of a Balloon in the Stented Segment

(A) Plots of the corresponding hyperemic coronary driving pressure and flow values. Aortic pressure (Pa) (red) and distal coronary pressure (Pd) (green) are corrected for a measured coronary wedge pressure (Pw) of 20 mm Hg. Hyperemic flow (Qs) is shown in blue. (B) From the initial 11,000 values, only 200 are displayed after random sampling (see text for details). LAD = left anterior descending coronary artery.

Figure 2 shows continuous thermodilution-derived hyperemic flow and pressure recordings during creation of a graded stenosis in the left anterior descending

coronary artery (LAD) and the corresponding hyperemic pressure-flow relationship obtained in a 61-year-old man immediately upon PCI of an isolated stenosis in the proximal LAD. The patient gave informed consent to perform intracoronary pressure and flow measurements in agreement with the local medical ethical committee. A drug-eluting stent (3.0 × 18 mm) was placed in the proximal LAD and post-dilated with a 3.5 noncompliant balloon. Immediately upon PCI of a proximal LAD, a RayFlow catheter (Hexacath, Paris, France) was advanced over a pressure/temperature sensor wire in the proximal LAD, connected to a Coroventis CoroFlow System (Uppsala, Sweden). Over the regular wire, an 8-mm-long semicompliant balloon (with a nominal diameter 0.5 mm smaller than the implanted stent) was advanced in the stented segment. Saline at room temperature was infused at 20 ml/min through the RayFlow catheter to measure hyperemic absolute flow. Under this steady state hyperemia, the balloon catheter was slowly inflated to obtain a graded, controlled stenosis. Figure 2A shows the simultaneously recorded aortic and distal coronary pressures and thermodilution-derived proximal LAD flow (QS) during steady state maximal hyperemia. Figure 2B shows the corresponding hyperemic pressure-flow relationship. Aortic and distal coronary pressures were corrected for a coronary wedge pressure of 20 mm Hg (Pw, measured but not displayed). This relationship is linear, and its intercept is close to zero ($y = 0.87x + 0.04$; $R = 0.99$ [95% confidence interval: 0.98 to 0.99]; $p < 0.001$).

These results confirm earlier animal data and demonstrate the linearity of the hyperemic pressure/flow relationship during hyperemia in humans, thus confirming the theoretical background of FFR measurements

Part II

Fractional Flow-Reserve in clinical practice

CHAPTER 4

Intracoronary Adenosine: Dose-Response Relationship With Hyperemia

The present study sought to establish the dosage of intracoronary (IC) adenosine associated with minimal side effects and above which no further increase in flow can be expected.

Background: Despite the widespread adoption of IC adenosine in clinical practice, no wide-ranging, dose-response study has been conducted. A recurring debate still exists regarding its optimal dose.

Methods: In 30 patients, Doppler-derived flow velocity measurements were obtained in 10 right coronary arteries (RCAs) and 20 left coronary arteries (LCAs) free of stenoses >20% in diameter. Flow velocity was measured at baseline and after 8 ml bolus administrations of arterial blood, saline, contrast medium, and 9 escalating doses of adenosine (4 to 500 µg). The hyperemic value was expressed in percent of the maximum flow velocity reached in a given artery (Q/Qmax, %).

Results: Q/Qmax did not increase significantly beyond dosages of 60 mg for the RCA and 160 mg for LCA. Heart rate did not change, whereas mean arterial blood pressure decreased by a maximum of 7% ($p < 0.05$) after bolus injections of intracoronary (IC) adenosine. The incidence of transient A-V blocks was 40% after injection of 100 µg in the RCA and was 15% after injection of 200 µg in the LCA. The duration of the plateau reached 12 13 s after injection of 100 µg in the RCA and 21 6 s after the injection of 200 µg in the LCA. A progressive prolongation of the time needed to return to baseline was observed. Hyperemic response after injection of 8 ml of contrast medium reached 65 36% of that achieved after injection of 200 µg of adenosine (Figure 3).

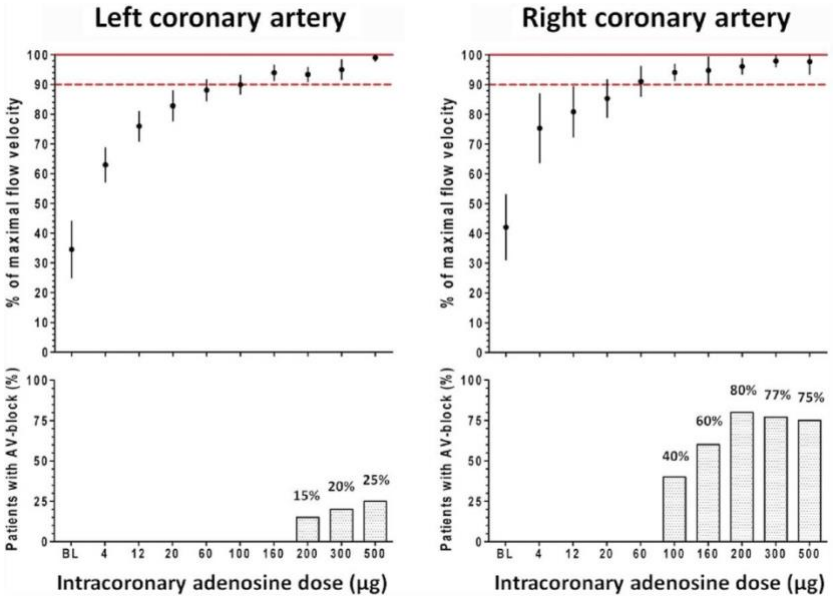


Figure 3: Intracoronary adenosine dose-flow relationship. (Top) Dose-response data for the right coronary artery (RCA) (left panel) and the left coronary artery (LCA) (right panel). The data are expressed as the percent of maximum for each patient (Q/Qmax) at each dose of intracoronary (IC) adenosine. The error bars represent the 95% confidence intervals for each value. (Bottom) The bars represent the percent of patients in whom high-grade atrioventricular (AV) block occurred with that dose of adenosine. BL: baseline.

Conclusions: This wide-ranging, dose-response study indicates that an IC adenosine bolus injection of 100 µg in the RCA and 200 µg in the LCA induces maximum hyperemia while being associated with minimal side effects.

CHAPTER 5

Significance of Intermediate Values of Fractional Flow Reserve in Patients With Coronary Artery Disease

Background: FFR represents the standard of reference for invasive functional evaluation of the ischemic potential of coronary stenosis and is a valuable tool to guide percutaneous revascularization. An FFR value ≤0.75 is almost uniformly associated with signs of ischemia, whereas an FFR >0.80 is usually associated with the absence of ischemia. Based on numerous randomized trials and registries in most subsets of lesions and patients, the threshold value of 0.80 has been widely accepted to guide clinical decision making. The best treatment strategy for intermediate stenosis with FFR in the narrow gray zone of values, that is, between 0.76 and 0.80, has been questioned. Therefore, we analyzed the long-term clinical outcome of patients with an isolated stenosis within the gray zone (0.76–0.80) or immediately next to the gray zone (0.70–0.75 and 0.81–0.85).

Methods: From February 1997 to June 2013, all patients with single-segment disease and an FFR value within the gray zone or within the 2 neighboring FFR strata (0.70–0.75 and 0.81–0.85) were included. Study end points consisted of major adverse cardiovascular events (death, myocardial infarction, and any revascularization) up to 5 years.

Results: Of 17 380 FFR measurements, 1459 patients were included. Of them, 449 patients were treated with revascularization and 1010 patients were treated with medical therapy (Figure 8). In the gray zone, the major adverse cardiovascular events rate was similar (37 [13.9%] versus 21 [11.2%], respectively; P=0.3) between medical therapy and revascularization, whereas a strong trend toward a higher rate of death or myocardial infarction (MI) (25 [9.4] versus 9 [4.8], P=0.06) and overall death (20 [7.5] versus 6 [3.2], P=0.059) was observed in the medical therapy group (Figure 4). Among medical therapy patients, a significant step-up increase in major adverse

cardiovascular events rate was observed across the 3 FFR strata, especially with proximal lesion location. In revascularization patients, the major adverse cardiovascular events rate was not different across the 3 FFR strata (Figure 5).

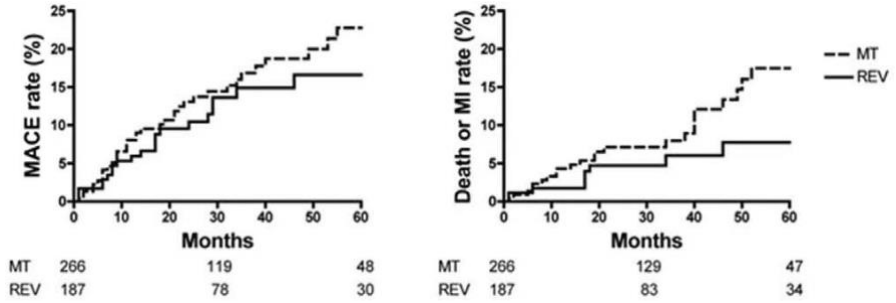


Figure 4: Cumulative rate (%) of MACE (log-rank, 0.87; P=0.3) and death or MI (log-rank, 2.96; P=0.08) in the gray-zone patients treated with medical therapy or revascularization. MACE indicates major adverse cardiovascular event; MI, myocardial infarction; MT, medical therapy; and REV, revascularization.

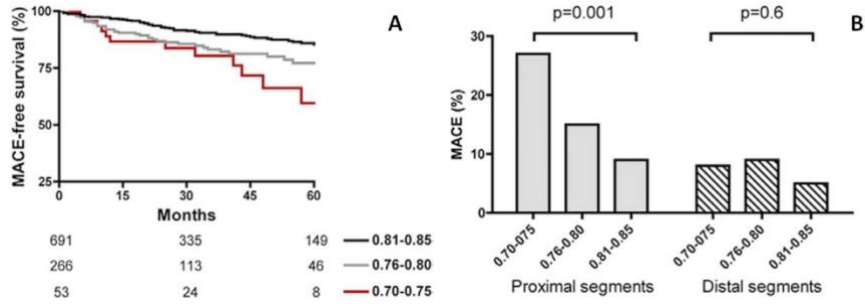


Figure 5: A) MACE-free survival (%) in patients of the medical therapy group stratified by FFR strata (log-rank, 15; P<0.001). B) MACE rate (%) in patients receiving medical therapy, stratified according to the FFR strata, and grouped according to the location of the lesions (proximal vs distal). FFR indicates fractional flow reserve; and MACE, major adverse cardiovascular event.

Conclusions: Patients with an isolated stenosis located in a proximal coronary segment and FFR within the gray zone of 0.76 to 0.80. demonstrate a clinical outcome that is suboptimal when deferred to medical therapy alone. These data

confirm the value of the 0.80 FFR threshold, and favor a revascularization strategy of coronary stenoses with FFR ≤0.80.

CHAPTER 6

Detect fractIonal flow reServe of Epicardial steNosis with Guiding cAtheter disenGagEment: DISENGAGE registry.

Background: During fractional flow reserve (FFR) measurement, the simple presence of the guiding catheter (GC) within the coronary ostium might create artificial ostial stenosis, affecting the hyperemic flow. We aimed to investigate whether selective GC engagement of the coronary ostium might impede hyperemic flow, and therefore impact FFR measurements and related clinical decision-making.

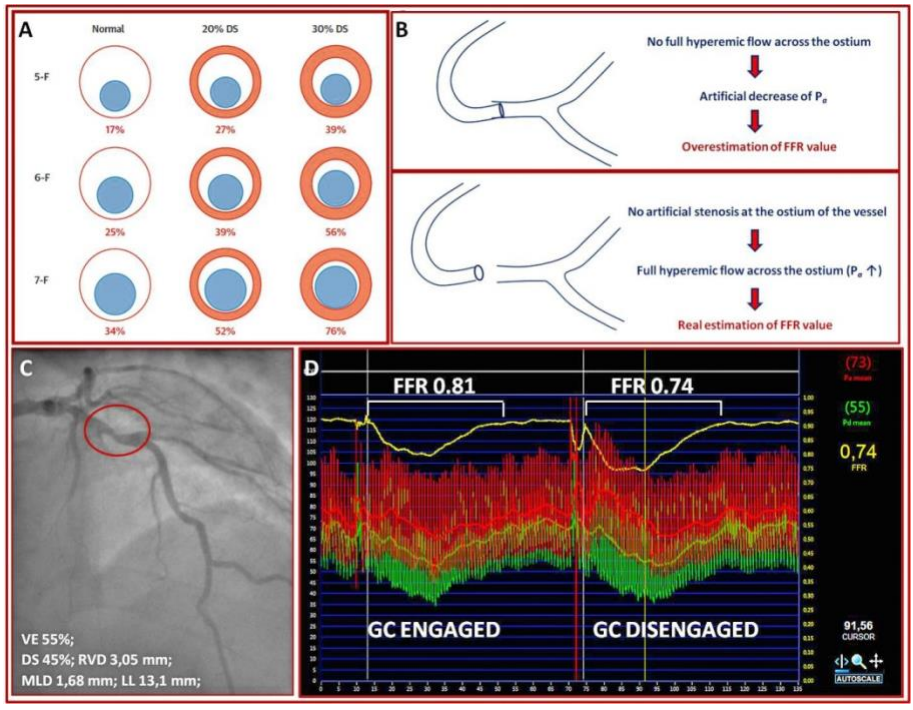


Figure 6: A) impact of different size of GCs on the relative diameter of the coronary ostium, with and without stenosis; B) mechanism of artificial decrease of the mean aortic pressure (P_a) and a final overestimation of FFR value; C) Angiographic example of intermediate stenosis and D) the corresponding FFR measurements with GC ingaged and GC disengaged. GC= guiding catheter; FFR= fractional flow reserve; VE= visual estimation; DS= diameter stenosis; RVD= reference vessel diameter; MLD= minimal lumen diameter; LL= lesion length.

Methods: In the DISENGAGE (Determination of Fractional Flow Reserve in Intermediate Coronary Stenosis With Guiding Catheter Disengagement) registry, FFR was prospectively measured twice (with GC engaged [FFReng] and disengaged [FFRdis]) in 202 intermediate stenoses (DS 46±10%; MLD 1.6±0.4 mm; RVD 3.0±1.6 mm; LL 15±8 mm) of 173 patients, mostly with stable angina or silent ischemia (98%). Patients with diffuse disease, tandem lesions, left main and aorto-ostial stenosis, and culprit lesions of ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) were excluded. We assessed (1) whether ΔFFReng–FFRdis was significantly different from the intrinsic variability of repeated FFR measurements (test-retest repeatability); (2) whether the extent of ΔFFReng–FFRdis could be clinically significant and therefore able to impact clinical decision-making; and (3) whether ΔFFReng–FFRdis related to the stenosis location, that is, proximal and middle versus distal coronary segments.

Results: Stenoses were located on left anterior descending artery (n=124), diagonal branch (n=3), left circumflex artery (n=28), obtuse marginal branch (n=14), intermediate branch (n=5) and right coronary artery (n=28). Overall, FFR significantly changed after GC disengagement: FFReng 0.84±0.08 versus FFRdis 0.80±0.09, P<0.001. Particularly, in 38 stenoses (19%) with FFR values in the 0.81 to 0.85 range, GC disengagement was associated with a shift from above to below the 0.80 clinical cutoff, resulting into a change of the treatment strategy from medical therapy to percutaneous coronary intervention. The impact of GC disengagement was significantly more pronounced with stenoses located in proximal and middle as compared with distal coronary segments (ΔFFReng–FFRdis, proximal and middle 0.04±0.03 versus distal segments 0.03±0.03; P=0.042).

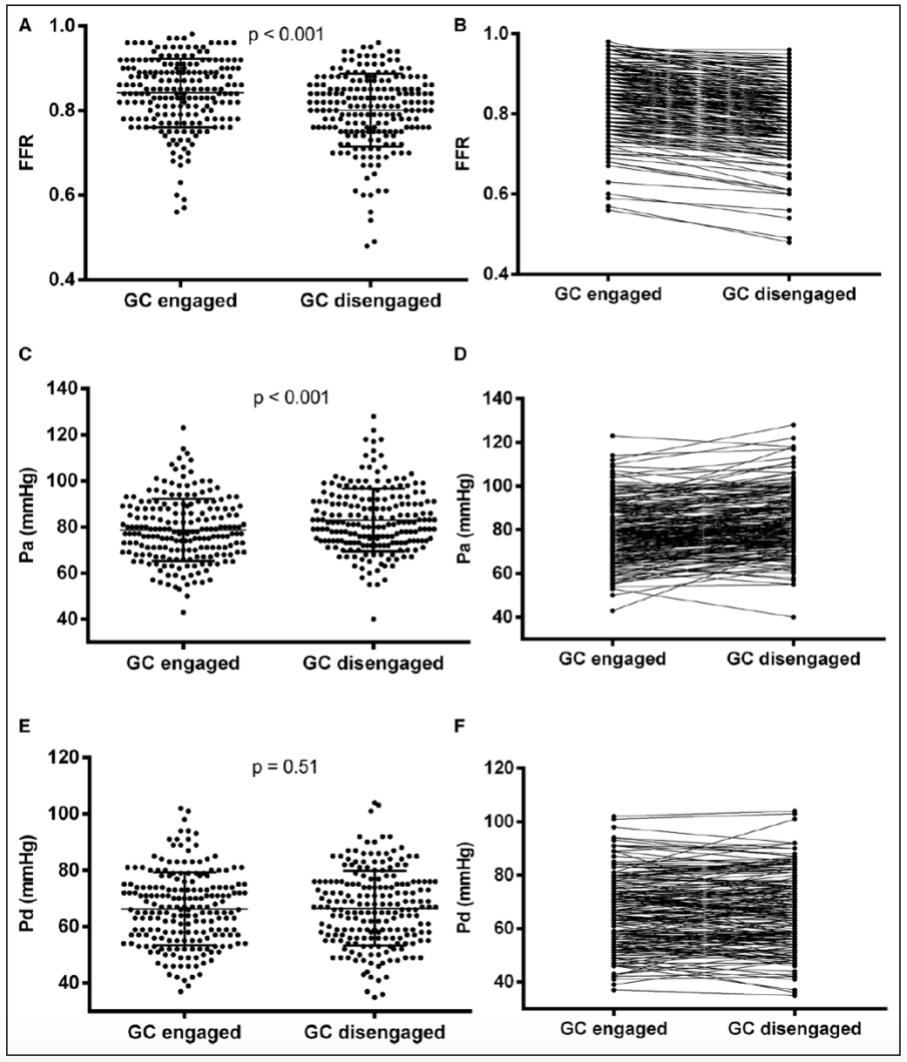


Figure 7. A and B, Fractional flow reserve (FFR) values changes after guiding catheter (GC) disengagement; (C and D) Pa values changes after GC disengagement; (E and F) Pd value changes after GC disengagement.

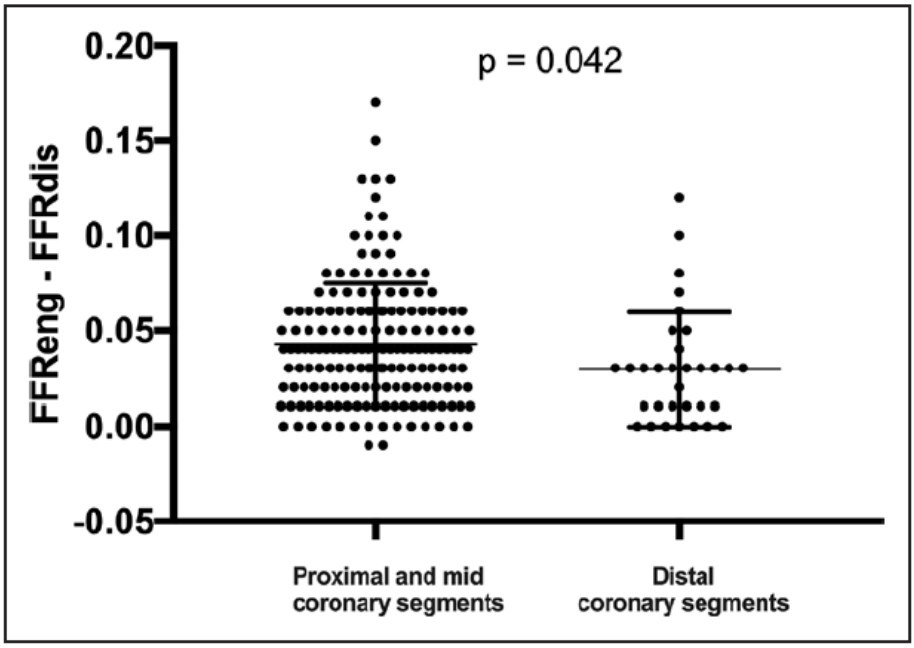


Figure 8. Differences in ΔFFReng–FFRdis between stenoses related to large amount of myocardium (proximal and midsegments) and stenoses related to small amount of myocardium (distal segments and side branches). Proximal and middle segments were proximal left anterior descending artery (LAD), mid-LAD, proximal right coronary artery (RCA), mid-RCA, and proximal left circumflex artery; all other coronary segments were considered as distal.

Conclusions: GC disengagement results in a shift of FFR values from above to below the clinical cutoff FFR value of 0.80 in 1 out of 5 measurements. This occurs mostly when the stenosis is located in proximal and middle coronary segments and the FFR value is close to the cutoff value.

CHAPTER 7

Revascularization Decisions in Patients With Stable Angina and Intermediate Lesions. Results of the International Survey on Interventional Strategy

Background: Fractional flow reserve (FFR) measurement of intermediate coronary stenoses is recommended by guidelines when demonstration of ischemia by noninvasive testing is unavailable. The study aims to evaluate the penetration of this recommendation into current thinking about revascularization strategies for stable coronary artery disease.

Methods: International Survey on Interventional Strategy was conducted via a web-based platform. First, participants' experiences in interventional cardiology were queried. The second part investigated personal strategies for evaluating angiographically intermediate stenoses in the catheterization laboratory. Here, participants evaluated 5 complete coronary angiograms presenting only focal stenoses (n=12) of intermediate severity by angiography. Cases were selected by independent interventional cardiologists from a database in which both QCA and FFR were known for each stenosis. Cases were ordered randomly, without any intention to make a pattern of progressive difficulty. Case order remained the same for all the participants. Of 12 lesions, 6 were functionally nonsignificant (FFR>0.80), whereas another 6 were functionally significant (FFR≤0.80). The true FFR and QCA values were never revealed to participants, not even after completion of the questionnaire. All cases were characterized as stable angina without relevant changes on resting ECG. No information about noninvasive testing was provided.

Participants were asked to (1) localize all relevant stenoses by indicating the involved segment; (2) define percent diameter stenosis (%DS) by visual estimate; and (3) determine the significance of the stenosis of interest. In cases of angiographic

uncertainty, the most appropriate diagnostic tool had to be selected from the arsenal available in the catheterization laboratory, namely QCA, IVUS, OCT, or FFR. Participants were asked to make their decisions assuming ideal world conditions, without considering any financial restrictions or local regulations, but only after the best clinical practice achievable in this virtual catheterization laboratory.

Results: International Survey on Interventional Strategy was taken by 495 participants who provided 4421 lesion evaluations. The visually estimated %DS showed an absolute overestimation of +18% (interquartile range, +4% to +28%) compared with the corresponding QCA-derived %DS values. The overestimation of stenosis severity, as compared with QCA-derived %DS was significantly more pronounced in the right coronary artery (+22% (+13% to +28%) compared with +18% (+8% to +19%) for the left circumflex and +8% (−6% to +24%) for the left anterior descending, respectively (P<0.001). Variances differed significantly among vessels, being largest for the left anterior descending (SD of 20%), intermediate for the left circumflex (SD of 15%), and smallest for the right coronary artery (SD of 12%; P<0.001 across groups and for every paired comparison; Figure 9).

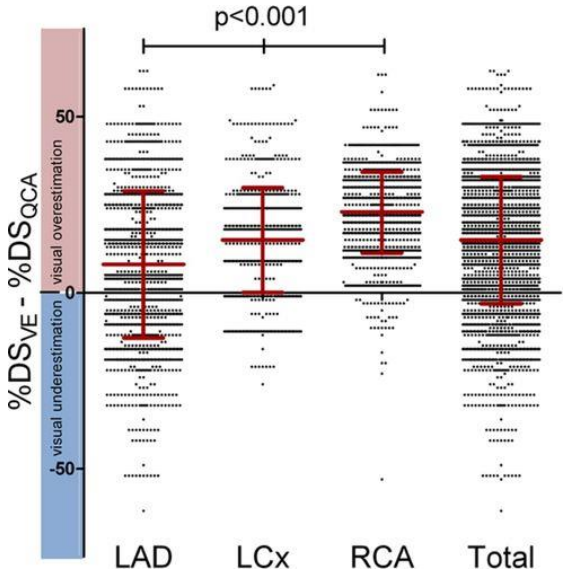


Figure 9. Discrepancy between visually estimated and quantitatively measured percent diameter stenosis (%DS). Absolute difference between visually estimated %DS and quantitatively measured %DS is indicated on the y axis. A value more than zero refers to visual overestimation (red zone), whereas a value less than zero refers to visual underestimation (blue zone). x axis indicates different anatomic localizations. Red bars mark the mean±SD of the underlying individual light gray survey responses. LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery.

In 3158 (71%) decisions, participants relied solely on angiographic appearance that was discordant in 47% with the known FFR, using 0.80 as cutoff value (Figure 10). The use of FFR and imaging modalities was requested in 21% and 8%, respectively. Comparing 4 groups of participants according to the experience in FFR, angiogram-based decisions were less frequent with increasing experience (77% versus 72% versus 69% versus 67%, respectively; P<0.001). As a result, requests for FFR were more frequent (14% versus 19% versus 24% versus 28%, respectively; P<0.001) and rates of discordant decisions decreased (51% versus 49% versus 47% versus 43%, respectively; P<0.022).

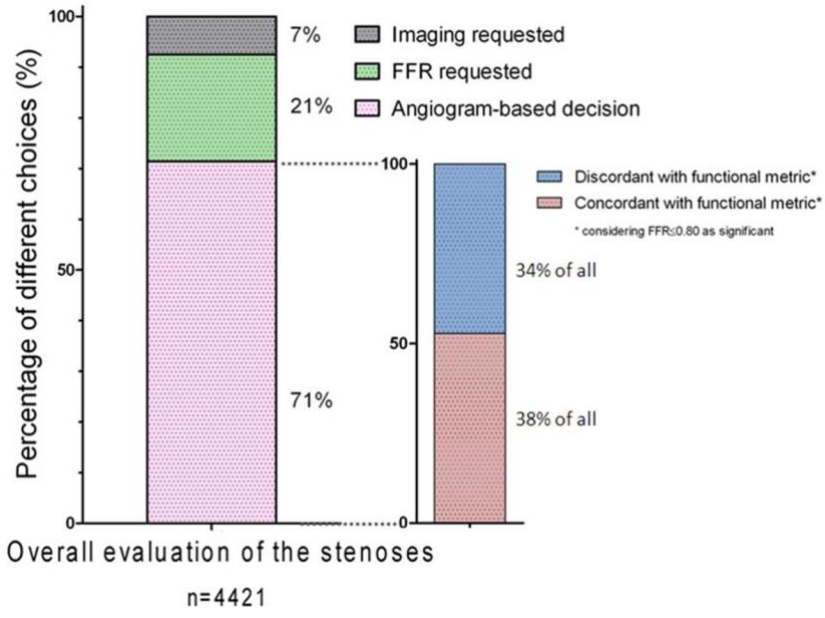


Figure 10. Distribution of different decisions and the appropriateness of purely angiogram-based decisions. Left, the distribution of decisions over the entire data set: in 7% of all evaluations an imaging modality (quantitative coronary angiography, intravascular ultrasound, or optical coherence tomography) was requested and in 21% the need for fractional flow reserve (FFR) was expressed. In the rest 71% angiography was found sufficient by the participants to decide about significance. Among the latter, the proportion of concordance and discordance with the known functional metric is depicted in the right.

Conclusions: The findings confirm that, even when all potential external constraints are virtually eliminated, visual estimation continues to dominate the treatment decisions for intermediate stenoses, indicative of a worrisome disconnect between recommendations and current practice.

CHAPTER 8

Global Fractional Flow Reserve Value Predicts 5-Year Outcomes in Patients With Coronary Atherosclerosis but Without Ischemia

Background: Global fractional flow reserve (FFR) (ie, the sum of the FFR values in the 3 major coronary arteries) is a physiologic correlate of global atherosclerotic burden. The objective of the present study was to investigate the value of global FFR in predicting long-term clinical outcome of patients with stable coronary artery disease but no ischemia-inducing stenosis.

Methods: In the present study, patients from the FFR group of FAME 1 trial, patients from the FFR-guided PCI group of FAME 2 trial, and patients from the registry group of FAME 2 trial were considered for inclusion. Patients were included in the present analysis only if the FFR values in all 3 major coronary arteries were >0.80. Global FFR consisted of the sum of the FFR values measured in the 3 major coronary arteries. Accordingly, for the present analysis, global FFR ranged from 2.43 to 3.0 (Figure 11). When a PCI was performed, the post-PCI value of the stented artery was used to calculate the global FFR. If the post PCI-FFR value was not available, an FFR value of 0.90 was used (it was the case in 841 patients). This value was chosen as being the median value of all post-PCI FFR values obtained in FAME 1 and FAME 2 trials.10 When the vessel was angiographically “normal,” an FFR value of 1 was imputed (it was the case in 206 patients). The angiographic extent of atherosclerosis was expressed as the number of lesions with a diameter stenosis of >50% by visual estimate. The primary outcome of the present study was a composite of major adverse cardiovascular events (MACEs), including overall death, myocardial infarction (MI), and any revascularization. The events were adjudicated by an independent clinical event committee blinded to the treatment allocation and to the global FFR values. Follow-up was censored at the time of the first event or, at the latest, 5 years after patient's enrollment in the studies.

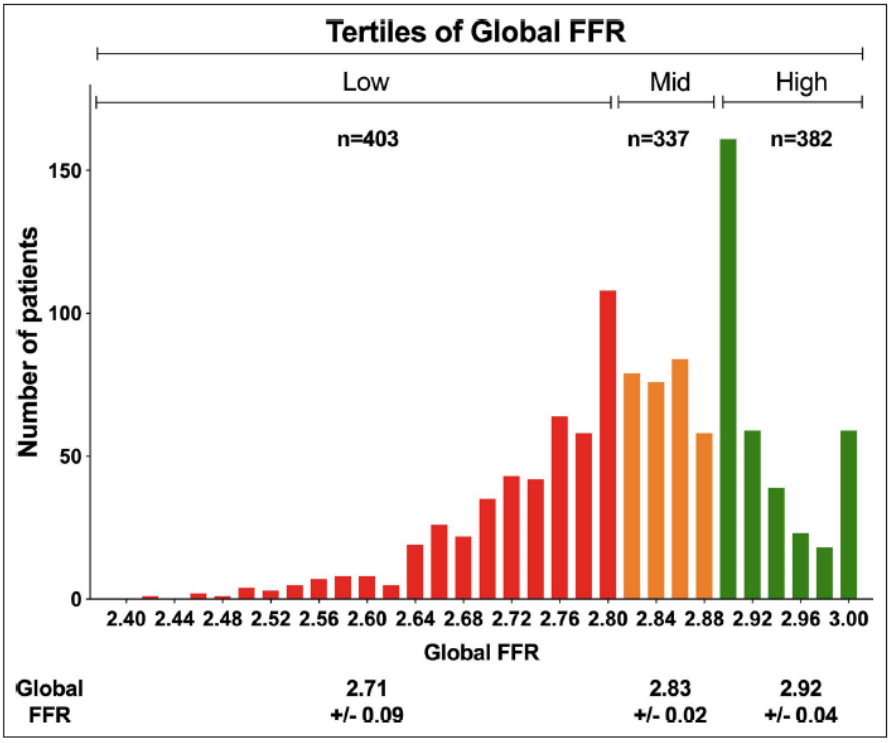


Figure 11. Frequency distribution of global fractional flow reserve (FFR) with classification into 3 tertiles.

Results: Patients in the lowest tertile of global FFR showed the highest 5-year MACE rate compared with those in the mid or high tertile of global FFR (27.5% versus 22.0% and 20.9%, respectively; log-rank P=0.040). The higher 5-year MACE rate was mainly driven by a higher rate of revascularization in the low global FFR group (16.4% versus 11.3% and 11.8%, respectively; log-rank P=0.038) (Figure 12). In a multivariable model, an increase in global FFR of 0.1 unit was associated with a significant reduction in the rates of MACE (hazard ratio [HR], 0.988; 95% CI, 0.977–0.998; P=0.023), myocardial infarction (HR, 0.982; 95% CI, 0.966–0.998; P=0.032), and revascularization (HR, 0.985; 95% CI, 0.972–0.999; P=0.040) (Figure 13).

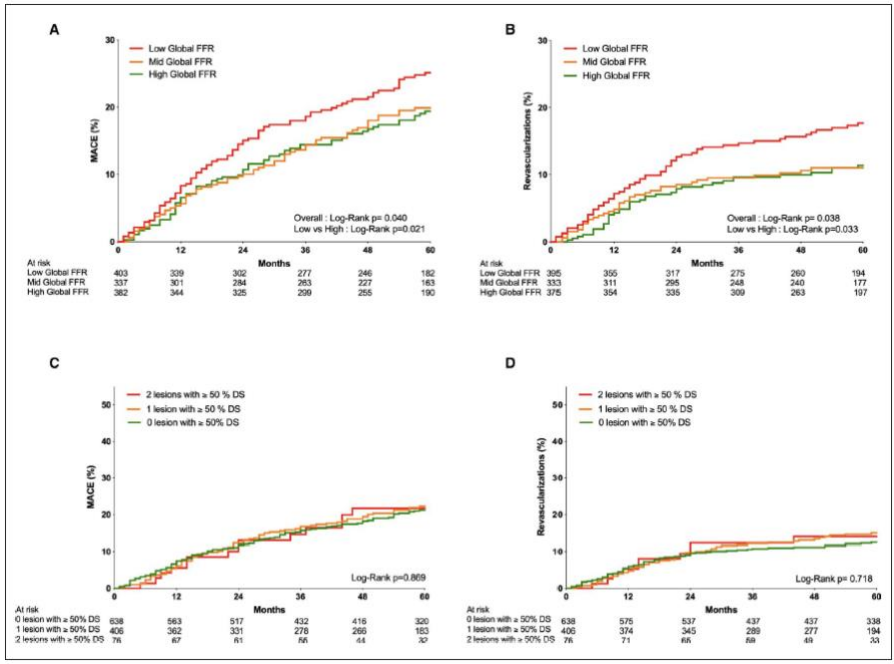


Figure 12. A, Kaplan-Meier graph reporting the cumulative incidence of major adverse cardiovascular events (MACEs) up to 5 years in the low global fractional flow reserve (FFR) group (red), mid global FFR group (yellow), and high global FFR group (green). **B,** Kaplan-Meier graph reporting the cumulative incidence of revascularization up to 5 years in the low global FFR group (red), mid global FFR group (yellow), and high global FFR group (green). **C,** Kaplan-Meier graph reporting the cumulative incidence of MACEs up to 5 years in patients with 0, 1, or 2 ≥50% stenoses at discharge (green, yellow, and red, respectively). **D,** Kaplan-Meier graph reporting the cumulative incidence of revascularization up to 5 years in patients with 0, 1, or 2 ≥50% stenoses at discharge (green, yellow, and red, respectively).

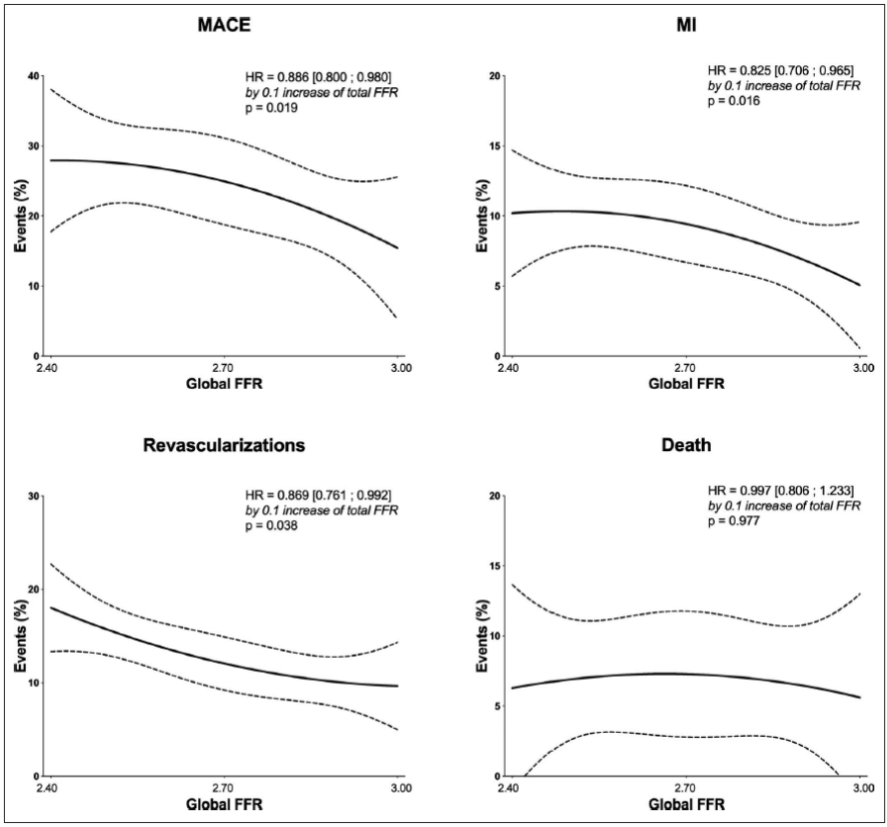


Figure 13. Hazard ratio (HR) with 95% CI of the different outcomes per increase of global fractional flow reserve (FFR) of 0.1. MACE indicates major adverse cardiovascular event; and MI, myocardial infarction.

Conclusions: Even in the absence of ischemia-producing stenoses, patients with a low global FFR, physiologic correlate of global atherosclerotic burden, present a higher risk of MACE at 5-year follow-up.

Part III

Coronary physiology in patients with comorbidities

IIIa - Aortic Valve Stenosis

CHAPTER 9

Clinical Outcome of Patients with Aortic Stenosis and Coronary Artery Disease Not Treated According to Current Recommendations

Background: Degenerative AS is the most common valvular heart disease in the developed countries and is associated with significant CAD in up to 50 % of the cases. When both conditions are present and symptoms occur, current guidelines recommend surgical treatment with combined AVR and CABG. Yet, due to frequent comorbidities in these patients, treatment might diverge from guideline recommendations.

Aim: In our study, we evaluated the real-world adoption of guideline recommendations in patients with combined moderate or severe aortic stenosis and significant coronary artery disease and assessed the impact of incomplete treatment strategies (i.e., diverging from classic AVR plus CABG) on the long-term clinical outcome.

Methods and results: From 2002 to 2010, we assessed death up to 5 years in 650 patients with moderate/severe aortic stenosis and at least one coronary lesion (>50 %): 23% were treated conservatively (medical therapy, MT), 17% with percutaneous coronary intervention (PCI), 11% with AVR, and 49% with combined CABG and AVR. Number of vessels treated per patient was higher in the combined CABG and AVR group as compared to the PCI-only group. In the latter, drug-eluting stents (DES) were used in 29 % of the cases. Surgical pump and clamp time was significantly longer in the combined CABG and AVR than in the AVR-only group.

Clinical follow-up was available for all patients at a median time of 58 (21–60) months. Figure 14 shows the survival curves for the four treatment groups.

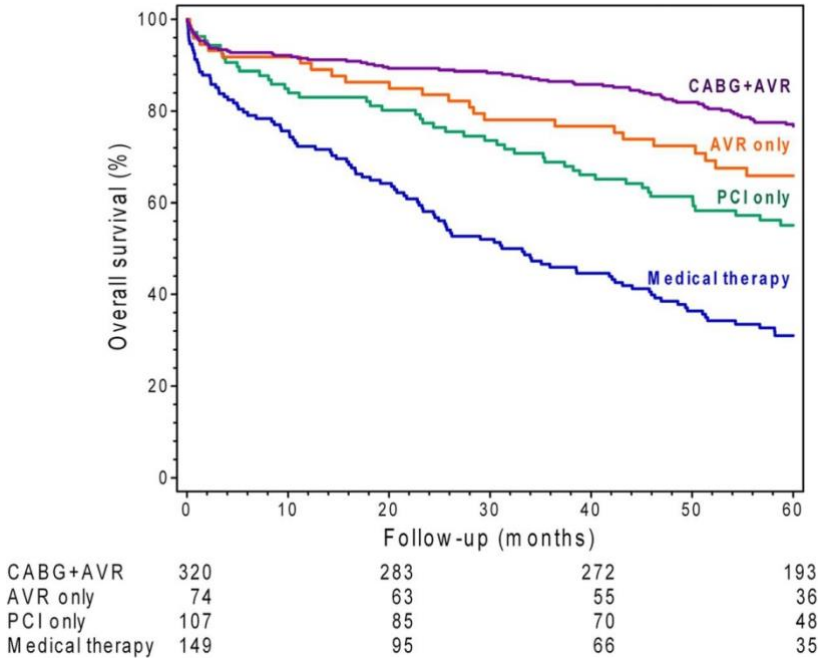


Figure 14: Overall survival in the four groups (log-rank 106.006; p<0.01). CABG: coronary artery bypass graft; AVR: aortic valve replacement; PCI: percutaneous coronary intervention.

The adjusted Cox regression analysis confirmed the beneficial effect in terms of mortality of the CABG and AVR, AVR-only, and PCI-only group as compared to MT group (p <0.01). Other factors significantly associated with overall death were logistic EuroSCORE, atrial fibrillation, hyperlipidemia, and peripheral vascular disease. Direct comparison between PCI-only and AVR-only groups showed a trend toward better survival in the AVR-only group (HR [95 % CI] 1.37 [0.85–2.2], p=0.19). As to the secondary endpoints, both AVR and revascularization at follow-up were significantly more frequent in the PCI group, followed by MT, with few or no events in the surgical groups. The time to AVR at follow-up was longer in the MT as compared to the PCI group (22 [19–37] vs. 11 [7–29] months, p=0.02). Kaplan-Meier curves showed improved survival in the MT group when AVR at follow-up was performed (p < 0.01), while a strong trend was observed in the PCI group (p=0.054) (Figure 15). At the adjusted Cox regression analysis corrected for confounders, AVR

at follow-up confirmed its protective value in the MT group (HR [95 % CI] 0.39 [0.16–0.96], p=0.04), but not in the PCI group (HR [95 % CI] 0.65 [0.27–1.55], p=0.33). When patients with AVR at follow-up were excluded from the analysis, survival was still significantly higher in the PCI group (p <0.01) as compared with the MT group (Figure 16), even after adjusting for confounders in the Cox regression analysis (HR [95 % CI] 0.62 [0.41–0.94], p=0.024).

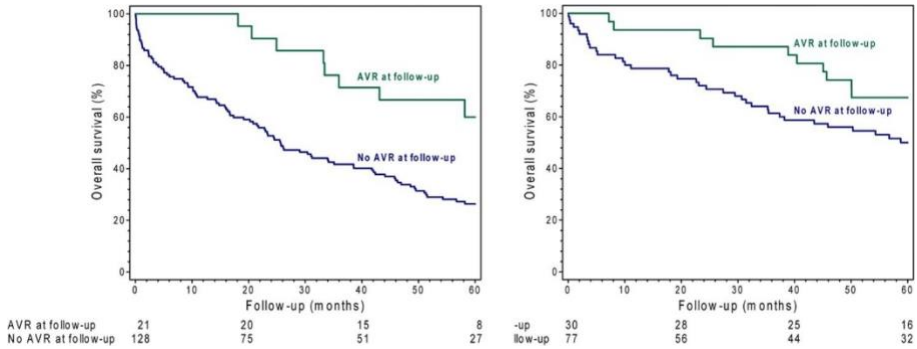


Figure 15: Impact of AVR performed at the follow-up on overall survival in the medical therapy (MT) group (log-rank 9.222; p < 0.01; on the *left*) and in the PCI group (log-rank 3.725; p=0.054; on the *right*).

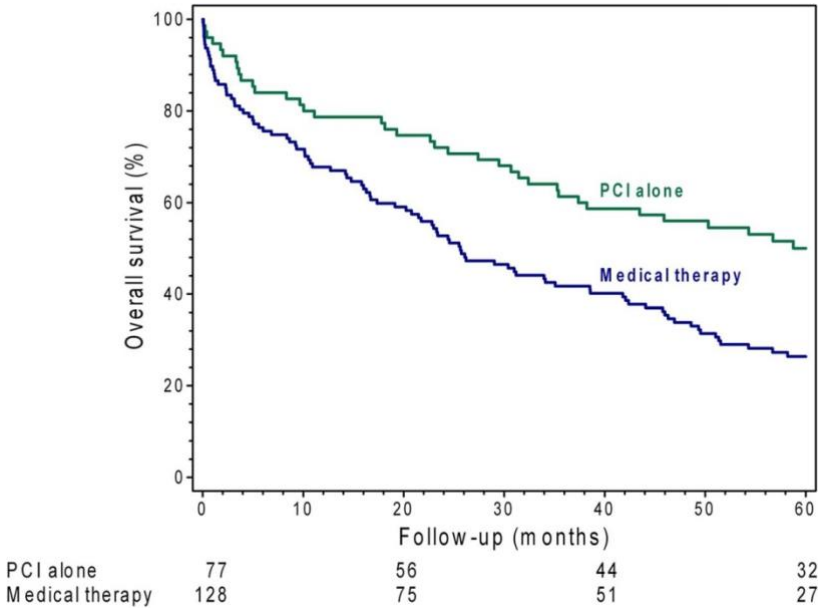


Figure 16: Overall survival in the medical therapy and PCI-alone groups after excluding patients undergoing AVR at the follow-up (log-rank 11.324; $p<0.01$).

Conclusions: In this real-world experience, only half of the symptomatic patients with moderate or severe AS and CAD initially underwent combined CABG and AVR as recommended by the guidelines. Our results confirm that this treatment strategy is associated with the best outcome at 5 years. Nevertheless, in patients in whom combined CABG and AVR was not performed, either PCI or AVR significantly improve survival at 5 years as compared to medical therapy. These findings might have important clinical implications especially in frail patients excluded even from TAVR but who might benefit from a percutaneous revascularization strategy.

CHAPTER 10

Fractional Flow Reserve-Guided Revascularization in Patients With Aortic Stenosis

Background: FFR-guided revascularization strategies have been shown beneficial in patients with intermediate stenoses and multivessel CAD. The reliability and clinical usefulness of FFR has not been tested in patients with concomitant aortic stenosis (AS). Nevertheless, these are the very patients difficult to investigate with noninvasive functional testing and presenting with associated CAD in up to 50% of the cases.

Aim: We aimed to investigate the impact of FFR measured at the time of the diagnostic coronary angiography on percutaneous and surgical revascularization strategies and its related clinical outcome in patients with AS.

Methods: From 2002 to 2010, we retrospectively identified 106 patients with AS and significant CAD in which at least 1 intermediate lesion was either revascularized with an FFR value ≤ 0.80 or deferred with FFR > 0.8 (FFR-guided group). Then, from 694 contemporary patients in which the decision to revascularize was based on angiography only, we matched 212 as comparator (Angio-guided group).
Inclusion criteria were: presence of at least 1 intermediate stenosis (diameter stenosis: 50-70%) of a major coronary artery at the time of angiography; aortic valve area ≤ 1.5 cm^2 and/or aortic mean pressure gradient ≥ 20 mmHg. Severe AS was defined with a valve area ≤ 1 cm^2 and/or aortic mean pressure gradient ≥ 40 mmHg. All patients underwent left/right sided heart catheterization. Aortic valve area was calculated with the Gorlin formula. PCI and surgical interventions were left to the operator's discretion. CABG and aortic valve replacement (AVR) performed within 6 months from the diagnostic coronary angiography were referred to the index procedure.

Primary end point was the rate of major adverse cardiac events (MACE), defined as overall death, MI, and repeat revascularization up to 5 years. Secondary end points were all the individual end points included in MACE and AVR. Follow-up was obtained through telephone contacts or outpatient visits. Date of death was retrieved from Belgium national death registry. Informed consent to the use of personal data was obtained from each patient.

Results: The 2 groups were well matched with respect to clinical characteristics and AS severity did not differ between the groups. More patients in the FFR-guided group underwent PCI, while there was a trend towards more CABG in the Angio-guided group. Patients treated with PCI had lower AS severity as compared with patients treated with CABG (aortic valve area: 0.95 ± 0.29 vs. 0.76 ± 0.28, p <0.01; aortic mean gradient: 27 ± 15 vs. 41 ± 20; p < 0.01). At baseline angiogram, number of diseased vessels was similar in the 2 groups. After functional assessment with FFR, the number of diseased vessels was significantly downgraded within the FFR-guided group (p<0.01) and when compared to the Angio-guided group (p<0.01). In patients undergoing CABG, number of arterial grafts and anastomoses per patient was similar between the 2 groups, while significantly less venous conduits were used in the FFR-guided group, along with less venous anastomoses. A trend towards less AVR was observed in the FFR-guided group. Clinical follow-up was available for all patients at a median time of 56 months. We found no difference in MACE up to 5 years, overall death, repeat revascularization and nonfatal MI between the 2 groups. Similar results were found in the subgroup of patients with severe AS. When stratified by initial treatment strategy, MACE rate was still not significantly different among FFR- and Angio-guided groups. Combined CABG and AVR was associated with the best clinical outcome and Medical Therapy with the worst, while intermediate outcomes were reported in patients initially treated with PCI or AVR only (Figure 17). AVR at follow-up was performed in 9% of patients in the FFR-guided group (time to AVR: 31 [22-43] months) vs. 6% in the Angio-guided group (time to AVR: 21 [7-54] months)

(p= 0.28). At the latest follow-up available, cumulative AVR rate was still lower in the FFR-guided group (59 [55%] vs. 135 [63%]; p=0.16).

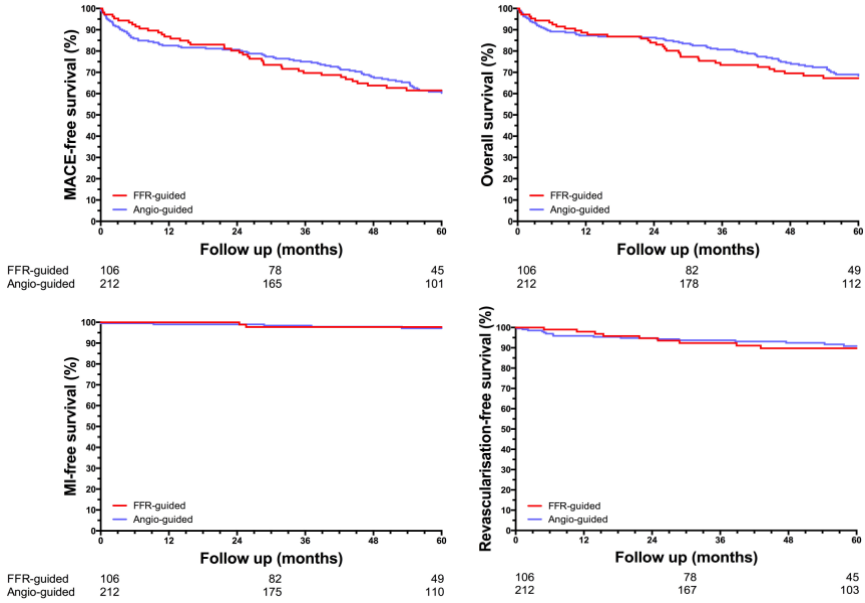


Figure 17: Kaplan-Meier curves for survival free from events in the FFR-guided and Angio-guided groups up to 5 years of follow-up: Survival free from MACE (upper left; p=0.98); Overall survival (upper right; p=0.68); Survival free from MI (lower left; p=0.83); Survival free from revascularization (lower right; p=0.76). MACE, major adverse cardiac events; MI, myocardial infarction.

Conclusions: FFR guidance impacts the management of selected patients with moderate or severe AS and coronary artery disease by resulting into deferral of aortic valve replacement, more patients treated with PCI, and in patients treated with CABG, into less venous grafts and anastomoses without increasing adverse event rates up to 5 years.

CHAPTER 11

Correlation between Angiographic and Physiologic Evaluation of Coronary Artery Narrowings in Patients With Aortic Valve Stenosis

Background: In patients with combined aortic stenosis (AS) and coronary artery disease (CAD), myocardial ischemia may relate to numerous factors other than epicardial stenoses, such as microcirculatory impairment, left ventricular hypertrophy, and hemodynamic alterations associated with the diseased aortic valve. These factors, along with the inability in AS patients to perform a reliable noninvasivefunctional evaluation, portend to an assessment of the bystander CAD largely based on the sole angiographic stenosis appearance. We aimed to assess the correlation between angiographic and physiologic evaluation of coronary lesions in aortic stenosis patients presenting with intermediate coronary stenoses at the angiography.

Methods: From 2002 to 2010, we included 163 patients from 2 centers with both moderate or severe AS and coronary artery disease, matched by age and gender with 163 contemporary patients with CAD alone. With both quantitative coronary angiography (QCA) and fractional flow reserve (FFR), we assessed 259 coronary stenoses in the AS + CAD group, and 256 in the CAD alone group.

Results: A significant correlation was found between diameter stenosis (DS) and FFR in both groups, though this was significantly stronger in the AS + CAD than in the CAD alone group ($R=-0.63$ vs. $R=-0.44$; $p<0.01$) (Figure 18).

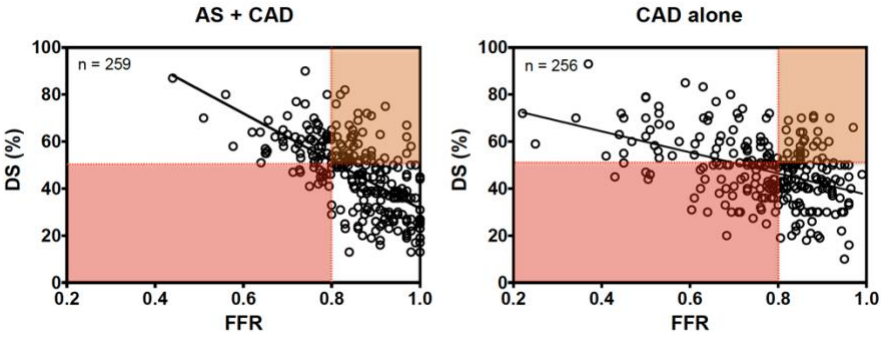


Figure 18. Correlation between diameter stenosis (DS) and fractional flow-reserve (FFR) in patients with aortic stenosis + coronary artery disease (AS + CAD) and in patients with stable CAD alone.

Likewise, the correlation between minimum lumen diameter and FFR was stronger in the AS + CAD than in the CAD alone group (R=-0.54 vs. R=- 0.41; p=0.05). ROC curves analysis showed that DS was a better predictor of hemodynamically significant coronary stenoses (FFR≤0.8) in the AS + CAD rather than in the CAD alone group (AUC = 0.83 vs. 0.67; p<0.01). With 50% DS cut-off value, the sensitivity, specificity and accuracy was 77%, 66% and 70% in AS + CAD group versus 59%, 63% and 61% in CAD alone group. In both groups, the diagnostic accuracy of DS in predicting FFR was higher in the right and circumflex coronary artery (Right/LC) as compared to the left anterior descending artery (LAD), although this was only statistically significant in the AS + CAD group (AUC 0.88 in Right/LC vs. 0.76 in LAD; p=0.03) (Figure 19).

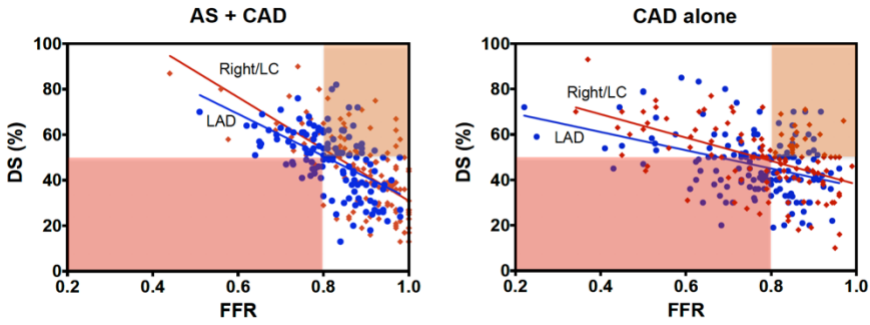


Figure 19. Correlation between diameter stenosis (DS) and fractional flow reserve (FFR) in lesions located in the left anterior descending artery (in blue) and in the right coronary/Left circumflex artery (in red).

Conclusions: the correlation between the angiographic and hemodynamic significance of coronary stenoses is modest also in AS patients. The assessment of CAD severity solely based on angiography poorly predicts the hemodynamic significance of the coronary stenosis especially when these are located in the LAD.

CHAPTER 12

The influence of Aortic Valve Obstruction on the Hyperemic Intracoronary Physiology: Difference between Resting Pd/Pa and FFR in Aortic Stenosis

Background: The reliability of FFR is based on the assumption that pressure and flow are closely correlated when microvascular resistances are minimized under hyperemic conditions. The intracoronary physiology hyperemic response can be described by the difference between resting and hyperemic Pd/Pa (ΔPd/Pa-FFR) after administration of adenosine. The aim of this study is to establish whether AS patients exhibit adequate hyperemic response to adenosine in the catheterization laboratory and to compare it with a matched control group of stable patients without valve disease.

Methods: A retrospective multicenter cohort of 114 AS patients who underwent coronary physiology assessment was compared with 154 controls before and after propensity matching adjustment.

Results: Intracoronary physiology revealed similar results between the two matched groups in terms of resting Pd/Pa (0.90 ± 0.07 vs 0.91 ± 0.07, p = 0.92), FFR (0.81 ± 0.1 vs 0.80 ± 0.1, p = 0.42), and the difference between resting distal coronary vs aortic pressure ratio (Pd/Pa) and FFR (ΔPd/Pa-FFR) (0.09 ± 0.07 vs 0.10 ± 0 .05, p = 0. 21). ΔPd/Pa-FFR was tested against the severity of AS. ΔPd/Pa-FFR was not influenced by the severity of AS in terms of aortic valve area (r = − 0.02, p = 0.83) and gradient (r = − 0.05, p = 0.64) or by the left ventricle hypertrophy (r = − 0.03, p = 0.88). Conversely, ΔPd/Pa-FFR was influenced by the presence of diabetes (r = − 0.24, p = 0.005),

peripheral vascular disease (r = − 0.16, p = 0.047), and chronic kidney disease (r = − 0.19, p = 0.03) (Figure 20).

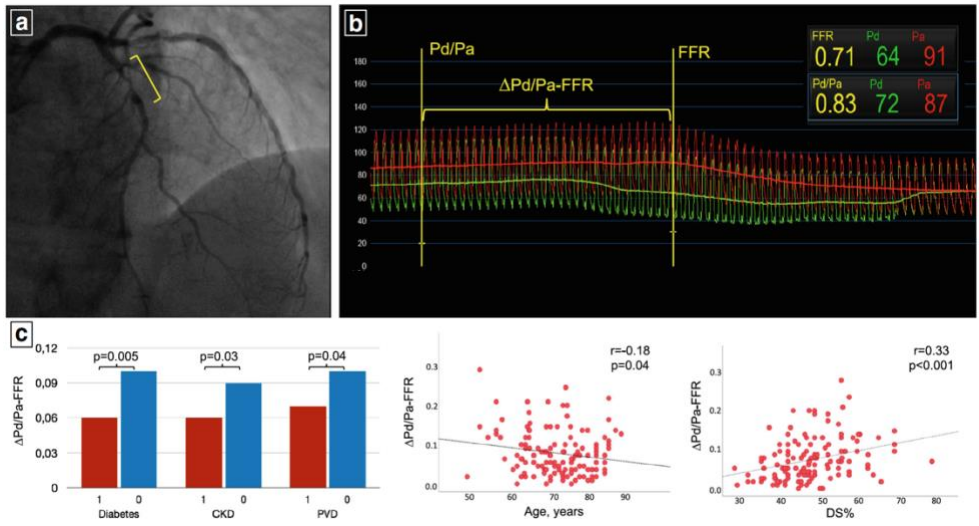


Figure 20. The influence of clinical variables onΔPd/Pa-FFR in patients with aortic stenosis. (a) Case example of coronary angiogram showing an intermediate lesion in the left anterior descending artery. (b) Pressure-wire waveforms. The ΔPd/Pa-FFR is calculated as the difference between resting Pd/Pa and FFR after adenosine administration. (c) Mean ΔPd/ Pa-FFR was significantly lower in patients with diabetes, CKD, and PVD compared with other patients. Age demonstrated a modest inverse correlation withΔPd/Pa-FFR. DS% was directly correlated with ΔPd/Pa-FFR

Conclusions: No significant difference was observed in the ΔPd/Pa-FFR between patients with AS and matched controls. Further studies are warranted to validate the FFR-guided revascularization in patients with AS.

CHAPTER 13

Pathophysiology, Diagnosis and Treatment of Patients with Concomitant Severe Aortic Stenosis and Coronary Artery Disease: A closer Look to the Unresolved Perplexity.

Summary: Degenerative aortic stenosis (AS) and coronary artery disease (CAD) are the most prevalent cardiovascular diseases in developed countries, and they coexist in up to 50% of patients. The pathophysiological rationale behind concomitant AS and CAD is discussed in detail in this review, together with prognostic implications. Detecting CAD in patients with AS may be challenging, as AS may mask the existence and symptoms of CAD. The safety and reliability of invasive and non-invasive physiological assessment for epicardial coronary disease are also a matter of debate. Finally, the selection and timing of optimal treatment of CAD in patients with severe AS are still unclear. Given the aging of the population, the increase in the prevalence of AS, and the ongoing paradigm shift in its treatment, controversies in the diagnosis and treatment of CAD in the setting of AS are deemed to grow in importance. In this paper, we present contemporary issues in the diagnosis and management of CAD in patients with severe AS who are transcatheter aortic valve implantation (TAVI) candidates and provide perspective on the treatment approach. In figure 21 we propose a treatment algorhytm for patients with concomitant CAD and severe AS.

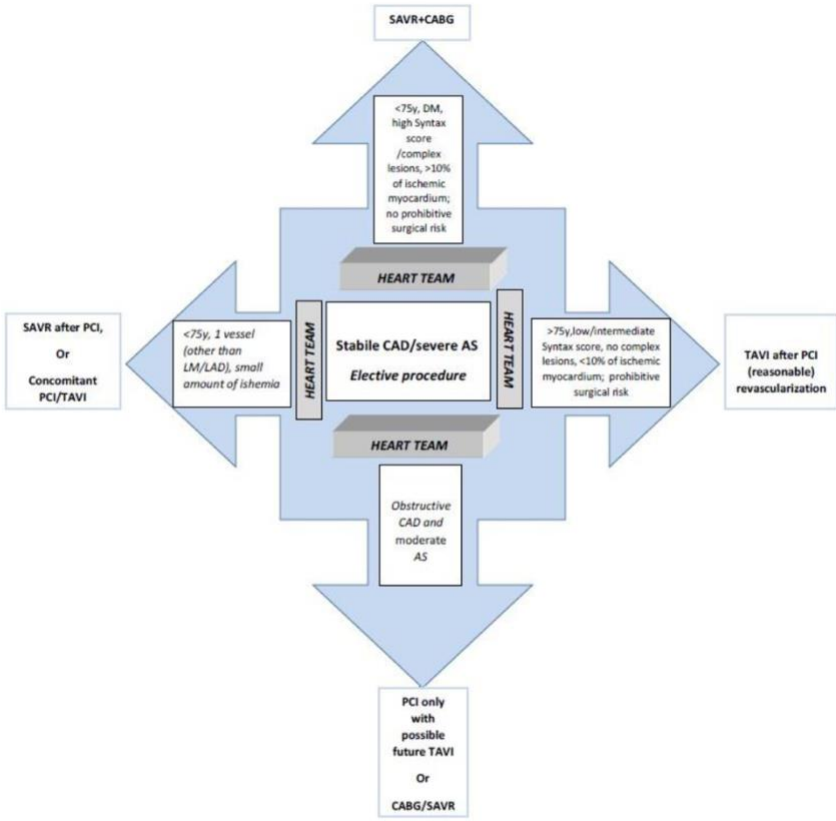


Figure 21. Proposed treatment algorhythm for patients with concomitant coronary artery disease (CAD) and severe aortic stenosis (AS). Of note, recently published 2020 ACC/AHA guidelines state that TAVI can be considered from 65 years of age in patients with no anatomic contraindications for transfemoral TAVI and after shared decision-making about the balance between expected patient longevity and valve durability [92]. SAVR: Surgical aortic valve replacement; CABG: Coronary artery bypass grafting; DM: Diabetes mellitus; LM: left main coronary; LAD: left anterior descending artery; CAD: Coronary artery disease; AS: Aortic stenosis; TAVI: Transcatheter aortic valve implantation; PCI: Percutaneous coronary intervention.

Part III

Coronary physiology in patients with comorbidities

IIIb – Heart Failure

CHAPTER 14

Fractional flow reserve in patients with reduced ejection fraction.

Background: Fractional flow reserve (FFR) has never been investigated in patients with reduced ejection fraction and associated coronary artery disease (CAD). We evaluated the impact of FFR on the management strategies of these patients and related outcomes.

Methods: From 2002 to 2010, all consecutive patients with left ventricular ejection fraction (LVEF) $\leq 50\%$ undergoing coronary angiography with ≥ 1 intermediate coronary stenosis [diameter stenosis (DS)% 50–70%] treated based on angiography (Angiography-guided group) or according to FFR (FFR-guided group) were screened for inclusion.

Results: In the FFR-guided group, 433 patients were matched with 866 contemporary patients of the Angiography-guided group. For outcome comparison, 617 control patients with LVEF >50% were included. After FFR, stenotic vessels per patient were significantly downgraded compared with the Angiography-guided group (1.43 ± 0.98 vs. 1.97 ± 0.84; P < 0.001). This was associated with significantly lower revascularization vs. the Angiography-guided group [225 (52%) vs. 535 (62%); P< 0.001]. Percutaneous coronary intervention was more frequent in the FFR-guided group [155 (36%) vs. 261 (30%) of the Angiography-guided group; P = 0.039]; whereas CABG was more frequent in the Angiography-guided group [274 (32%) vs. 70 (16%) of the FFR-guided group, P < 0.001]. Patients in the FFRguided group were more frequently deferred to medical therapy [208 (48%) vs. 331 (38%); P<0.001] (Figure 22).

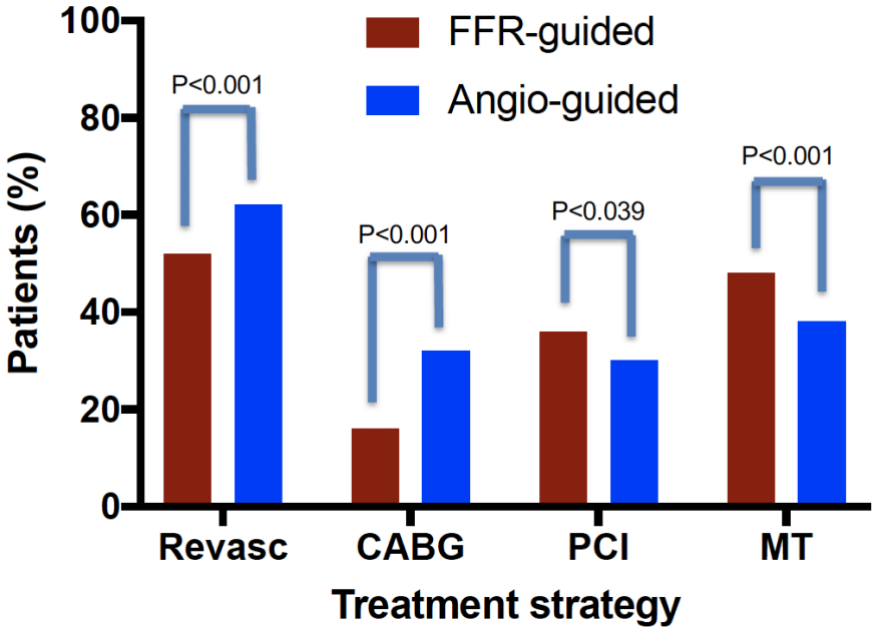


Figure 22. The difference in treatment strategies between fractional flow reserve- and Angiography-guided group. CABG, coronary artery bypass grafting; MT, medical therapy; PCI, percutaneous coronary intervention; Revasc, revascularization.

All-cause death at 5 years of follow-up was significantly lower in the FFR-guided as compared with Angiography-guided group [22% vs. 31%. HR (95% CI) 0.64 (0.51–0.81); P < 0.001]. Similarly, rate of major adverse cardiovascular and cerebrovascular events (MACCE: composite of all-cause death, myocardial infarction, revascularization, and stroke) was significantly lower in the FFR-guided group [40% vs. 46% in the Angiography-guided group. HR (95% CI) 0.81 (0.67–0.97); P = 0.019]. Higher rates of death and MACCE were observed in patients with reduced LVEF compared with the control cohort (Figure 23)

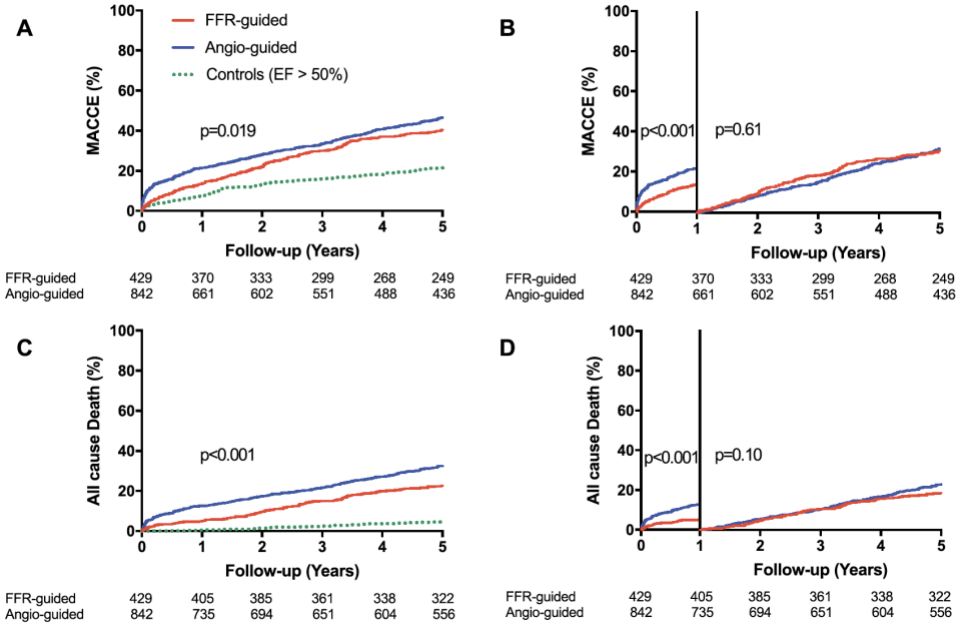


Figure 23. Cumulative incidences and landmark analysis for MACCE and all cause Death. Cumulative incidence of MACCE (A) and all-cause Death (C); landmark analysis before and after 1-year timepoint for MACCE (B) and all cause Death (D). The dotted green line represents the control cohort with preserved LVEF, for visual comparison. P values are referred to the FFR-guided and the Angiography-guided groups.

When stratifying according to LVEF, the clinical benefit of the FFR-guided strategy in all-cause death was confirmed both in patients with LVEF ≤ 35% (n = 419) (HR [95% CI] 0.48 [0.31-0.75]) and with LVEF > 35% (n = 852) (HR [95% CI] 0.74 [0.56-0.98]). An FFR-guided strategy was also associated with improved MACCE in patients with LVEF ≤ 35% (HR [95% CI] 0.67 [0.47-0.94]), while there was only a trend in patients with LVEF between 36% and 50% (HR [95% CI] 0.87 [0.71-1.08] (Figure 24).

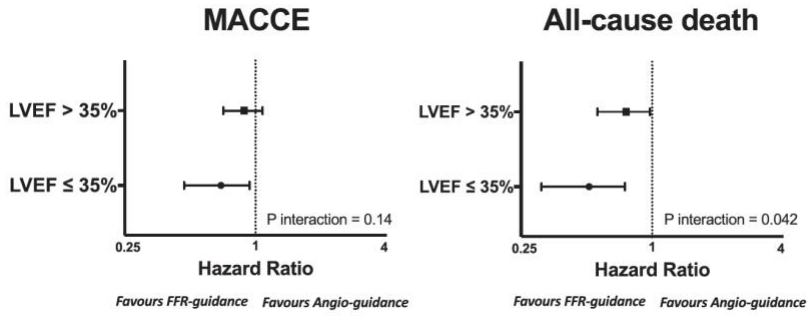


Figure 24. Impact of FFR on MACCE and all-cause death in patients with LVEF ≤ 35% and with LVEF 36% - 50%.

Conclusions: In patients with reduced LVEF and CAD, FFR-guided revascularization was associated with lower rates of death and MACCE at 5 years as compared with the Angiography-guided strategy. This beneficial impact was observed in parallel with less coronary artery bypass grafting and more patients deferred to percutaneous coronary intervention or medical therapy.

CHAPTER 15

Impact of Right Atrial Pressure on Fractional Flow Reserve Measurements: Comparison of Fractional Flow Reserve and Myocardial Fractional Flow Reserve in 1,600 Coronary Stenoses

Background: FFR is defined as the ratio of maximal blood flow in the stenotic coronary artery to the maximal blood flow if the same artery were normal. Accordingly, FFR expresses to what extent a given stenosis limits the maximal achievable myocardial flow, and, as a corollary, to what extent myocardial flow can be improved by revascularization of the epicardial segment. This ratio of 2 flows can be derived from the ratio of their respective driving pressures during maximal hyperemia. In fact, the concept of FFR enables the assessment of the separate contribution of maximum coronary and collateral blood flow to myocardial blood flow, all expressed as a ratio to their normal values. The latter is called then myocardial FFR (FFR_{myo}), and for its calculation theoretically right atrial pressure should be included. Because in the majority of patients with coronary artery disease right atrial pressure is low, the latter is neglected in the calculation of FFR. Yet whether FFR measurement is still reliable across a wide range of hemodynamic conditions, such as in patients with heart failure, is not clear.

Aim: This study sought to assess the impact of a wide range of mean right atrial pressure (P_{ra}) on FFR measurements.

Methods and results: In 1,676 stenoses of 1,235 patients undergoing left-right heart catheterization for ischemic (642 [52%]) or valvular heart disease (593 [48%]), we compared the FFR values calculated without accounting for P_{ra} ($FFR=P_d/P_a$) to the corresponding myocardial fractional flow reserve (FFR_{myo}) values accounting for Pra

(FFR_{myo}= P_d - P_{ra}/P_a - P_{ra}). The FFR and FFR_{myo} were measured and calculated for every coronary stenosis in the range between 30% and 90% diameter stenosis by visual estimate.

The average FFR value was 0.85 (interquartile range [IQR]: 0.78 to 0.91), and the average FFR_{myo} was 0.83 (IQR: 0.76 to 0.90). Correlation and agreement between the 2 parameters were excellent (r^2= 0.987; slope 1.096±0.003). The median difference between FFR and FFR_{myo} was 0.01 (IQR: 0.01 to 0.02) (Figure 25). In patients, with normal right atrial pressure (P_{ra}≤5 mmHg), the median difference between FFR and FFR_{myo} was minimal: 0.01 (IQR: 0.00 to 0.01). When grouping the patients into tertiles of P_{ra}, a statistically significant increase was observed in the difference between FFR and FFR_{myo} over the 3 groups: 0.01 (IQR: 0.00 to 0.01) versus 0.01 (IQR: 0.01 to 0.02) versus 0.02 (IQR: 0.01 to 0.03), respectively; p<0.001 (Figure 26).

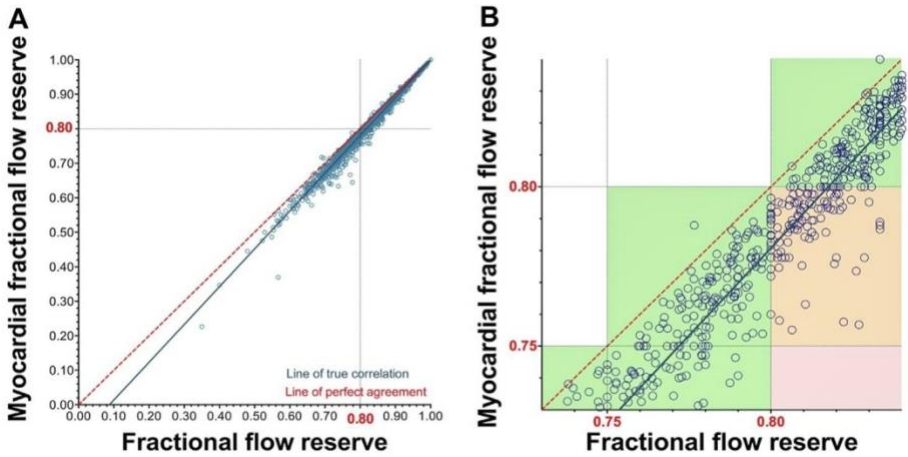


Figure 25. (A) The correlation and agreement between fractional flow reserve (FFR) and myocardial fractional flow reserve (FFR_{myo}) in the overall population. Note that there is minimal deviation between FFR and FFR_{myo} at the lower third of the entire range of FFR 0 to 1. (B) Despite the deviation between FFR and FFR_{myo}, the vast majority of the measurements have clinical agreement (green areas), a minor portion of FFR above 0.80 yields an FFR_{myo} ≤0.80 (orange area), and no FFR above 0.80 yields an FFR_{myo} ≤0.75 (pink area).

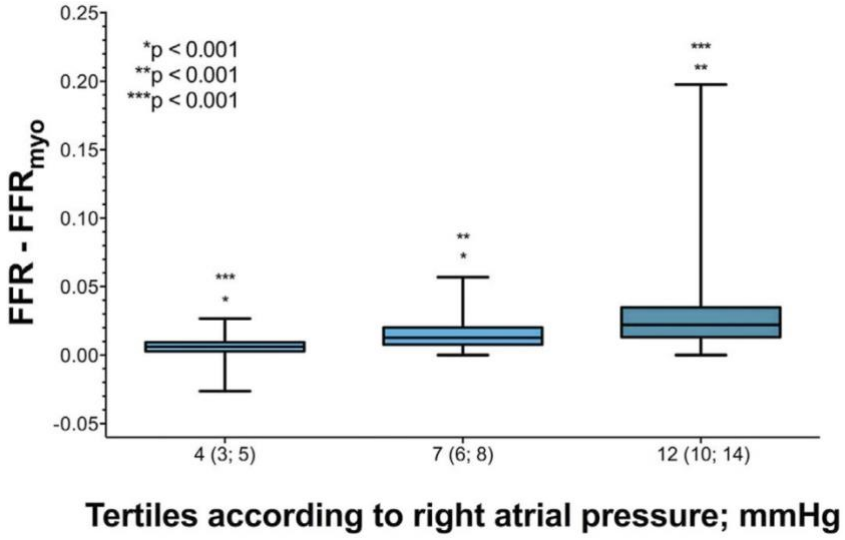


Figure 26. A significant constant increase was observed in the difference between fractional flow reserve (FFR) and myocardial fractional flow reserve (FFR_{myo}) over the tertiles by right atrial pressure. However, even in the highest tertile the mean difference remained clinically minimal.

The median difference between FFR and FFR_{myo} in lesions with FFR above 0.80 was 0.01 (IQR: 0.00 to 0.01). Out of 1,146 stenoses with an FFR >0.80, none had an FFR_{myo} ≤0.75, and 110 (9%) stenoses had an FFR_{myo} ≤0.80. In the latter group, the difference between FFR and FFR_{myo} was 0.02 (IQR: 0.02 to 0.03), yet with a P_{ra} statistically significantly higher than in the overall population (9 mm Hg [IQR: 7 to 12 mm Hg]; p < 0.001). Receiver operator characteristic analysis showed that an 0.80 FFR value has 83% sensitivity and 100% specificity in predicting an FFR_{myo} ≤0.80. Diagnostic accuracy expressed as area under the curve was 0.913 (95% confidence interval: 0.896 to 0.931). The best cutoff value of FFR for predicting an FFR_{myo} ≤0.80 was found to be 0.82, with 96% sensitivity and 97% specificity. These findings remained unchanged when accounting for multiple lesions for some patients or when selecting at most 1 lesion per patient in a random fashion, justifying the negligible impact of any clustering effect.

We assessed 2 models of possible impact of P_{ra} on FFR measurements based on the available data set. In the first model, FFR_{myo} was calculated for the same patient population by applying 3 fixed values of potential P_{ra}: 5 mmHg, 10 mmHg, and 20 mmHg. A statistically significant increase was observed in the difference between FFR and FFR_{myo} over the 3 values, but it remained remarkably low (0.01 [IQR: 0.01 to 0.01] vs. 0.02 [IQR: 0.01 to 0.03] vs. 0.04 [IQR: 0.03 to 0.07], respectively; $p < 0.001$). In the 5 and 10 mmHg groups, values of FFR >0.80 never yielded an FFR_{myo} ≤0.75; whereas in the 20 mmHg group, this occurred in 4% of the cases. In addition, no FFR values >0.82, >0.83, or >0.87 would have yielded an FFR_{myo} ≤0.80 in the 3 groups, respectively (Figure 27). In the second model, we investigated in the same population what P_{ra} value could have a relevant impact on the following threshold values of FFR: 1) FFR >0.80 and FFR_{myo} ≤0.80; or 2) FFR >0.80 and FFR_{myo} ≤0.75. With a normal P_{ra}, FFR >0.80 never yields an FFR_{myo} ≤0.80 with FFR >0.82. With normal P_{ra} (≤5 mm Hg), FFR >0.80 never yields an FFR_{myo} ≤0.75. The latter might only occur when the FFR is close to the cutoff value of 0.80 or P_{ra} is particularly (even nonphysiological) high.

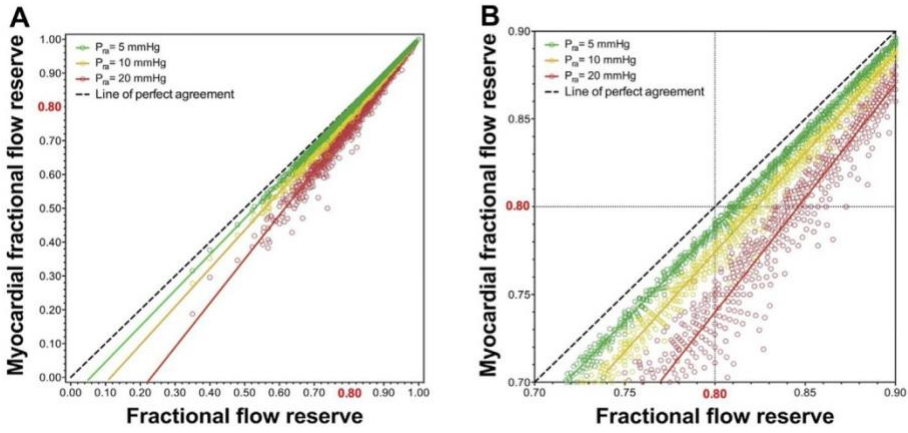


Figure 27. (A) Fractional flow reserve (FFR) and related myocardial fractional flow reserve (FFR_{myo}) values, calculated by applying 3 different potential P_{ra} values: 5, 10, and 20 mm Hg. A statistically significant increase was observed in the deviance from agreement between FFR and FFR_{myo} over the 3 groups. (B) No FFR values >0.82, >0.83, or >0.87 would have yielded an FFR_{myo} ≤0.80 in the 5, 10, or 20 mm Hg groups, respectively.

Conclusions: The difference between FFR and FFR_{myo} was minimal even in patients with markedly increased P_{ra}. FFR values above the gray zone (i.e., >0.80) did not yield values below the gray zone (i.e., ≤0.75) in any case, which suggests that the impact of right atrial pressure on FFR measurement is indeed negligible.

CHAPTER 16

Angiography- Versus FFR-Based Deferral of Revascularization in Patients with Reduced Ejection Fraction: 10-Year Follow-Up Study

Background. Deferring percutaneous coronary intervention (PCI) in patients with non-significant stenoses based on fractional flow reserve (FFR) is associated with favorable clinical outcomes up to 15 years. Whether this holds true in patients with reduced left ventricular ejection fraction (LVEF) is unclear. We aimed to investigate whether FFR provides adjunctive clinical benefit compared to coronary angiography in deferring revascularization of patients with intermediate coronary stenoses and reduced LVEF.

Methods. Consecutive patients (n = 4,577) with reduced LVEF (≤50%) undergoing coronary angiography between 2002 and 2010 were screened. We eventually included patients with at least one intermediate coronary stenosis (diameter stenosis ≥40%) in whom revascularization was deferred based either on angiography plus FFR (FFR-guided) or angiography alone (angiography-guided). The primary endpoint of the study was the cumulative incidence of all-cause death at 10 years. The secondary endpoint, (the incidence of major adverse cardiovascular and cerebrovascular events ([MACCE]), was a composite of all-cause death, myocardial infarction, any revascularization and stroke.

Results. A total of 840 patients were included (206 in the FFR-guided and 634 in the angiography-guided group). Median clinical follow-up was 7 years (IQR [3.22 - 11.08]). After 1:1 propensity score matching, baseline characteristics between the two groups were similar. All-cause death was significantly lower in the FFR-guided group compared with the angiography-guided group (94 [45.6%] vs. 119 [57.8%], HR 0.65 [95%CI 0.49 - 0.85], p < 0.01). The rate of major adverse cardiovascular and cerebrovascular events ([MACCE], a composite of all-cause death, myocardial

infarction, any revascularization and stroke) was lower in the FFR-guided group (123 [59.7%] vs. 139 [67.5%], HR 0.75 [95%CI 0.59 - 0.95], p = 0.02) (Figure 28).

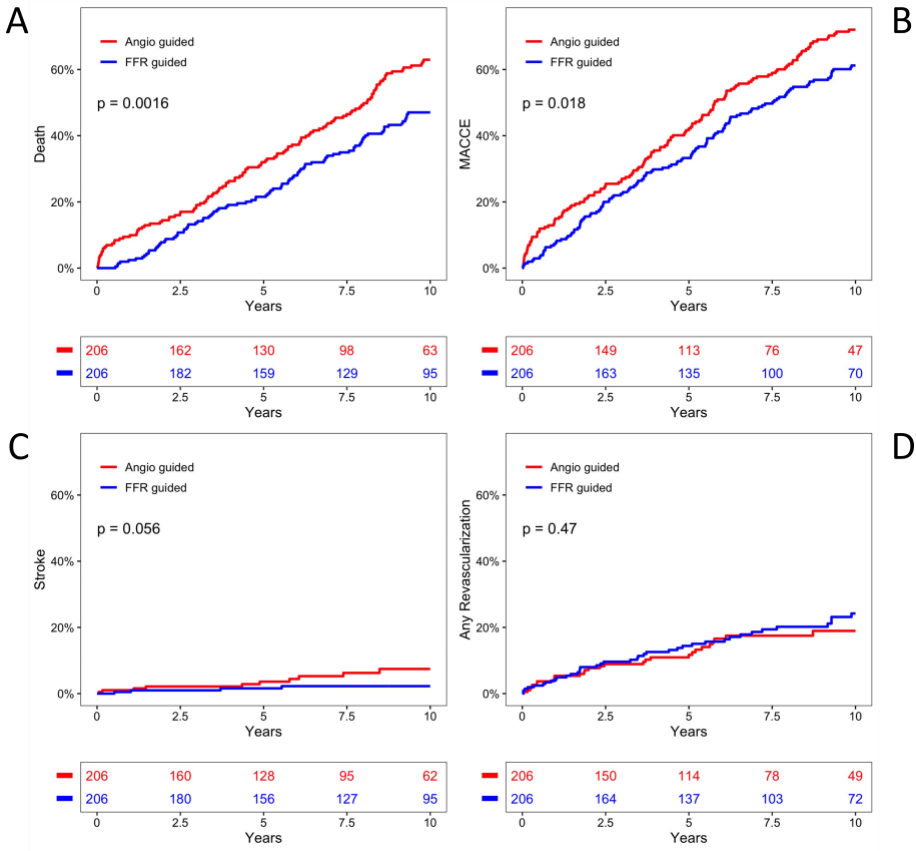


Figure 28. Kaplan–Meier event curves for clinical outcomes in the matched cohort (A) All-cause death; (B) Major Adverse Cardiovascular and Cerebrovascular Events; (C) Stroke; (D) Any revascularization.

The impact of deferring revascularization based on FFR was assessed as continuum of LVEF. Interestingly, when an FFR guided strategy was compared with an angiography-guided strategy by using LVEF as continuous variable, the FFR-guided group showed lower probability of death especially for LVEF values >25% (Figure 29).

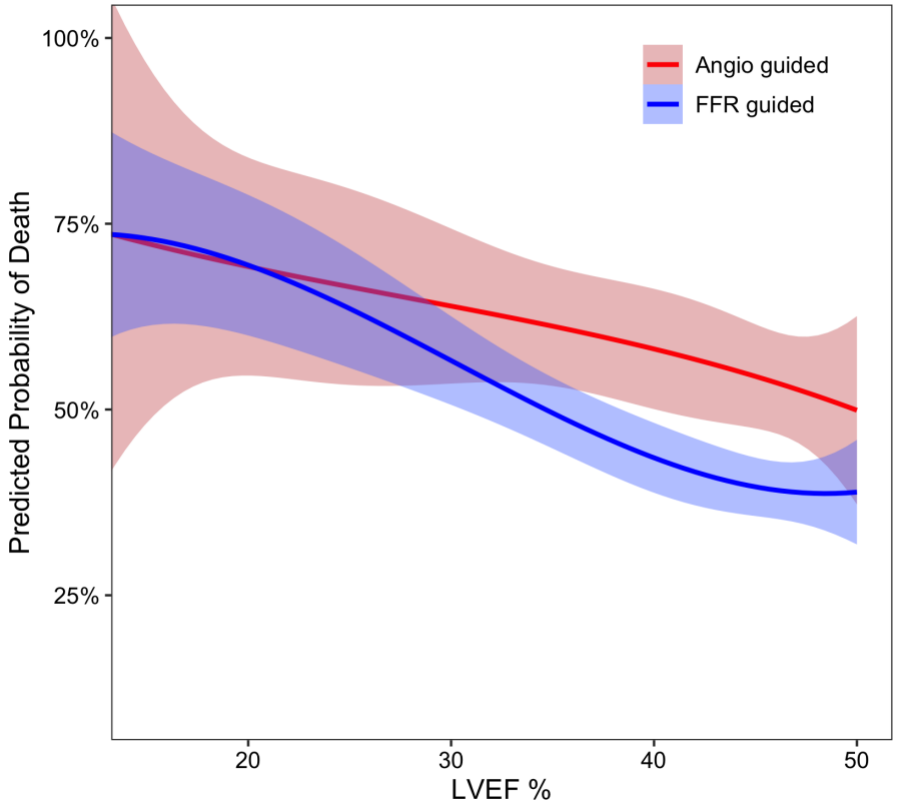


Figure 29. Predicted probability of death per group in the matched cohort according to the LVEF presented as continuous variable.

Conclusions. In patients with reduced LVEF, deferring revascularization of intermediate coronary stenoses based on FFR is associated with a lower incidence of death and MACCE at 10 years.

Chapter 17

Intra-coronary pressures to predict myocardial viability in patients with ischemic left ventricular dysfunction

Background. In patients with ischemic left ventricular dysfunction, the presence of myocardial viability is related to the expected benefits derived from coronary revascularization. The aim of this study was to investigate the role of intra-coronary pressure parameters in the assessment of viability in the myocardium subtending a significant coronary stenosis.

Methods. Intra-coronary pressure wire-based measurements were performed in 64 coronary lesions of ≥50% stenosis severity of 59 patients with post-ischemic left ventricular dysfunction, segmental left ventricular wall motion abnormalities and substantial viability in the myocardial territory subtending the investigated stenotic coronaries, defined as the percent summed rest score in the target territory (%SRStarget) ≤60% at the single-photon emission tomography. Invasive pressure-derived indexes like resting and hyperemic Pd/Pa, ΔPd/Pa and %ΔPd/Pa (defined as the absolute difference and percent decrease between resting and hyperemic Pd/Pa respectively) were compared with %SRStarget.

Results. A significant correlation was found between ΔPd/Pa (Spearman's rho: -0.760, p<0.001) and %ΔPd/Pa (rho: -0.733; p<0.001) with %SRStarget (Figure 28). These results were confirmed after correction for potential confounders (Figure 30).

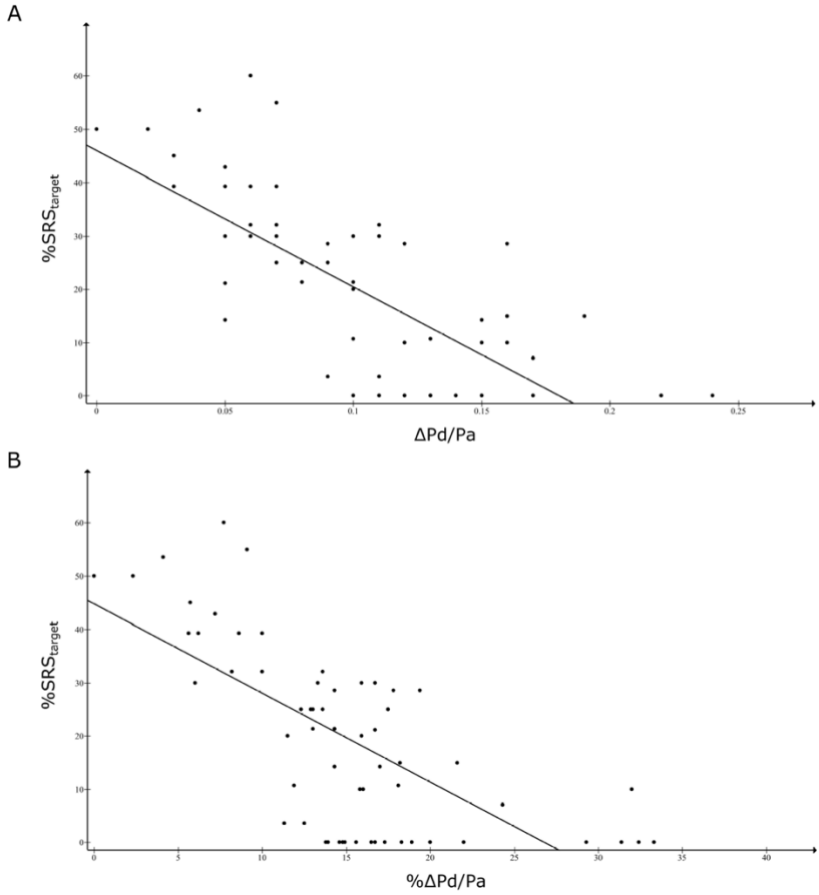


Figure 30. Correlations between ΔPd/Pa and viability in the target myocardial territory. Legend: Scatterplot of A) %SRStarget vs ΔPd/Pa (beta coefficient: -2.5, p<0.001) and B) %SRStarget vs %ΔPd/Pa (beta coefficient: -1.7, p<0.001). ΔPd/Pa and %ΔPd/Pa: the absolute difference and % decrease between resting and hyperemic Pd/Pa respectively; %SRStarget: the summed rest score (percentage of the maximum score) calculated in vessel-specific coronary perfusion territory.

According to %SRStarget median value, myocardial areas with high and low viability were compared: ΔPd/Pa and %ΔPd/Pa were significantly higher in areas with high viability (p<0.001 for both) (Figure 31). According to ROC curves, we identified two cut-offs (ΔPd/Pa >0.11 and %ΔPd/Pa >15%) able to predict >80% viability with good sensitivity and specificity.

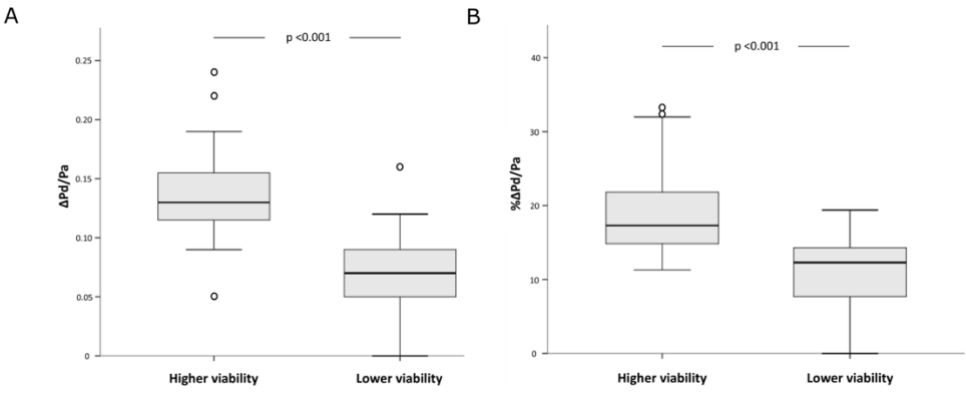


Figure 31. ΔPd/Pa and %ΔPd/Pa values according to %SRStarget median value. Boxplot of A) ΔPd/Pa and B) %ΔPd/Pa by %SRStarget median value.

Conclusions. Our study suggests that, in patients with post-ischemic left ventricular dysfunction and significant coronary stenosis, intra-coronary pressures indexes like ΔPd/Pa and %ΔPd/Pa are able to predict the magnitude of downstream myocardial viability.

Part III

Coronary physiology in patients with comorbidities

IIIc – Diabetes Mellitus

Chapter 18

Severity of Coronary Atherosclerosis and Risk of Diabetes Mellitus

Background: Cardio-vascular target organ damage predicts the onset of type 2 diabetes mellitus (DM) in hypertensive patients. Whether an increased incidence of DM is also in relation to the severity of coronary atherosclerosis is unknown. Thus, we evaluated the onset of DM in relation to the extent and severity of coronary atherosclerosis, using the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score (SS), in patients with stable angina or acute coronary syndromes, referred for coronary angiography (CA).

Methods: We screened all of the consecutive patients who underwent CA at the Cardiovascular Center Aalst (Belgium), between 1 January 2009 and 31 December 2009. The exclusion criteria were as follows: previous coronary angiogram, history of myocardial infarction or coronary artery bypass graft, or the diagnosis of pre-existing diabetes. The primary endpoint of the study was the incidence of type 2 DM after index hospitalization. Predictors of DM onset in low, medium, and high SSs were investigated.

Results: Five hundred and seventy patients were included, and the mean SS was 6.3 ± 7.6. During a median follow-up of 79 months (interquartile range (IQR): 67–94), 74 patients (13%) developed DM. The incidence of diabetes was significantly higher in the patients with a high SS (41%), than in patients with a medium (12%) and low SS (2%; p for trend < 0.0001; Figure 32).

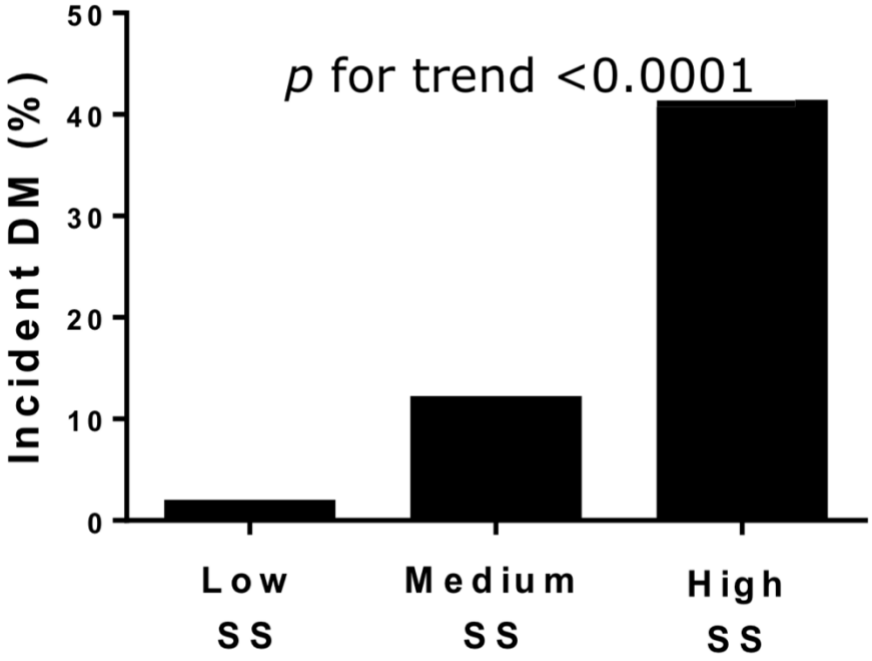
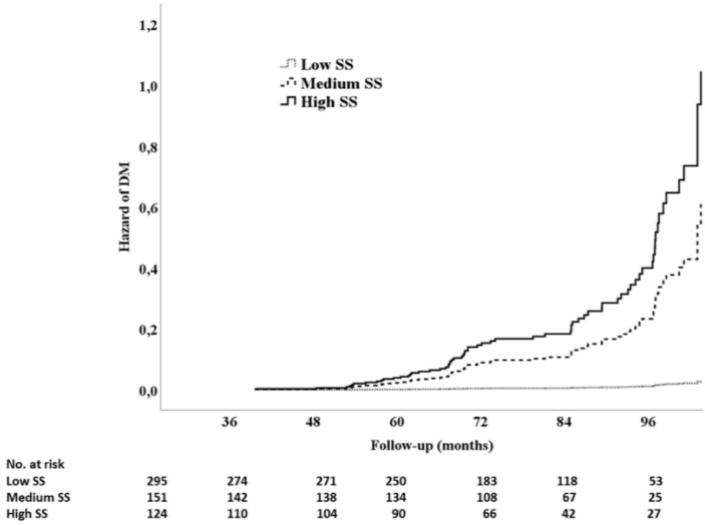


Figure 32. Rate of type 2 diabetes mellitus (DM) in the three SYNTAX score (SS) levels.

In the Cox regression analysis, the predictors of DM onset during follow-up had higher baseline values of fasting plasma glucose (HR = 1.043; (95% CI 1.011–1.075); $p < 0.008$), medium SS (HR = 6.630; (95% CI 2.394–18.358); $p < 0.0001$), and high SS (HR = 14.789; (95% CI 5.796–37.737); $p < 0.0001$). The three curves (Figure 33) started to separate after 48–52 months from the index hospitalization, and further diverged after five years of follow-up.



No. at risk							
Low SS	295	274	271	250	183	118	53
Medium SS	151	142	138	134	108	67	25
High SS	124	110	104	90	66	42	27

Figure 33. Cox regression time to event analysis for type 2 diabetes mellitus onset, in the function of the three SS levels.

Conclusions: The severity and extent of the coronary atherosclerosis, evaluated by the SS, is a strong and independent predictor of the development of DM in patients, referred to CA.

Chapter 19

Insulin Resistance Predicts Severity of Coronary Atherosclerotic Disease in Non-Diabetic Patients

Background: Insulin resistance (IR) in patients with type 2 diabetes mellitus (T2DM) represents a predictor of coronary artery disease (CAD). However, how IR is able to impact the severity of coronary atherosclerosis in non-diabetic patients is unknown. We investigated the relation between the IR and the extent and severity of coronary atherosclerosis in non-diabetic patients referred to coronary angiography (CA).

Methods: We prospectively analyzed consecutive patients undergoing coronary angiography (CA) for ACS or stable angina in the Catheterization Laboratories of the University of Naples Federico II (Italy) and of the OLV Heart Centrum in Aalst (Belgium) from February 2018 to June 2019. Exclusion criteria were age < 18 years, pregnancy or breastfeeding, and presence of pre-diabetes or overt diabetes. Pre-diabetes and diabetes were diagnosed based on the fasting plasma glucose or the glycated hemoglobin according to the current guidelines (FPG ≥ 100–125 mg/dL and Hb1Ac ≥ 5.6–6.4% for pre-diabetes; FPG ≥ 126 mg/dL and Hb1Ac ≥ 6.5%. The IR was assessed by mean of the homeostasis model assessment of insulin resistance (HOMA-IR), defined as [fasting insulin × fasting glucose] / 22.5. Results of the HOMA-IR were divided into percentiles and a value ≥ the 75th percentile was considered pathologic. The SYNTAX score (SS) was used as index of the severity of coronary atherosclerosis.

Results: Overall, 126 patients were included, with a median SS of 12 (IQR 5.25–20.5). Patients were divided in four groups according to the distribution in quartiles of SS (SS1-2-3-4). A significant correlation between HOMA-IR and SS was observed, especially in women. A progressive increase of HOMA-IR was observed in parallel with the increasing severity (from SS1 to SS4) and extension (1-2-3-vessel disease) of coronary atherosclerosis (Figures 34 and 35).

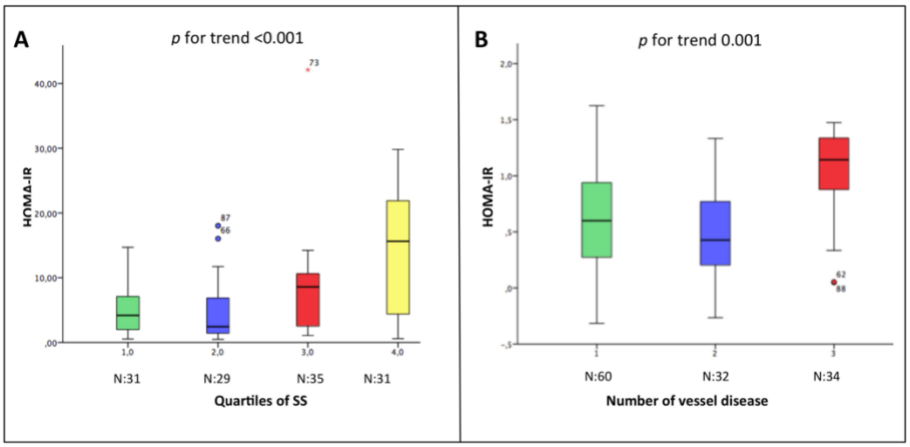


Figure 34. Relation between the HOMA-IR and the severity (Panel A) and the extension (Panel B) of coronary atherosclerosis. In Panel A, patients are divided per tertiles of Syntax Score. In Panel B, patients are divided based on the number of vessel disease. * Outliers.

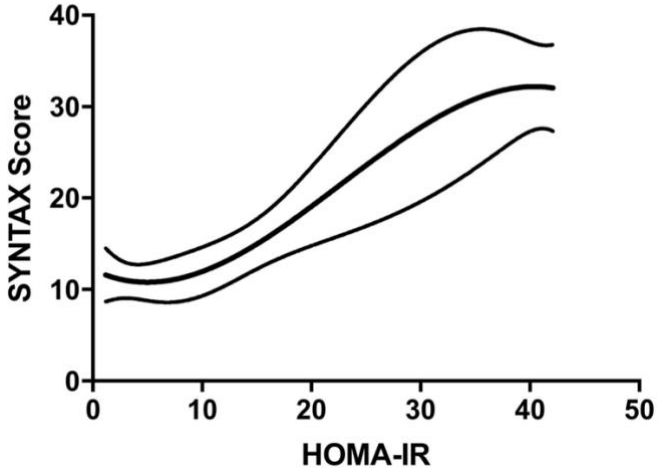


Figure 35. Plot of the non-parametric regression with natural cubic splines, showing the correlation between HOMA-IR and SS. This plot shows the correlation between HOMA-IR and SS. The upper and lower lines represent the 95% confidence intervals (CI). The equation used is the following: SS = 12.19 − 0.5812 * HOMA-IR + 0.06551 * (HOMA-IR)2 −0.0009619 * (HOMA-IR)3.

Multivariable analysis showed that the HOMA-IR was the strongest independent predictor of severe (SS4) and extensive (three-vessel disease) coronary atherosclerosis.

Conclusion: Insulin resistance goes hand in hand with the extension and severity of coronary atherosclerosis in non-diabetic patients. The HOMA index is an independent predictor of three-vessel disease at CA. The HOMA index could be useful for risk stratification of CAD even in absence of T2DM.

Chapter 20

Coronary Artery Bypass Grafting or Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Diabetic Patients With Multivessel Disease

Background. In diabetic patients with multivessel coronary disease (MVD), coronary artery bypass grafting (CABG) has shown long-term benefits over percutaneous coronary revascularization (PCI). Physiology-guided PCI has shown to improve clinical outcomes in MVD, though its impact in diabetic patients has never been investigated. We evaluated long-term clinical outcomes of diabetic patients with MVD treated with FFR-guided PCI compared to CABG.

Methods. From 2010 to 2018, 4622 diabetic patients undergoing coronary angiography were screened for inclusion. The inclusion criterion was presence of at least two-vessels disease defined as with DS ≥ 50%, in which at least 1 intermediate stenosis (DS 30-70%) was treated or deferred according to FFR. Exclusion criteria were ST-segment elevation myocardial infarction, previous CABG, left main stenosis, and moderate or severe valvular heart disease requiring surgical or percutaneous repair or replacement. Inverse probability of treatment weighting analysis was used to account for baseline differences with a contemporary cohort of patients treated with CABG. The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE), defined as all-cause death, myocardial infarction, revascularization, or stroke. Multivariate unweighted cox-regression analysis was then performed using as covariates the predictors of 4-year mortality in the SYNTAX trial, and insulin therapy as a marker of diabetes severity.

Results: A total of 418 patients were included in the analysis. Among them, 209 patients underwent CABG and 209 FFR-guided PCI. At 5 years, the incidence of MACCE was higher in the FFR-guided PCI vs. the CABG group (44.5% vs. 31.9%. HR [95% CI] 1.60 [1.15-2.22]; p = 0.005). No difference was found in the composite of

all-cause death, MI or stroke (28.8% vs. 27.5%. HR [95% CI] 1.05 [0.72-1.53]; p = 0.81) (Figure 36). Repeat revascularization was more frequent with FFR-guided PCI (24.9% vs. 8.2%. HR [95% CI] 3.51 [1.93-6.40]; p < 0.001). Similar results were obtained with multivariate cox-regression analysis after adjustment for age, sex, glomerular filtration rate, chronic obstructive pulmonary disease, peripheral vascular disease, left ventricular ejection fraction, Syntax score and insulin therapy.

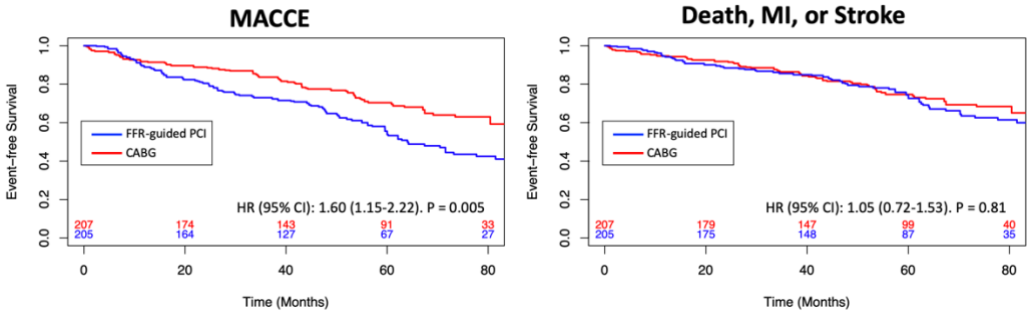


Figure 36. IPTW Adjusted Kaplan-Meier curves depicting event-free survival for MACCE and for the composite of all-cause death, MI, or stroke.

In the FFR-guided PCI group, 155 stenoses in 134 patients were deferred to medical therapy on the basis of an FFR value > 0.80. Revascularization at follow-up was performed for 13 lesions (8%) in 12 patients (9%) at a follow-up of 46 (29-53) months. The indication for revascularization was recurrent angina in 9 patients; NSTEMI in 1 patient; while 2 patients were referred for coronary angiography with atypical chest pain and were revascularized despite angiographic absence of lesion progression (Figure 37).

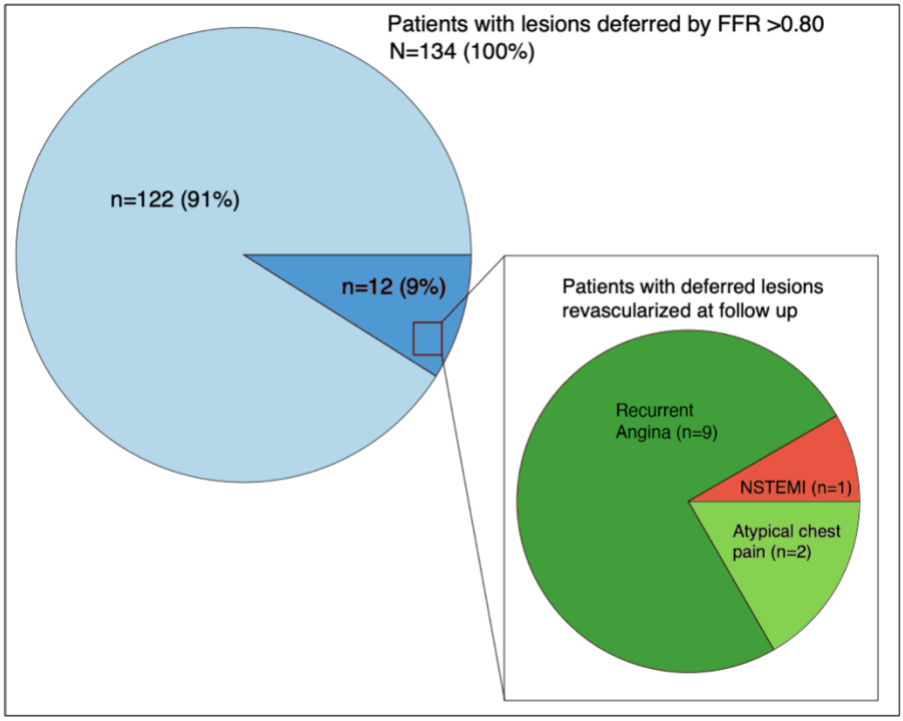


Figure 37. Revascularization events in lesions deferred to medical therapy on the basis of FFR >0.80 at the index procedure.

Conclusions: In diabetic patients with MVD, CABG was associated with a lower rate of MACCE compared with FFR-guided PCI, driven by a higher rate of repeat revascularization. At 5-year follow-up, no difference was observed in in the composite of all-cause death, MI, or stroke between CABG and FFR-guided PCI.

Part IV

Characterization of pattern of epicardial atherosclerosis

Chapter 21

Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis

Background: Diffuse atherosclerosis is commonly observed in angiographically normal segments in patients with stable coronary artery disease (CAD). The distribution of epicardial resistance along the vessel can be evaluated using coronary physiology. The objective of the present study was to characterize the pathophysiological patterns of CAD using motorized coronary pressure pullbacks during continuous hyperemia and propose a quantitative assessment of the spatial distribution of the epicardial resistance in patients with stable CAD.

Methods: In this prospective, multicenter study of patients undergoing clinically-indicated coronary angiography due to stable angina, a pressure-wire pullback device was set at a speed of 1 mm/s. In brief, the pressure wire sensor was positioned in the distal coronary segments of >2mm of diameter by visual estimation. Pressure wire position was recorded using contrast injection to identify the pullback start position. The RadiAnalyzer Xpress (St. Jude Medical, Minneapolis, Minnesota) and QUANTIEN Integrated FFR System (Abbott Vascular, Abbott Park, Illinois) were used to measure invasive coronary pressures. Following intracoronary nitrate administration, a continuous intravenous adenosine infusion was given at a dose of 140 mg/kg/min via a peripheral or central vein to obtain steady-state hyperemia for at least 2 min. A pullback device (Volcano R 100, San Diego, California), adapted to grip the coronary pressure wire (PressureWire X, St. Jude Medical), was set at a speed of 1 mm/s to pull back the pressure wire sensor up to the tip of the guiding catheter during continuous pressure recording. The maximal pullback length was 130 mm per vessel. If FFR drift (>0.03) was observed, the FFR pullback was repeated. An FFR value was extracted from the pressure tracing every 10 mm. FFR

was defined as the ratio of between distal and proximal coronary pressures. Offline FFR pullback curves were created and analyzed by an independent core laboratory.

Based on coronary angiography and on the fractional flow reserve (FFR) pullback curve, the patterns of CAD were adjudicated as focal, diffuse, or a combination of both. The distribution of epicardial resistance was characterized using the hyperemic pullback pressure gradients (PPGs). The PPG index, a continuous metric based on the magnitude of pressure drop over 20 mm and on the extent of functional disease was computed to determine the pattern of CAD. Specifically, PPG index is defined as:

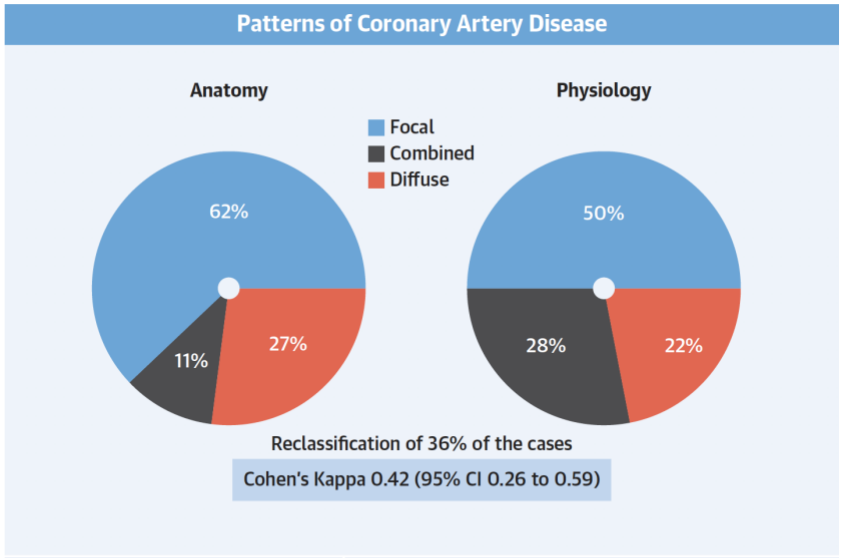
$$\frac{\left\{\frac{MaxPPG_{20mm}}{\Delta \mathrm{FFR}_{vessel}} + \left(1 - \frac{\text{Length with functional disease (mm)}}{\text{Total vessel length (mm)}}\right)\right\}}{2}$$

Maximal PPG was defined as the maximum pressure gradients over 20 mm, and delta FFR vessel as the

difference between FFR values obtained at the ostium of the vessel and at the most distal anatomical location.

The length of functional disease and the total vessel length were derived from the motorized pullback pressure tracing. The length of functional CAD was defined as the length, in millimeters, with FFR drop $\geq$ 0.0015/mm. This cut-off was selected based on the analysis of curve variations in segments without functional disease. This was defined as FFR pullback curves with slope equal to zero. Subsequently, the 95th percentile of FFR curve variation was selected as the cut-off to minimize the effect of minor artifacts on this parameter. The combination of these 2 ratios was used to calculate the PPG index, a metric that characterizes the pattern of CAD based on coronary physiology. The PPG index is a continuous metric: values approaching 1.0 represent focal hemodynamically focal CAD, whereas values close to 0 diffuse CAD.

Results. A total of 158 vessels (n = 117) were included. Overall, 984,813 FFR values were used to generate 100 FFR pullback curves. Using coronary physiology, 36% of the vessel disease patterns were reclassified compared to angiography (Figure 38).



		Anatomy		
		Diffuse	Combined	Focal
Physiology	Diffuse	10	0	9
	Combined	10	7	7
	Focal	3	2	37

Figure 38. Reclassification Between Anatomical and Physiological Assessment on the Pattern of CAD. The left pie chart presents the classification of the pattern and CAD based on coronary angiography (n = 85 vessels). The right pie chart shows declassification of the CAD patterns by visual assessment of the motorized FFR pullback curve. CAD = coronary artery disease; CI = confidence interval; FFR = fractional flow reserve.

The median of maximal PPG over 20 mm was 0.083 (interquartile range: 0.063 to 0.118) FFR units, and the mean extent of functional disease was 39.3 $\pm$ 21.3 mm. The mean PPG index was 0.58 $\pm$ 0.18 and differentiated pathophysiological focal and diffuse disease ($p < 0.001$). Examples of pathophysiological patterns of CAD with the corresponding PPG indexes are shown in Figure 39.

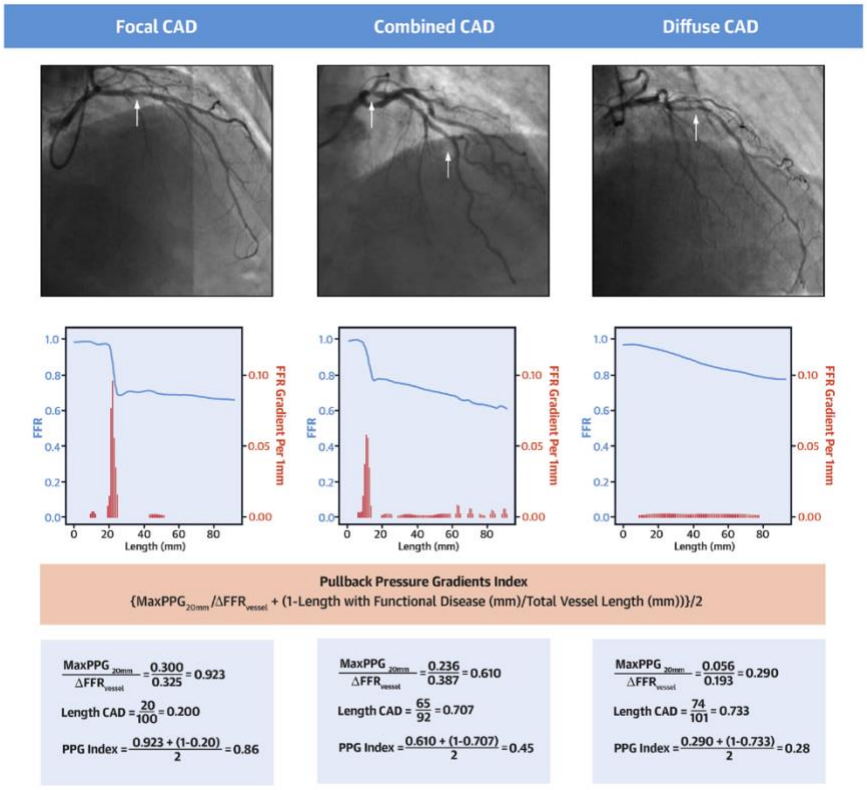


Figure 39. Pathophysiological Coronary Artery Disease Patterns and PPG Index. Three case examples depicting the pathophysiological patterns of CAD. (Top) Conventional coronary angiography; (middle) the FFR pullback curves; and histograms depicting the magnitude and extension of FFR drop; and (bottom) details of the PPG calculation. The red bars indicate FFR drops $0.0015. On the top left panel, the angiography shows a severe lesion in the mid LAD (white arrow) with a distal FFR of 0.68. This lesion produced an FFR drop responsible for 86% of the distal FFR with a maximum pullback pressure gradient over 20 mm of 0.30 FFR units. Only 20% of the vessel showed functional disease. The PPG index was 0.86, indicating physiological focal CAD. The top middle panel shows a severe lesion at the proximal LAD and a moderate lesion at mid LAD (white arrows). The maximum pullback pressure gradient over 20 mm was 0.236 FFR units, with 70.7% of the vessel length showing FFR deterioration, and the PPG index was 0.45. In the top right panel, an anatomical lesion at the mid LAD (white arrow) was observed with distal FFR of 0.78. The maximum pullback pressure gradient over 20 mm was 0.056, while 73.3% of the vessel length showed physiological disease. The PPG index was 0.28, indicating physiological diffuse CAD. CAD = coronary artery disease; FFR = fractional flow reserve; LAD = left anterior descending artery; PPG = pullback pressure gradient.

Conclusions: Pathophysiological patterns of CAD can be characterized by motorized hyperemic PPGs. The evaluation of the FFR pullback curve reclassified one-third of the vessels' disease patterns compared with conventional angiography. The PPG index is a novel metric that quantifies the distribution of epicardial resistance and discriminates focal from diffuse CAD.

Chapter 22

Hyperemic hemodynamic characteristics of serial coronary lesions assessed by pullback pressure gradients

Background: The presence of more than one stenosis within the same coronary artery is common. These serial stenoses often represent a physiological conundrum because of the interaction (cross talk) between the different stenoses. This prevents merely summing up the transstenotic pressure gradients taken in isolation. As a consequence, isolating the functional contribution of each lesion in a serial circuit either in resting or hyperemic conditions remains challenging. Traditionally, serial lesions have been defined based on coronary angiography. Nonetheless, this approach neglects the known discordance between angiographic stenosis and its physiological effect, which is further affected by the distance between the stenoses and the microcirculatory function. Intracoronary pressure pullbacks are essential to understand the physiological effect of serial lesions. The present study aims at characterizing the functional pattern of CAD in vessels with serial lesions using mechanized FFR pullbacks and the PPG.

Methods: One-hundred seventeen patients undergoing coronary angiography or stable angina were prospectively recruited. Serial lesions were defined as two or more narrowings with visual diameter stenosis >50% on conventional angiography. Motorized FFR pullback tracings were obtained at 1 mm/s. Pullbacks were visually adjudicated as presenting two, one, and no focal pressure drops (Figure 40). The pattern of disease (i.e., focal or diffuse) was quantified using the PPG index.

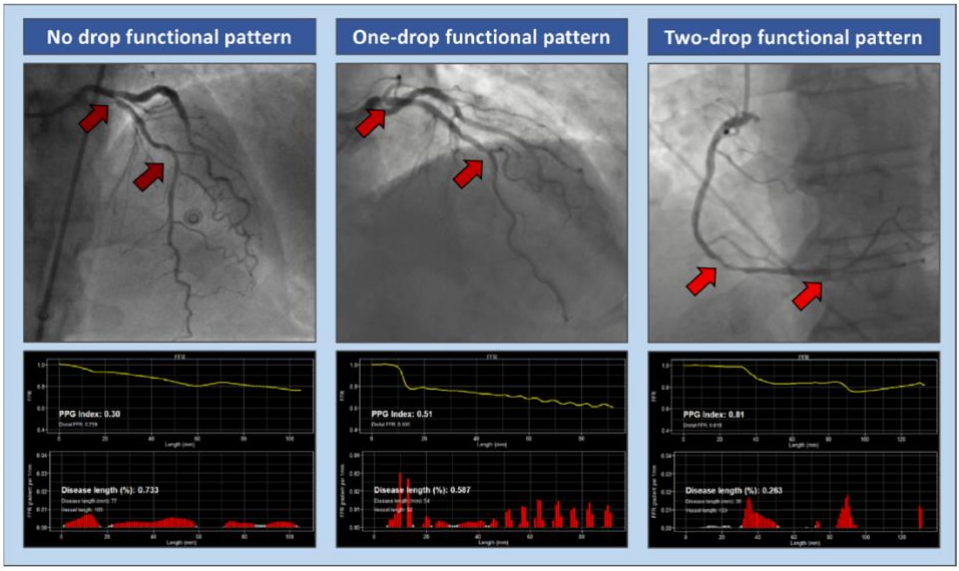


Figure 40. Serial lesions were independently adjudicated by visual inspection of patients coronary angiograms (upper panels) as presenting 2 or more narrowings (arrows) with visual diameter stenosis >50%, separated at least by 3 times the reference vessel diameter in the same coronary vessel. In turn, the visual analysis of the pullback pressure gradients (PPG) tracings was used to categorized the pressure drop patterns along the vessel presenting a serial lesion, thus resulting in three patterns (lower panels): absence of focal drops (left), presence of only one focal drop, either proximally or distally, (central panel), and presence of two focal pressure drops (right). FFR= fractional flow reserve; PPG = pullback pressure gradient.

Results: Twenty-five vessels presented serial lesions (mean PPG 0.48 ± 0.17). Two, one or no focal pressure drops were observed in 40% (n = 10; PPG 0.59 ± 0.17), 52% (n = 13; PPG 0.44 ± 0.12) and 8% of cases (n = 2; PPG 0.27 ± 0.01; p-value = 0.01) (Figure 41). Distal FFR was similar between vessels with two, one and no focal pressure drops in the pullback curve (p-value = 0.27). The PPG index independently predicted the presence of two focal pressure drops in the pullback curve (p = 0.04) (Figure 42).

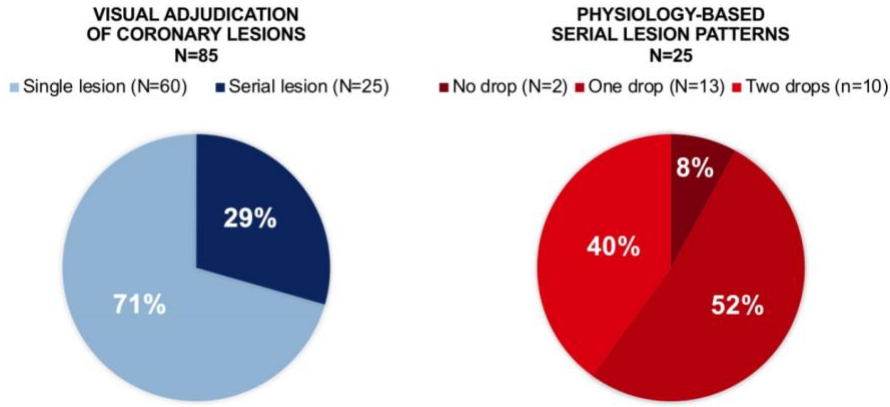


Figure 41. The left pie chart displays the percentages of vessels visually adjudicated as presenting a single lesion or serial lesions from the cohort of patients included in the Physiological Patterns of Coronary Artery Disease clinical trial (n=85). The right pie chart shows the distributions of serial lesions pullback patterns.

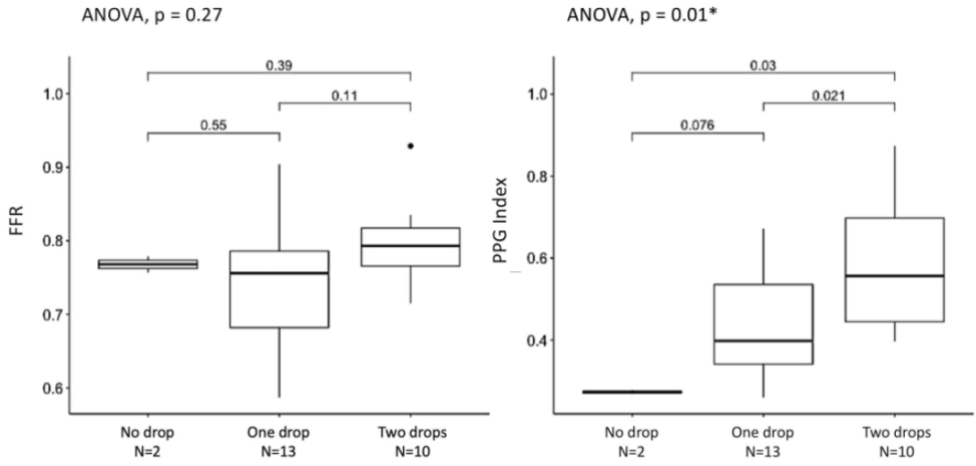


Figure 42. Distributions of the fractional flow reserve (left panel) and pullback pressure gradient index (right panel) according to the adjudicated functional pattern, underlining the inability for the distal FFR to capture difference among the three functional patterns. On the other hand, higher PPG index values were significantly associated with the two focal serial lesion patterns. FFR, functional flow reserve; PPG, pullback pressure gradient

Conclusions: FFR pullbacks in serial coronary lesions exhibit three distinct functional patterns. High PPG was associated with pullback curves presenting two pressure drops. The PPG provides a quantitative assessment of the pattern of coronary artery disease in cases with serial lesions and might be useful to assess the appropriateness of percutaneous revascularization.

Part V

Invasive assessment of coronary microcirculation

Chapter 23

Effects of Prasugrel Versus Clopidogrel on Coronary Microvascular Function in Patients Undergoing Elective PCI

Background: Microvascular impairment has been reported in patients on clopidogrel undergoing elective PCI. The related potential mechanisms might include the high residual platelet reactivity (PR) observed in a substantial proportion of these patients pretreated with clopidogrel at the time of PCI. Alternatively, microvascular constriction could occur possibly as consequence of transient endothelial dysfunction related to impaired platelet response to clopidogrel.

Aim: to evaluate whether prasugrel might exert a protective effect on microcirculation during elective PCI in patients with stable CAD scheduled for elective PCI.

Methods: The prospective randomized double-blind controlled PROMICRO-2 (PROtecting MICROcirculation during coronary angioplasty) trial enrolled thienopyridine-naive patients with stable CAD referred to elective PCI of an isolated, functionally significant (FFR <0.80) lesion located in the proximal twothirds of a major coronary artery. Patients were randomized to either prasugrel (60 mg) or clopidogrel (600 mg) at least 12 h before PCI. All patients received a 500-mg loading dose of aspirin the day before the procedure. CFR, IMR, and FFR were measured in each patient before and after PCI. High-sensitivity troponin T (hs-TnT) was assessed in blood samples before, and 8 and 24 h after PCI.

Results: At baseline, FFR, CFR, and IMR were similar in the 2 study groups. Patients in the prasugrel group showed significantly lower post-PCI IMR values compared

with those in the clopidogrel group. Compared with baseline, IMR increased post-PCI in the clopidogrel group (p= 0.009), but not in the prasugrel group (p= 0.299). Repeated measures 2-way analysis of variance (ANOVA) showed a significant interaction between treatment (i.e., prasugrel vs. clopidogrel) and time in determining IMR values (p= 0.047). Consistently, post-PCI CFR was significantly higher in the prasugrel compared with the clopidogrel group. Compared with baseline, CFR remained unchanged post-PCI in the clopidogrel group (p= 0.563), whereas increased in the prasugrel group (p= 0.036). Repeated-measures 2-way ANOVA showed a nonsignificant interaction between treatment (i.e., prasugrel vs. clopidogrel) and time in determining CFR values (p= 0.053). Baseline Hs-TnT was 4.8 (IQR: 3.2 to 10.1) ng/ml in the prasugrel group versus 5.1 (IQR: 3.0 to 12.8) ng/ml in the clopidogrel group (p= 0.845). Post-PCI Hs-TnT was 12.8 (IQR: 7.7 to 23.6) ng/ml in the prasugrel group versus 25.6 (11.8 to 50.6) ng/ml in the clopidogrel group (p= 0.032). Repeated-measures 2-way ANOVA showed a significant interaction between treatmentand time in determining log-transformed Hs-TnT values (p= 0.044). Periprocedural Hs-TnT increase (i.e., difference between baseline and highest post-procedural values) was significantly lower in the prasugrel group compared with the clopidogrel group (6.6 [2.5 to 9.7] ng/ml vs. 15.8 [5.9 to 38.0] ng/ml; p= 0.034).

Conclusions: the results of the PROMICRO-2 trial suggest that more intensive antiplatelet regimens might offer additional benefit compared with clopidogrel also in the setting of elective PCI.

Chapter 24

Platelet Reactivity and Coronary Microvascular Impairment After Percutaneous Revascularization in Stable Patients Receiving Clopidogrel or Prasugrel

Background: Currently recommended antiplatelet therapy for patients with stable CAD undergoing elective PCI is unable to provide effective platelet inhibition in all patients. Despite pretreatment with aspirin and clopidogrel, a large proportion of these patients show high residual PR at the time of PCI. Coronary vessel manipulation especially during complex PCI is an additional trigger for transient increase in PR. Prasugrel provides more potent platelet inhibition than clopidogrel, though it is unknown whether it might also prevent PCI-related platelet activation.

Aim: In stable patients undergoing elective PCI, we compared: (1) the effects of prasugrel vs. clopidogrel on peri-procedural variations of PR; (2) the correlation of platelet inhibition potency with PCI-induced coronary microvascular impairment.

Methods: forty thienopyridine-naive patients were randomly assigned to a loading dose of either prasugrel 60 mg (n=20) or clopidogrel 600 mg (n=20) at least 12 hours before PCI. At the time of PCI, we assessed adenosine diphosphate (ADP)-induced PR with the Multiplate Analyzer, and IMR in the treated coronary, both at baseline and post-procedure.

Results: Patients in the prasugrel group showed significantly lower ADP-induced PR both at baseline (16.0±8.7 vs. 33.9±18.0 AU, $p<0.001$) and post-PCI (16.2±9.0 vs. 39.0±18.6 AU, $p<0.001$) as compared with the clopidogrel group. While a significant peri-procedural increase in PR was observed in the clopidogrel group ($p=0.008$), PR was not significantly different before and after PCI in the prasugrel group ($p=0.822$) (Figure 43). Repeated measures 2-way ANOVA showed a significant interaction

between treatment and time in determining PR values (p=0.022). Periprocedural variation (defined as the difference between after and before PCI) of PR (ΔPR) was 5.1±7.6 AU in the clopidogrel group and 0.3±4.9 in the prasugrel group (p=0.014).

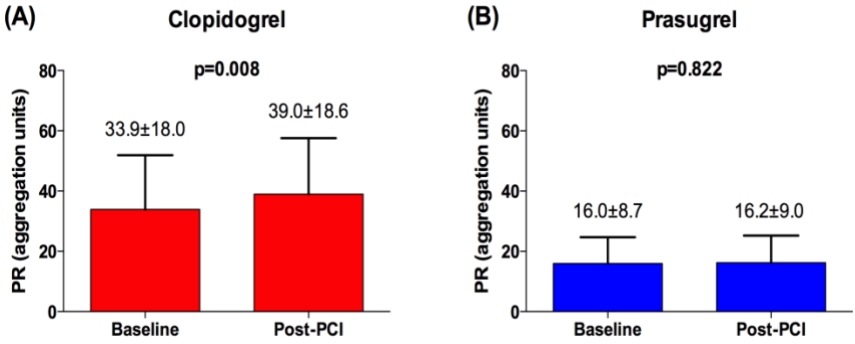


Figure 43: Platelet reactivity. Adenosine diphosphate-induced platelet reactivity (PR) at baseline and post-PCI. Panel A: patients treated with clopidogrel. Panel B: patients treated with prasugrel. Data shown as mean and standard deviation.

A significant correlation was observed between baseline and post-PCI IMR, both in the overall population (r=0.689, p<0.0001) and in the two study groups separately (clopidogrel: r=0.623, p=0.003; prasugrel: r=0.751, p<0.0001). The change between baseline and post-PCI IMR was not significantly different between the two study groups, neither when considering the net numerical difference (6±9 in the clopidogrel group vs. 2±7 in the prasugrel group; p=0.118), nor when considering the percent difference (38±52% in the clopidogrel group vs. 42±98% in the prasugrel group; p=0.871). Considering the whole study population altogether, a significant correlation was found between IMR and PR both at baseline (r=0.458, p=0.003) and post-PCI (r=0.487, p=0.001) (Figure 44 panel A and B). A total of 24 patients showed a periprocedural increase in PR (15 in the clopidogrel group and 9 in the prasugrel group). In these patients, IMR post-PCI was significantly higher compared with patients who did not show a periprocedural increase in PR (24.6±10.9 vs. 17.3±8.7, p=0.029) (Figure 44, panel C). In patients with periprocedural increase in PR, a

significant correlation was found between ΔPR and ΔIMR (r=0.453, p=0.026) (Figure 44, panel D).

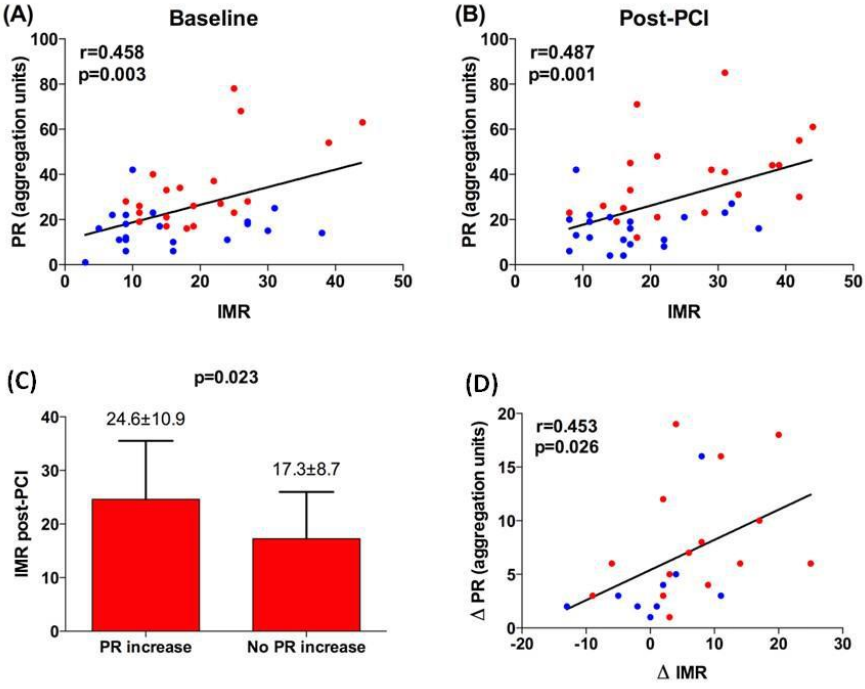


Figure 44: Microvascular function and platelet reactivity. Correlation between IMR and adenosine diphosphate-induced PR. Panel A: baseline. Panel B: post- PCI. Red dots indicate patients in the clopidogrel group; blue dots indicate patients in the prasugrel group. **Periprocedural variations of platelet reactivity and microvascular function.** Panel C: IMR post-PCI in patients with and without periprocedural increase in adenosine diphosphate-induced PR. Data shown as mean and standard deviation. Panel D: correlation between variations of PR (ΔPR) and variations of IMR (ΔIMR) in patients with periprocedural increase in PR. Red dots indicate patients in the clopidogrel group; blue dots indicate patients in the prasugrel group. PCI: percutaneous coronary intervention; IMR: index of microvascular resistance; PR: platelet reactivity;

Conclusions: a loading dose of prasugrel compared with clopidogrel is able to attenuate PCI-related increase in PR in patients with stable CAD undergoing PCI, which might contribute to the beneficial effect of this drug on peri-procedural coronary microvascular function.

Chapter 25

Coronary microcirculation and peri-procedural myocardial injury during elective percutaneous coronary intervention

Background: Coronary microvascular dysfunction before percutaneous coronary intervention (PCI) predicts PCI-related myocardial injury in patients with stable coronary artery disease (CAD). Whether the dynamic changes of the microcirculation during PCI might be associated with the occurrence of procedure-related myocardial injury and infarction is still unclear. We aimed to investigate the impact of pre- and post-PCI microvascular function, evaluated with the index of microvascular resistance (IMR) on the occurrence of PCI-related myocardial injury and infarction.

Methods: In consecutive patients with stable CAD referred for elective PCI, coronary physiological indexes, including IMR, were measured before and after revascularization. High sensitivity Troponin T (hs-TnT) was assessed up to 24 hours after PCI, and PCI-related myocardial injury and type 4a myocardial infarction (MI) were defined according to the fourth universal definition of myocardial infarction.

Results: In the 50 patients enrolled, a significant correlation was found between maximum post-PCI hs-Tn and IMR, both at baseline (rho=0.309, p=0.029) and post-PCI (rho=0.378, p=0.007). Patients who developed type 4a MI, compared with patients who did not, presented significantly higher IMR levels, both at baseline (28.3±12.2 vs. 19.6±8.8, p=0.020) and post-PCI (45.4±21.3 vs. 21.6±11.2, p<0.0001) (Figure 45).

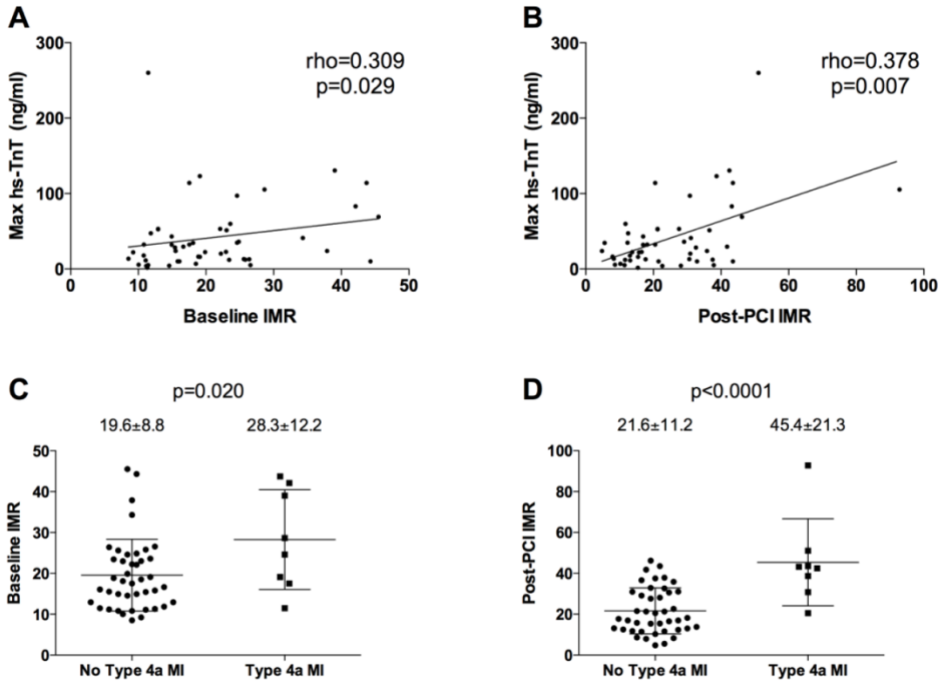


Figure 45. Figure 1. Microvascular function, peri-procedural myocardial injury and type 4a myocardial infarction (MI). Correlation between high-sensitivity Troponin T (hs-TnT) and index of microvascular resistance (IMR) at baseline (Panel A) and postpercutaneous coronary intervention (PCI) (Panel B). Index of microvascular resistance (IMR) at baseline (Panel C) and post-percutaneous coronary intervention (PCI) (Panel D) according to the occurrence of type 4a MI.

Patients with post-PCI IMR > 38 showed significantly higher maximum post-PCI hs-Tn levels (105.4 [49.4-126.9] vs. 22.4 [11.7-38.6] ng/ml, p<0.0001), and developed type 4a MI more frequently (66.8% vs. 4.9%, p<0.0001) (Figure 46).

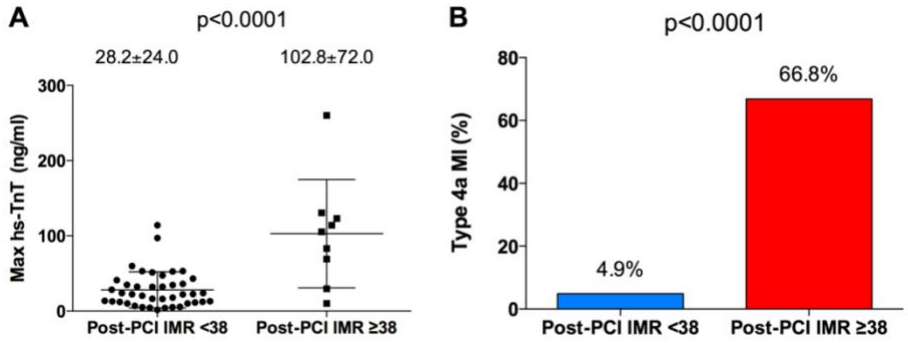


Figure 46. Peri-procedural myocardial injury and type 4a MI according to postprocedural microvascular function. High-sensitivity Troponin T (hs-TnT) (Panel A) and type 4a MI (Panel B) in patients with post-percutaneous coronary intervention (PCI) index of microvascular resistance (IMR) <38 and ≥38.

Conclusions: Dynamic changes of microvascular resistance post-PCI are strongly correlated with PCI-related myocardial injury and post-PCI IMR is a strong predictor of type 4a MI in patients with stable CAD undergoing elective PCI.

Chapter 26

Procedural microvascular activation in long lesions treated with bioresorbable vascular scaffolds or everolimus-eluting stents: the PROACTIVE trial

Background: Significant platelet activation has been observed with long stented coronary segments, despite ongoing anti-platelet therapy. This has been associated with peri-procedural microvascular impairment and myonecrosis probably secondary to distal embolization. Compared with DES, Bioresorbable vascular scaffolds (BVS) has different interaction with the vessel wall, mostly due to the fact that scaffold is made of poly-L-lactic acid (PLLA), with lower stiffness as compared with metallic stents. In addition, BVS is not associated with an increased compliance at the inflow segment, but conversely tended to decrease compliance at the outflow segment, therefore resulting into a potentially lower degree of compliance mismatch. It is not yet clear what might be the relative impact of the expected lower compliance vascular mismatch of BVS on microvascular function especially in relation to platelet inhibition during and after PCI. Given the inherent flexibility, we hypothesized that BVS Absorb™ might be associated with less platelet activation, thrombus formation and downstream microvascular impairment as compared with metallic EES Xience™ in stable patients undergoing PCI of long coronary stenoses.

Aim: In long lesions treated either with everolimus-eluting bioresorbable vascular scaffold (BVS) or everolimus-eluting stent (EES), we sought to investigate (a) procedure-related microvascular impairment, and (b) the relationship of platelet activation with microvascular function and related myonecrosis.

Methods: The PROACTIVE study was a prospective randomized (1:1) open-label, superiority, controlled trial in which 66 patients with stable coronary artery disease and long lesions (e.g. lesions to be treated with stent ≥ 25 mm long) were enrolled. Exclusion criteria were: a) ACS; b) contraindication to DAPT; c) bifurcations with a

side branch > 2.0 mm; d) need for rotational atherectomy; e) atrial fibrillation and treatment with oral anticoagulants. Primary endpoint was the difference between groups in changes of pressure-derived corrected index of microvascular resistance (cIMR) after PCI. CFR, FFR and peri-procedural myonecrosis by hs-cTnT were also evaluated. Platelet reactivity was assessed by high-sensitivity adenosine diphosphate (hs-ADP)-induced platelet reactivity with the Multiplate Analyzer™ before, after PCI, then at 24 hours and at 30 days follow up.

Results: 66 patients were enrolled in this trial: 33 randomized to BVS Absorb™, and 33 to EES Xience Xpedition™ or Xience Alpine™ implantation. Baseline clinical characteristics were not different between the 2 groups. No in-hospital major adverse events occurred. No differences between the two groups in terms of number of vessel diseased, vessels and Syntax segments treated as well as complexity of the lesions defined according to the ACC/AHA classification of coronary lesions were observed. Semi-compliant balloons were more frequently used in patients treated with EES implantation, although there were no significant differences between the two group in terms of lesion preparation, as well as for maximum and minimum stent/scaffold diameter, number of stent/scaffolds implanted per patient and total stent/scaffold length. As expected by recommendations, post-dilatation was more frequently performed in patients treated with BVS implantation, with associated longer procedure time in these patients. However, in the stent/scaffold optimization, no difference between the two groups have been observed regarding use of semi-compliant and non-compliant balloon, maximal diameter balloon, maximal pressure and total time of balloon inflation. No significant between groups differences were observed in FFR, CFR and cIMR both before and after-PCI. Yet, a significant difference in cIMR was observed within the BVS group after PCI versus baseline (19 ± 8 vs. 24 ± 12, p= 0.04), but not in the EES group (21 ± 9 vs. 21 ± 13, p= 0.84 (Figure 47). A significant difference in the primary endpoint of ΔcIMR was observed between the 2 groups (EES group -0,3 ± 13,6 vs. BVS group -4,7 ± 13,2; p= 0,04) (Figure 48).

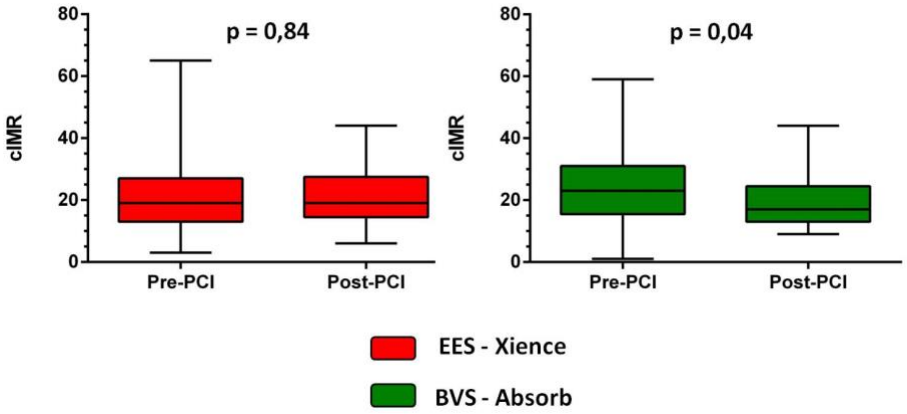


Figure 47. Changes in cIMR after PCI in the two group. Left panel: patients treated with EES - Xience; right panel: patients treated with BVS – Absorb. cIMR: corrected index of microvascular resistance.

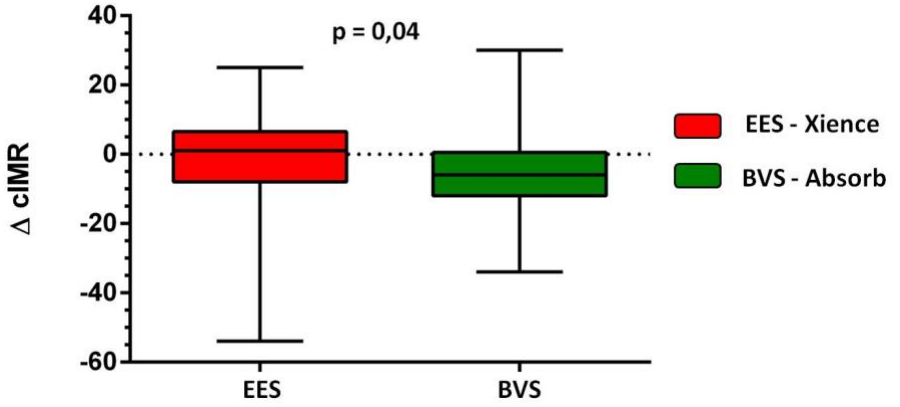


Figure 48: Difference between the two groups in ΔcIMR. Significant difference between the two groups in the primary endpoint, in favor of the BVS group. ΔcIMR: delta corrected index of microvascular resistance.

A significant reduction of hs-ADP was observed after PCI in both EES (hs-ADP: pre-PCI 18,4 ± 9,3 AU vs post-PCI 6,7 ± 4,8 AU; $p < 0,0001$) and BVS group (hs-ADP: pre-PCI 21,6 ± 11,1 AU vs post-PCI 13,8 ± 7,2 AU; $p < 0,0001$) without any difference between the two groups at baseline, post-PCI, and at 30 days follow-up. Also, no

consistent trends of hs-ADP values across the three main time of measurements up to 30 days follow-up has been detected (ANOVA for trend p= 0,29). Hs-cTnT significantly increased in both groups after PCI (EES: hs-cTnT pre-PCI 11,4 ± 13,3 ng/L vs hs-cTnT post-PCI 84,9 ± 195,2 ng/L; p<0,0001. BRS: hs-cTnT pre-PCI 10,7 ± 16,1 ng/L vs hs-cTnT post-PCI 104,2 ± 182 ng/L; p<0,0001), without difference at baseline and after PCI between the two groups. Also, no significant difference in terms of Δhs-cTnT between EES and BVS group has been observed (Δhs-cTnT EES group 73,4 ± 195,1 vs Δhs-cTnT BRS group 93,4 ± 185,3; p= 0,38).

Conclusions: In long lesions, BVS implantation is associated with a significant reduction in cIMR as compared with EES. The limited acute impact of BVS on the microcirculation effect is associated with an optimal peri-procedural and short-term platelet inhibition, without significant difference in peri-procedural myonecrosis as compared with patients treated with EES.

Chapter 27

Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans.

Background. Absolute hyperaemic coronary blood flow (Q, in mL/min) and resistance (R, in Wood units [WU]) can be measured invasively by continuous thermodilution. The aim of this study was to assess normal reference values of Q and R.

Methods. In 177 arteries (69 patients: 25 controls, i.e., without identifiable coronary atherosclerosis; 44 patients with mild, non-obstructive atherosclerosis), thermodilution-derived hyperaemic Q and total, epicardial, and microvascular absolute resistances (Rtot, Repi, and Rmicro) were measured: A 6 Fr arterial sheath was introduced into the radial or femoral artery, 100 U of heparin/kg of body weight was administered intravenously and intracoronary nitroglycerine (0.2 mg) was administered. A pressure/temperature sensor-tipped guidewire (PressureWire™ X; Abbott Vascular, Santa Clara, CA, USA) was zeroed, passed through the guiding catheter and, after proper equalisation with central aortic pressure, advanced into the distal part of the coronary artery. First, the FFR value was measured. Then, a dedicated monorail infusion catheter (RayFlow®; Hexacath, Paris, France) was connected to an infusion pump (Medrad Stellant; Medrad Inc, Warrendale, PA, USA), and flushed with saline at room temperature. The RayFlow catheter was advanced over the guidewire into the proximal segment of the artery to be measured. All coronary pressure and temperature tracings are wirelessly transmitted and analysed by a dedicated console equipped with a software (CoroFlow™; Coroventis, Uppsala, Sweden) that automatically calculates coronary blood flow (Q) and microvascular

resistance (Rmicro). A visual representation of the involved formulas is depicted in figure 49

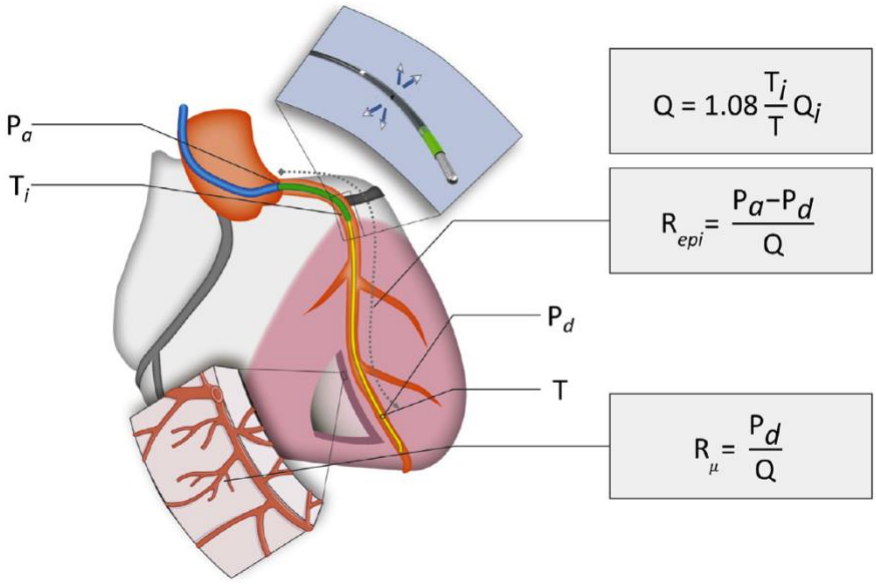


Figure 49. Continuous thermodilution makes it possible to calculate absolute coronary blood flow (Q; in ml/min) and the total resistance of the coronary vessel under examination (Rtot, in Wood Units) as well as its components, namely, epicardial resistance (Repi) and microcirculatory resistance (Rm). Pa =mean aortic pressure recorded by the guiding catheter (in mm Hg); Pd = mean distal coronary pressure recorded by the pressure wire (in mm Hg); Q = volumetric coronary blood flow (in ml/min); Qi = fixed infusion rate of saline at room temperature; T = temperature of the blood mixed with the indicator (in °C); Ti = temperature of the saline (in °C).

In 20 controls and 29 patients, measurements were obtained in all three major coronary arteries, thus allowing calculations of Q and R for the whole heart. In 15 controls (41 vessels) and 25 patients (71 vessels), vessel-specific myocardial mass was derived from coronary computed tomography angiography by an independent core lab (HeartFlow Inc, Redwood City, CA, USA) blinded to the results of the invasive measurements.

Results. Whole heart hyperaemic Q tended to be higher in controls compared to patients (668±185 vs 582±138 mL/min, p=0.068). In the left anterior descending coronary artery (LAD), hyperaemic Q was significantly higher (293±102 mL/min versus 228±71 mL/min, p=0.004) in controls than in patients (Figure 50). This was driven mainly by a difference in Repi (43±23 vs 83±41 WU, p=0.048), without significant differences in Rmicro (Figure 51). After adjustment for vessel-specific myocardial mass, hyperaemic Q was similar in the three vascular territories (5.9±1.9, 4.9±1.7, and 5.3±2.1 mL/min/g, p=0.44, in the LAD, left circumflex and right coronary artery, respectively).

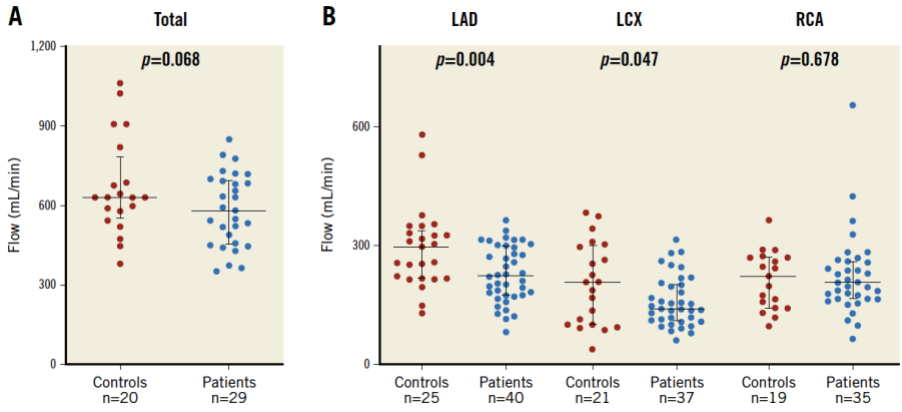


Figure 50. Absolute coronary artery blood flow. A) Individual values of whole heart coronary blood flow in normals and in patients with mild, non-obstructive atherosclerosis, i.e., sum of the flow in the LAD, the LCX and the RCA. B) Individual values of flow as stratified by coronary artery in normals and in patients with mild atherosclerosis.

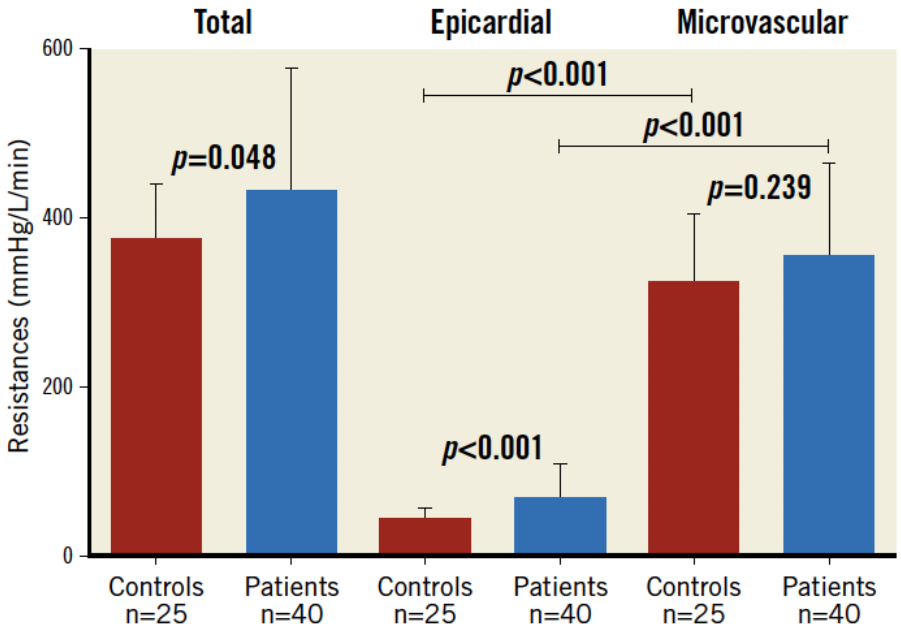


Figure 51. Total, epicardial, and microvascular resistances for the LAD in normals (red bars) and in patients with mild, non-obstructive atherosclerosis (blue bars) (mean±SD).

Conclusions. The present report provides reference values of absolute coronary hyperaemic Q and R. Q was homogeneously distributed in the three major myocardial territories but the large ranges of observed hyperaemic values of flow and of microvascular resistance preclude their clinical use for inter-patient comparison.

Chapter 28

Thermodilution-Derived Volumetric Resting Coronary Blood Flow Measurement in Humans

Background. Quantification of microvascular function requires the measurement of flow and resistance at rest and during hyperemia. Continuous intracoronary thermodilution accurately measures coronary flow during hyperemia. We aimed to study whether continuous coronary thermodilution using lower infusion rates also enables volumetric coronary blood flow measurements (in mL/min) at rest.

Methods. In 59 patients (88 arteries), the ratio of distal to proximal coronary pressure (Pd/Pa), as well as absolute blood flow (in mL/min) by continuous thermodilution, were recorded using a pressure/temperature guide wire. Saline was infused at rates of 10 and 20 mL/min. In 27 arteries, Doppler average peak velocity (APV) was measured simultaneously. Pd/Pa, APV, thermodilutionderived coronary flow reserve (CFRthermo) and coronary flow velocity reserve (CFVR) were assessed. In 10 arteries, simultaneous recordings were obtained at saline infusion rates of 6, 8, 10 and 20 mL/min.

Results. Compared to baseline, saline infusion at 10 mL/min did not change Pd/Pa (0.95±0.05 versus 0.94±0.05, p=0.49) nor APV (22±8 versus 23±8 cm/s, p=0.60); conversely, an infusion rate of 20 mL/min induced a decrease in Pd/Pa and an increase in APV (Figures 52 and 53).

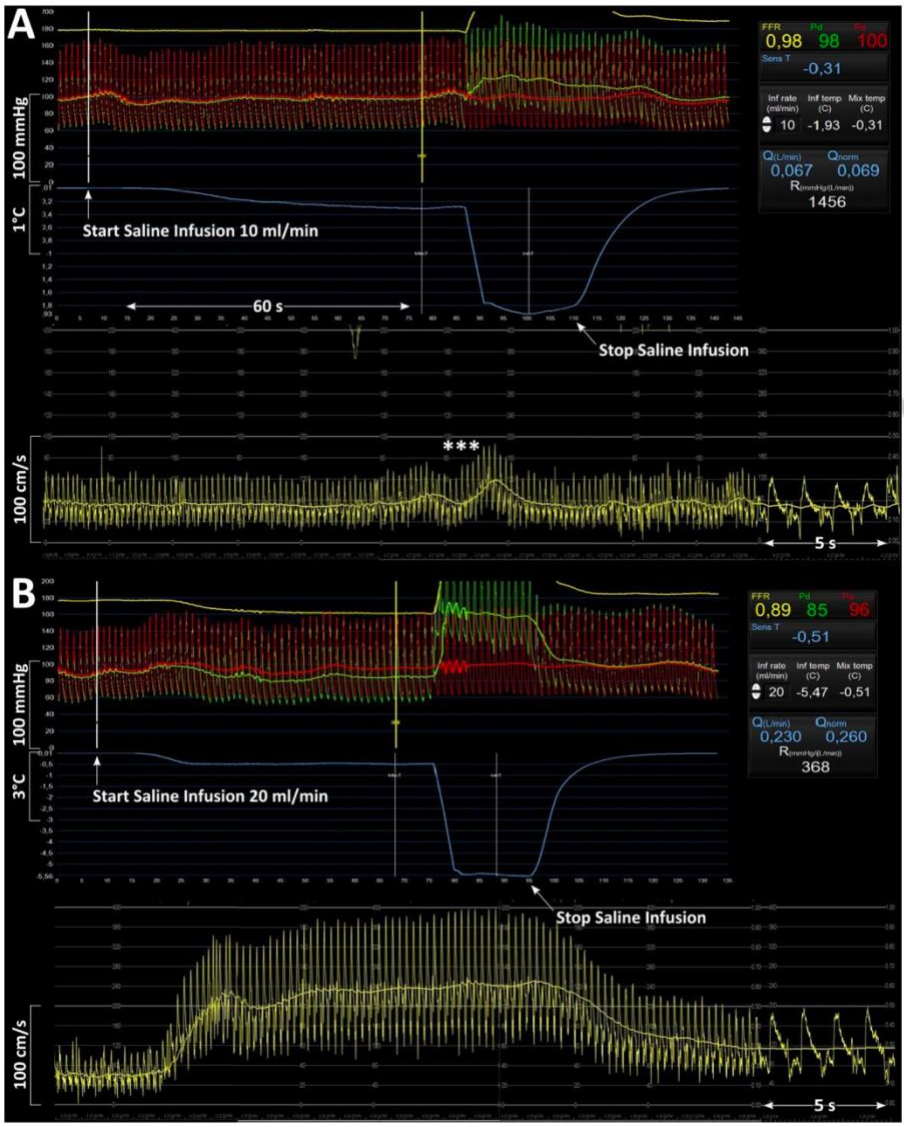


Figure 52. Example of simultaneous tracings of phasic and mean central aortic pressure, distal coronary pressure, average peak velocity and thermodilution during the infusion of 10 mL/min (Panel A) and of 20 mL/min (Panel B) in the LAD of a 77-year-old male patients with mild wall irregularities. Panel A: after the start and during the next 70 s of the infusion of saline at 10 mL/min through the RayFlowTM catheter located in the proximal LAD, no changes in distal coronary pressure, in Pd / Pa, or in APV were observed (reflecting a resting state). The slight oscillations in flow velocities (***) are caused by the pull-back of the pressure/temperature pressure wire. Panel B: in contrast, after the start and during the next 70 s of the infusion of saline at 20 mL/min through the RayFlowTM catheter located in the proximal LAD, a decrease in Pd, a decrease in Pd/Pa, and an increase in APV were observed. After cessation of the

intracoronary saline infusion, these indices returned to their baseline level. On the right-hand side, the CoroflowTM software displays instantaneously all relevant parameters, including infusion rate, flow and resistance.

Abbreviations: APV = Average peak velocity; LAD = left anterior descending coronary artery; Pd= distal coronary pressure; Pa aortic pressure

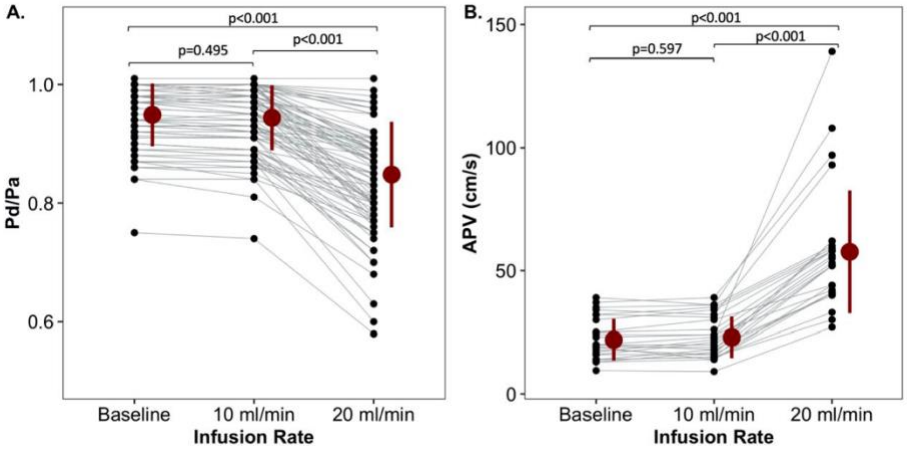


Figure 53. Individual values, mean and SD of Pd/Pa (Panel A) and APV (Panel B) observed at baseline and during saline infusion at 10 and 20 mL/min.

Abbreviations: APV = Average peak velocity; Pd= distal coronary pressure; Pa aortic pressure

Stable thermodilution tracings were obtained during saline infusion at 8 and 10 mL/min, but not at 6 mL/min. Mean values of CFRthermo and CFVR were similar (2.78±0.91 versus 2.76±1.06, p=0.935) and their individual values correlated closely (r=0.89, 95%CI 0.78 - 0.95, p<0.001) (Figure 54).

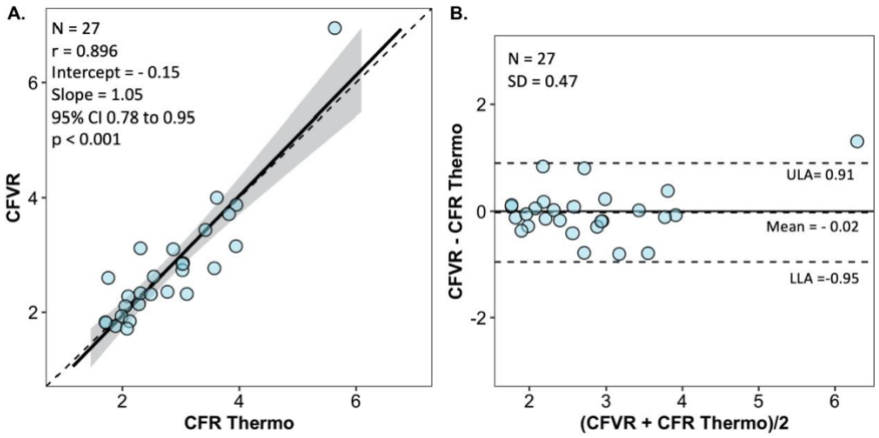


Figure 54. Correlation (Panel A) and agreement (Panel B) between thermodilution-derived coronary flow reserve (CFRthermo) and coronary flow velocity reserve (CFVR).

Conclusions. In addition to hyperemic flow, continuous thermodilution can quantify absolute resting coronary blood flow; therefore it can be used to calculate coronary flow reserve and microvascular resistance reserve.

Chapter 29

Basics of Coronary Thermodilution

Introduction: In patients with chest pain, coronary microvascular dysfunction (CMD) is highly prevalent. CMD causes or exacerbates ischemia in patients with or without obstructive coronary artery disease and is linked to poor clinical outcomes. CMD affects especially, although not only, women and deserves a targeted treatment. To understand the mechanisms regulating coronary blood flow, it is convenient to consider the coronary arterial circulation as a 2-compartment model. The epicardial compartment consists of conductance arteries with cross-sectional diameter >400 mm. They are visible on angiography and are often the site of obstructive atherosclerosis. Fractional flow reserve (FFR) is the metric of choice to quantify the functional significance of stenotic lesions in the epicardial arteries (9). The microcirculation includes vessels with cross-sectional diameter <400 mm. Small arteries and arterioles are resistive arteries and regulate myocardial blood flow supply. Capillaries form an interconnecting network, are made of 1 or 2 layers of endothelial cells surrounded by a basal membrane, and are in direct contact with the myofilament and their contractile apparatus, which they feed. The capillary bed is not considered a direct contributor to the resistance of the microvasculature. Although the microvasculature represents the major part of the volume of the coronary circulation, it remains poorly understood for at least 3 reasons: 1) it cannot be directly visualized; 2) there is no satisfactory animal model; and 3) microvascular resistance, its quintessential metric, has not until recently been quantified in absolute terms. In this review, we summarize the basic principles of indicator-dilution techniques and focus on intracoronary thermodilution techniques that allow the assessment of microvascular resistance.

The general indicator-dilution theory: Virtually all approaches to measure cardiac output apply the principles of the indicator-dilution theory. An “indicator,” in the

sense used here, is a traceable substance or a physical property (e.g., temperature, concentration, pH) that makes it possible to quantify the flow of the fluid in which the indicator under study is diluted. Depending on the way the indicator is added to the fluid, there are 2 general methods for performing indicator dilution–based measurements. Either the indicator can be injected as a bolus or it can be infused continuously. In the remainder of this review, we focus on "cold" as the indicator. Saline at room temperature (i.e., colder than body temperature) can be injected as a bolus ("bolus thermodilution") or can be infused continuously at a fixed rate ("continuous thermodilution").

Thermodilution by bolus injection: When briskly injecting a bolus of saline, at a temperature lower than that of blood, through the guiding catheter, a V-shaped time-based temperature change can be recorded in the distal part of the artery. When the exact volume of the indicator is not known, Q (in ml/s) can be approximated by dividing the vascular volume (V; in ml) by the mean transit time of the indicator (Tmn; in s):

$$Q = V/Tmn$$

Vascular volume (V) is not known. However, assuming V to be constant during consecutive measurements and under hyperemic conditions, Tmn is an index of flow inversely proportional to flow:

$$Q \approx 1/Tmn$$

Therefore, coronary bolus thermodilution does not allow quantification of flow in milliliters per minute. As an index of flow, Tmn has been used to evaluate coronary flow reserve (CFR) and to calculate the index of microcirculatory resistance (IMR).

CFR represents the extent to which myocardial or coronary flow can increase above its baseline value. Accordingly, bolus thermodilution–derived CFR has been described as the ratio between resting and hyperemic Tmn:

CFRthermo = Qhyper/Qrest = Tmn,rest/Tmn,hyper

IMR has been introduced by Fearon as the first index to specifically address the microcirculation. By analogy with Ohm's law for electric resistance, the absolute minimal resistance (R) across the microvascular bed equals the ratio of the pressure gradient across a given vascular territory (DP; in mm Hg) divided by the hyperemic blood flow across this territory (Q; in ml/min):

$$R = \frac{\Delta P}{Q} or\ R = \frac{Pd - Pv}{Q}$$

where Pd is the pressure at the distal segment of a coronary artery and Pv is the coronary venous pressure. Assuming that Pv is negligible compared with Pd, and given Q z1/Tmn, equation 6 can be rearranged as follows:

$$R \approx \frac{Pd}{\frac{1}{Tmn}} and\ thus = Pd \cdot Tmn$$

An example of coronary bolus thermodilution measurement is reported in figure 55

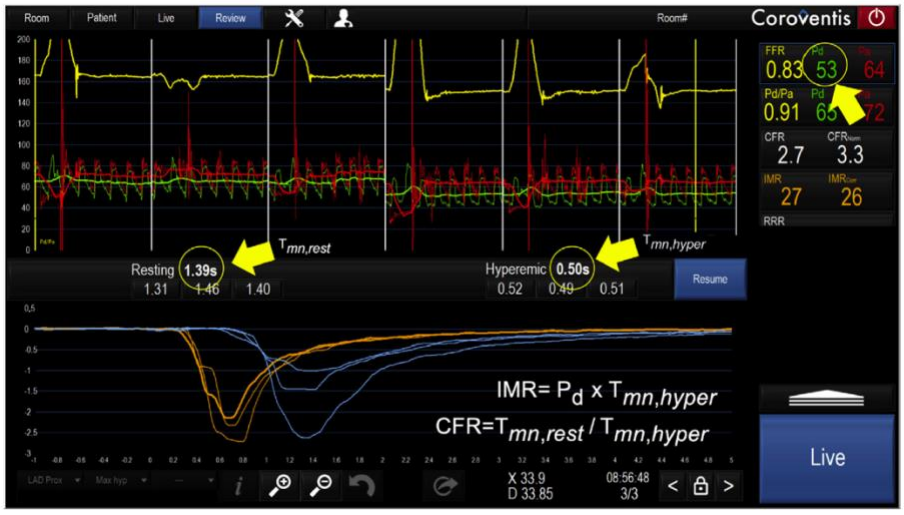


Figure 55. Illustration of simultaneous recordings of aortic pressure (Pa; red tracing), distal coronary pressure (Pd; green tracing), their ratio (Pd/Pa; yellow tracing), and intracoronary temperature after consecutive injections of 3 boluses at rest (blue tracings) and 3 boluses

during steady-state hyperemia (orange tracings). Hyperemia can be induced by intravenous adenosine or intracoronary papaverine. These recordings allow simultaneous measurement of fractional flow reserve (FFR), coronary flow reserve (CFR), and the index of microvascular resistance (IMR). The yellow arrows point to the average values of resting and hyperemic mean transient time (Tmn) as well as to the average distal coronary pressure (Pd) during hyperemia. These values are needed to derive CFR and IMR.

Thermodilution by continuous infusion: The basic principle of continuous thermodilution is relatively simple. Assuming that heat exchanges with the arterial wall are negligible and that the indicator, in this case the "cold" of saline, is homogeneously mixed in the volume of blood to be measured and can therefore be considered a constant fraction of this volume, a simple rule of 3 makes it possible to derive the absolute flow (in ml/min) as follows:

$$Q = 1.08 \left[\frac{Tb - Ti}{Tb - T}\right] Qi$$

where Q is the volumetric coronary blood flow (in ml/min), Qi is the infusion rate of saline at room temperature (typically a fixed rate between 8 and 25 ml/min, set up on the infusion pump), T is the temperature (in °C) of the blood mixed with the indicator as measured in the distal part of the coronary artery, Tb is the temperature (in °C) of blood, Ti is the temperature (in °C) of the saline when it enters the coronary artery; and the constant 1.08 accounts for the densities and specific heat of blood and saline. When Tb is set to zero, and Ti and T represent the deviation of the respective temperatures from Tb, the equation can be further simplified:

$$Q = 1.08 \left[\frac{Ti}{T}\right] Qi$$

Absolute resistances (R) are calculated, by analogy to Ohm's law, as the ratio of pressure and flow (expressed in dyn s cm^{-5}, mPa s m^{-3}, or mmHg/l/ min [Wood units]). The latter units are traditionally used in human cardiovascular physiology.

An example of coronary thermodilution by continuous infusion is reported in figure 56

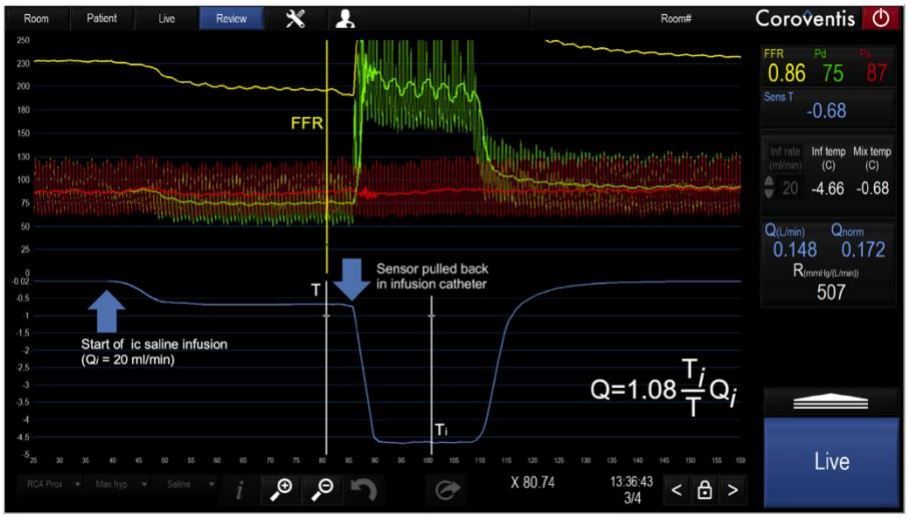


Figure 56. Example of simultaneous recording of aortic pressure (red tracing), distal coronary pressure (green tracing), and coronary temperature (blue tracing) during continuous thermodilution to measure absolute coronary flow (Q) and absolute microvascular resistance ®. The saline infusion flow rate (Qi) in this example is 20 ml/min. These recordings make it possible to simultaneously measure fractional flow reserve (FFR), absolute hyperemic coronary blood flow (Q; in ml/min), and hyperemic microvascular resistance (R; in mm Hg/l/min or Wood Units). The blue arrows indicate the start of the saline infusion and the pull back of the pressure/temperature sensor to be placed in the tip of the infusion catheter. T = mixed temperature (in °C); Ti = infusion temperature (in °C).

Practical considerations: To obtain continuous thermodilution–based absolute Q and R, the following equipment is needed:

- A pressure/temperature wire (PressureWire, Abbott Vascular, Santa Clara, California) advanced into the distal part of the artery. The sensor is to be placed in the distal part of the artery as during PCI or FFR measurements.
- A dedicated monorail infusion catheter with 4 side holes (RayFlow, Hexacath, Paris, France) to enable instantaneous and complete mixing of saline and blood in the proximal part of the artery.
- Saline at room temperature.

- A regular contrast injector or infusion pump to infuse saline at a steady flow rate ranging from 8 to 20 ml/min during several minutes.
- Dedicated software (CoroFlow, Cardiovascular System, Coroventis Research, Uppsala, Sweden) to display all measurements in real time.

Hyperemic flow was initially measured during concomitant intravenous infusion of adenosine. Subsequently, it was observed that the infusion of saline in a proximal epicardial artery by itself induced a maximal steady-state microvascular dilatation in the territory supplied by the artery under study. This was the case only when saline was infused through a specially designed catheter with 4 side holes at flow rates >15 ml/min. The accuracy of these hyperemic absolute flow measurements has recently been confirmed against [15O]H_2O positron emission tomography and has been extensively validated

in animals. Resting flow measurements were recently proposed and validated against simultaneous intracoronary pressure and Doppler measurements. Infusion rates between 8 and 10 ml/min were seen to allow proper delta temperature detection without significant changes in Pd/Pa or averaged peak velocity and with an optimal signal-to-noise ratio during infusion in comparison with baseline. Obtaining these measurements is safe, accurate, operator independent, and highly reproducible.

Conclusions: Intracoronary bolus thermodilution and continuous thermodilution have the potential to assess the function of the coronary microcirculation. IMR as derived from bolus thermodilution has been shown to carry prognostic value after myocardial infarction and in patients with chronic coronary syndromes. Continuous coronary thermodilution enables, for the first time, highly accurate measurement of absolute coronary Q and absolute Rm at rest and during hyperemia. The clinical correlates of these measurements still need to be established. Yet these developments pave the way for more specific and quantitative approaches to

studying the microcirculatory compartment and, subsequently, to applying novel therapies targeting the dysfunctional coronary microcirculation.

Part VI

Discussion and conclusions

Discussion

Over the course of these last few years we investigated several aspects related to hot topics in coronary physiology. In particular:

a) We were able to replicate in humans some of the experiments that were originally performed in conscious animals, confirming the applicability in clinical practice of the basis of coronary physiology assessment;

b) We investigated procedural aspects of FFR measurements, as well as the prognostic impact of FFR, either considered as a vessel-specific ischemia metric or as a global marker of epicardial resistance in patients without significant ischemia (Global-FFR);

c) We assessed the reliability of invasive physiology evaluation of coronary disease in patients with comorbidities, specifically aortic valve disease, heart failure, and diabetes mellitus. In addition, we reported long-term clinical outcomes of these patients when FFR was used for decision-making regarding revascularization;

d) We characterized the physiological pattern of coronary atherosclerosis in focal, diffuse or combined disease, by means of motorized pullback gradients. In addition, we introduced a new metric of focality/diffuseness of atherosclerosis, the PPG index;

e) We evaluated the effect on microvascular function (estimated by IMR) of specific antiplatelet drugs or devices, before and/or after PCI. Also, we reported normal values of thermodilution-derived absolute flow and resistance, and show the feasibility of resting coronary flow calculation by continuous thermodilution.

Invasive coronary physiology assessment was introduced at the beginning of the 1990's with the introduction of FFR[3,4], and currently represents a rapidly growing

field of interest for researchers and interventionalists. In our work, we gave our contribution for a proper and standardized FFR measurement by identifying the correct dose of intracoronary adenosine bolus to maximize hyperemia and reduce adverse events (temporary AV blocks), namely 100 μg for the right coronary artery and 200 μg for the left coronary artery[31]. In addition, we proved that the mere presence of a guiding catheter engaged in the coronary ostium during FFR measurement may cause an underestimation of functional stenosis severity by underestimating the Pa, thus mandating catheter disengagement after adenosine injection to avoid stenosis misclassifications[32].

We also focused on the prognostic impact of FFR in patients with CAD. In our work investigating the significance of intermediate values of FFR, we showed that FFR represents a risk continuum, since the rate of adverse events was proportionally lower for higher FFR values when the lesion was left untreated[33]. This seems to also hold true when no pathologic FFR value is reported. In patients enrolled in FAME studies without significant stenoses, the sum of the FFR of the 3 major vessels was computed to generate a Global FFR value that was associated with 5-year clinical outcome[34].

As previously discussed, the reliability and diagnostic value of coronary physiology has been questioned in patients with specific comorbidities. In patients with aortic valve stenosis, we showed that an FFR-guided treatment strategy was associated with a downgrade in the number of diseased vessels, a simplified surgical procedure and a trend towards less aortic valve replacement, without an excess of cardiac events up to 5 years, including overall death, repeat revascularization and nonfatal MI[35]. In another study we showed that, similarly to patients with stable CAD, coronary angiography poorly predicts physiology in patients with aortic stenosis[36]. Finally, we found that the difference between resting distal coronary vs aortic pressure ratio (Pd/Pa) and FFR (ΔPd/Pa-FFR) was not statistically different between patients with or without aortic stenosis and was not influenced by aortic

stenosis severity[37]. These data are reassuring regarding the possibility of obtaining adequate hyperemia in these patients.

In patients with reduced ejection fraction and at least 1 intermediate coronary stenosis (DS 50-70%) treated based on angiography or according to FFR, we evaluated treatment strategies and clinical outcomes[15]. Due to a significant downgrade of the number of diseased vessels, less patients were revascularized in the FFR-guided group, and the chosen type of revascularization was more frequently PCI in the FFR-group, and CABG in the angiography-guided group. All-cause death and major adverse cardiovascular and cerebrovascular events at 5 years of follow-up were significantly lower in the FFR-guided as compared with Angiography-guided group. In another study we assessed the outcome of coronary lesions deferred to medical therapy in patients with reduced ejection fraction. Patients with stenoses deferred according to a negative FFR value (>0.80), had a significant lower rate of all cause death and adverse events up to 10 years[38].

In classical FFR measurement, right atrial pressure (Pra) is neglected because is often close to zero. However, in patients with HF Pra may be elevated and potentially influence FFR measurement. We compared the FFR values calculated without accounting for Pra (FFR=Pd/Pa) to the corresponding myocardial fractional flow reserve (FFRmyo) values accounting for Pra (FFRmyo= Pd - Pra/Pa - Pra). The difference between FFR and FFRmyo was minimal even in patients with markedly increased Pra. FFR values above the gray zone (i.e., >0.80) did not yield values below the gray zone (i.e., ≤0.75) in any case, which suggests that the impact of right atrial pressure on FFR measurement is indeed negligible[39].

In patients with ischemic left ventricular dysfunction, the presence of myocardial viability is related to the expected benefits derived from coronary revascularization. Thus, we investigated the role of intra-coronary pressure parameters in the assessment of viability in the myocardium subtending a significant coronary stenosis. We found a significant correlation between ΔPd/Pa and %ΔPd/Pa with %SRStarget.

According to ROC curves, we identified two cut-offs (ΔPd/Pa >0.11 and %ΔPd/Pa >15%) able to predict >80% viability with good sensitivity and specificity[40].

In patients with diabetes mellitus, atherosclerosis often presents characteristics that make correct diagnosis challenging. Diffuse atherosclerosis is highly prevalent among diabetics, with a trend toward negative vessel remodeling that can lead to underestimation of the degree of coronary obstruction on angiography. Recently, though, the reliability of fractional flow reserve (FFR)–based PCI deferral has been questioned in diabetic patients due to accelerated atherosclerosis[41,42]. There are little available data on the safety and long-term outcome of FFR guidance for PCI in diabetic patients. Therefore, we compared long-term clinical outcomes of diabetic patients with multivessel coronary disease treated with FFR-guided PCI or CABG. We found an excess of revascularizations at follow-up in patients treated with PCI. However, no difference was found in the safety endpoint of death, myocardial infarction, or stroke at 5 years. In addition, only 9% of lesions deferred with a negative FFR measurement were revascularized at follow-up[43]. Integration of coronary physiology with intracoronary imaging will be essential to identify unstable placques that may warrant revascularization despite a negative FFR value.

In the fourth part of our thesis we presented studies aimed at characterizing the physiological patterns of epicardial coronary disease. Pressure drops along a coronary artery may occur abruptly or gradually, but the focality or diffuseness of atherosclerosis is not reliably identified by angiography alone. By means of motorized hyperemic pullbacks of a pressure wire, pullback curves were built and a new metric of the focality (or diffuseness) of the disease was introduced (Pullback pressure gradient index, PPG index). The PPG index, alongside the qualitative interpretation of pullback curves, is able to identify focal stenosis, that are those that benefit most from PCI[16,44]. Notably, diffuse functional disease may be present also in patients with angiographically identifiable stenosis. What to do with these patients in terms of streatment strategy is unknown at the moment, opening up a whole new line of research.

Over the last few years, the study of coronary microcirculation has gained a lot of attention from researchers and interventionalists, since microvascular dysfunction is able to cause ischemic symptoms concomitantly or even in the absence of epicardial coronary disease. The introduction of new metrics, calculated using bolus or continuous thermodilution have made possible to quantify coronary flow and resistence, and thus to estimate microvascular function. In our thesis, we report a state of the art review describing in detail all theoretical and procedural aspects of thermodilution based indexes[45]. Also, we assessed the effect of prasugrel vs. clopidogrel preload on IMR, platelet reactivity and periprocedural myocardial injury in patients with stable coronary artery disease[46,47]. Patients in the prasugrel group showed significantly lower post-PCI IMR values compared with those in the clopidogrel group. Consistently, post-PCI CFR was significantly higher in the prasugrel compared with the clopidogrel group. Post-PCI Hs-TnT was significantly lower in the prasugrel group compared to the clopidogrel group. The results of the PROMICRO-2 trial suggest that more intensive antiplatelet regimens might offer additional benefit compared with clopidogrel also in the setting of elective PCI. Interestingly, in another study, we showed that IMR is a strong predictor of periprocedural myocardial infarction[48]. Thus, reducing post-PCI IMR through pharmacologic intervention might be an effective strategy to improve PCI outcome.

In the PROACTIVE trial, patients with long lesions (> 20 mm) were randomized to BVS Absorb or EES implantation. The use of BVS was associated with a significant reduction in cIMR as compared with EES. The limited acute impact of BVS on the the microcirculation was associated with an optimal peri-procedural and short-term platelet inhibition, without significant difference in peri-procedural myonecrosis as compared with patients treated with EES[49]. Unfortunately, the use of BVS has been almost completely abandoned due to an excess in scaffold thrombosis at mid-term follow-up. However, future amelioration in scaffold technology might provide this line of research with new life, considering the favourable results in terms of microvascular resistance and vasomotility[49,50].

Finally, we reported studies in which we used a novel continuous thermodilution technology to investigate normal values of absolute coronary hyperaemic flow and resistance[51]. Unfortunately, the large ranges of observed hyperaemic values of flow and of microvascular resistance preclude their clinical use for inter-patient comparison. However, the measurement of these parameter in the same patient at different time points (i.e. before and after PCI, before and after TAVI), will certainly shed some light on the mechanism of microcirculatory dysfunction. In addition, the use of lower infusion rates (8-10 ml/m^2) was shown not to induce hyperemia and to reliably be able to measure absolute resting flow and resistence[52]. Therefore, continuous thermodilution can also be used to calculate coronary flow reserve and microvascular resistance reserve.

Conclusions

In conclusion, the field of coronary physiology is experiencing a time of continuous growth. Invasive physiology assessment is shifting from "just" measuring FFR to a comprehensive assessment of coronary circulation that includes the characterization of patterns of epicardial coronary atherosclerosis and the assessment of microcirculatory function. Hopefully, this will be the sparkle that ignites new lines of research leading to a more complete understanding of coronary disease and to improvement in clinical outcomes.

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Curriculum Vitae

Curriculum Vitae

PERSONAL INFORMATION

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EDUCATION AND TRAINING

Nov 2018-Present	**International Cardovascular Pathophysiology and Therapeutics (CardioPaTh) PhD Programme** Federico II University of Naples (Italy) – Cardiovascular Center Aalst (Belgium)
Jan 2020-Present	**Interventional cardiologist** Montevergine Clinic, Mercogliano, Italy
Jan 2018–Dec 2019	**Fellowship in Clinical Research and Interventional Cardiology** Cardiovascular center Aalst, OLV Hospital, Aalst (Belgium)
Dec 2014–Dec 2018	**Diploma of specialist in Cardiology** Federico II University, Naples, Italy. Final marks: 50/50 cum laude Graduation Thesis: Fractional Flow Reserve in patients with reduced ejection fraction.
Feb 2014-Dec 2014	**Departmental research contract** Successful candidate in a competition issued by the Department of Medical Translational Sciences, Federico II University, Naples, for 1 research contract to investigate the following topic: “Evaluation of platelet aggregation in elderly patients undergoing percutaneous coronary intervention” (Rif. Co.Co.Co. 11/2013; Scientific director: Prof. R. Izzo)
Oct 2013–Oct 2014	**Research fellowship in Interventional Cardiology** Cardiovascular center Aalst, OLV Hospital, Aalst (Belgium)
03 Nov 2012–07 Mar 2013	**Postgraduate medical training and National Board Examination** Federico II University, Naples, Italy. Final marks: 270/270 February 2014: license for medical practice in Belgium (VISA n° 94163)
20 Sep 2006–19 Ju 2012	**Master Degree in Medicine and Surgery** Federico II University, Naples, Italy. Final marks: 110/110 cum laude

PERSONAL SKILLS

Mother tongue(s) Italian

Other language(s)

	UNDERSTANDING		SPEAKING		WRITING
	Listening	Reading	Spoken interaction	Spoken production	
English	C2	C2	C2	C2	C2

Levels: A1/A2: Basic user - B1/B2: Independent user - C1/C2: Proficient user
Common European Framework of Reference for Languages

Computer skills Excellent command of Office suite (Word, Excel, Power-Point)

Excellent knowledge of SPSS statistical software and PRISM Graph PAD

Fair knowledge of R statistical software

▪ ADDITIONAL INFORMATION

Committees and boards Member of the EAPCI New Initiatives for Young Interventionalists Committee (2018-2020 and 2020-2022)

Member of the ESC Young Committee as EAPCI representative (2020 -)

Member of JACC-Case reports Editorial Board

Member of the PCRonline Editorial Board

Young EAPCI/PCR Journal Club reviewer

Member of the Social Media team for the digital coverage of EuroPCR 2019 and ESC 2019

Reviewer for international medical journals, including the European Heart Journal, Circulation: Cardiovascular Interventions, American Journal of Cardiology, JACC Case Reports, Eurointervention, Journal of Cardiovascular Translational Research, Journal of Cardiovascular Medicine, Journal of Interventional Cardiology.

AWARDS

2017 EAPCI Education and Training Grant Awardee

2018 "Programma STAR" (linea 2) grant winner for Federico II University researchers working abroad

Finalist of the PCR got talent competition (best abstract award) at EuroPCR 2019

Book Chapters and invited articles

Co-author of the chapter on "Coronary Flow Reserve (CFR), Fractional Flow Reserve (FFR), and Novel Nonhyperemic Indexes of Functional Coronary Stenosis Severity" of the Textbook of Interventional Cardiology: Global Perspective by Samir Kapadia, Derek Chew, Fernando Cura, Philippe L L'Allier, Marco Roffi, Emin Murat Tuzcu; Edited by Jaypee Brothers, Medical Publishers Pvt. Limited, 2017

Co-author of the chapters "Vascular access: evolving from femoral to distal radial artery" and "Physiological assessment techniques (FFR)" of the Percutaneous Cardiac Intervention Textbook. Tips and tricks of new techniques beyond stenting, edited by Manel Sabaté and

Salvatore Brugaletta. 2019

Co-author of the chapter "Invasive physiology: technology and interpretation" of Percutaneous Treatment of Complex Higher-Risk (and Indicated) Patients (CHIP), edited by Giuseppe Tarantini, Giovanni Esposito, Juan Granada, Alaide Chieffo. Minerva Medica. In press.

Co-author of an Expert Analysis on acc.org published on Dec 18, 2017 on "Hemodynamic Assessment of Stable, Intermediate Lesions in the Catheterization Laboratory Using FFR or iFR".

List of publications

- Bellis A, Di Gioia G, Mauro C, Mancusi C, Barbato E, Izzo R, Trimarco B, Morisco C. Reducing Cardiac Injury during ST-Elevation Myocardial Infarction: A Reasoned Approach to a Multitarget Therapeutic Strategy. J Clin Med 2021 Jul 1;10(13):2968.
- Candreva A, Mizukami T, Sonck J, Munhoz D, Nagumo S, Di Gioia G, Gallinoro E, Mileva N, Bartunek J, Wyffels E, Barbato E, De Bruyne B, Perera D, Collet C. Hyperemic hemodynamic characteristics of serial coronary lesions assessed by pullback pressure gradients. Catheter Cardiovasc Interv 2021 Jul 15. doi: 10.1002/ccd.29868. Online ahead of print.
- Di Gioia G, Bartunek J, Tesorio T, Vukcevic V, Aleksandric S, Dobric M, Franco D, Barbato E, Banovic M. Pathophysiology, Diagnosis, and Treatment of Patients with Concomitant Severe Aortic Stenosis and Coronary Artery Disease: A Closer Look to the Unresolved Perplexity. J Clin Med 2021;10(8):1617.
- Candreva A, Gallinoro E, van 't Veer M, Sonck J, Collet C, Di Gioia G, Kodeboina M, Mizukami T, Nagumo S, Keulards D, Fournier S, Pijls NHJ, De Bruyne B. Basics of Coronary Thermodilution. JACC Cardiovasc Interv 2021;14(6):595-605.
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