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Programvezető: Dr. Igaz Péter, egyetemi tanár

Témavezető: Dr. Piróth Zsolt, szintvezető főorvos

Measurement, comparison, and application of FFR and non-hyperemic Pd/Pa to estimate prognosis in non-culprit vessels of patients with acute coronary syndrome

PhD thesis

Gábor Fülöp, MD

Károly Rácz Doctoral School of Clinical Medicine

Semmelweis University

Supervisor:	Zsolt Piróth, MD, PhD
Official reviewers:	András Komócsi, MD, DSc. Endre Zima, MD, PhD
Head of the Complex Examination Committee:	Zoltán Járai, MD, PhD
Members of the Complex Examination Committee:	Jenő Szolnoky, MD, PhD István Osztheimer, MD, PhD

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACS	acute coronary syndrome
AUC	area under the curve
ΔP	change in pressure
CCS	chronic coronary syndrome
CFR	coronary flow reserve
CRP	C-reactive protein
CV	cardiovascular
DICOM	Digital imaging and communications in medicine
DFR	diastolic hyperemia-free ratio
dPR	diastolic pressure ratio
DS	diameter stenosis
ESC	European Society of Cardiology
F	viscous friction pressure loss coefficient
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
IMR	index of microcirculatory resistance
IRA	infarct-related artery
IVUS	intravascular ultrasound
LAD	left anterior descending
Lcx	left circumflex
LVEDP	left ventricular end-diastolic pressure
MACE	major adverse cardiovascular event
MI	myocardial infarction
MRI	magnetic resonance imaging
nIRA	non-infarct related artery
NSTE-ACS	non-ST-elevation acute coronary syndrome
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
Pd/Pa	distal coronary pressure/aortic pressure
PET	positron emission tomography

QCA	quantitative coronary angiography
Qsmax	maximal coronary flow during hyperemia
Qnmax	maximal coronary flow under normal circumstances
RCA	right coronary artery
RFR	resting full-cycle ratio
ROC	receiver operating characteristic
RRR	resistive reserve ratio
S	flow separation pressure loss coefficient
SCD	stable coronary disease
STEMI	ST-elevation myocardial infarction
TVF	target vessel failure
TVMI	target vessel myocardial infarction
TVR	target vessel revascularization
V	velocity

1. INTRODUCTION

Coronary artery disease is a leading cause of morbidity and mortality worldwide as well as nationwide in Hungary [1]. We use both non-invasive as well as invasive methods to diagnose and assess the severity or prognosis of ischemic heart disease. To assess disease burden, we use coronary angiography. This gives us an "anatomical" result and the functional severity is not evident simply by stenosis grade. Also, coronary angiography has limitations in the assessment of eccentric lesions and diffuse disease, e.g., if the contrast filling is suboptimal or if there is an overlap of vessels. Functional severity can be assessed based on the result of non-invasive diagnostic tests (e.g., stress echocardiography, myocardial perfusion scan, etc.). It is important since symptoms and prognosis can be improved with the revascularization of functionally significant lesions/vessels. However, frequently no non-invasive assessment of ischemia has been performed prior to coronary angiography. Invasive functional testing has been developed by which we can assess the potential of lesions to produce ischemia with adequate sensitivity and specificity. There are some special modifications of these tests by which the assessment of diffuse or multiplex lesions is also possible [2].

1.1 Invasive functional tests

Invasive functional tests can be divided broadly into hyperemic and non-hyperemic tests (**Table 1**). The former uses a vasodilating agent (most frequently by the intravenous administration of adenosine at 140 μg/kg/min or by intracoronary bolus) to achieve maximal hyperemia whereas the other types are performed in a resting state without the administration of such agents.

Table 1 Invasive functional indexes

Hyperemic index	
FFR (fractional flow reserve)	Distal to aortic mean pressure during maximal hyperemia
Non-hyperemic indexes	
Pd/Pa	Distal coronary to aortic mean pressure without hyperemia
iFR (instantaneous wave-free ratio)	Distal to aortic pressure measured during the special phase of diastole (wave-free period)
RFR (resting full-cycle ratio)	Lowest Pd/Pa during the whole cardiac cycle
DFR (diastolic hyperemia-free ratio)	Mean Pd/Pa averaged over five consecutive cycles where Pa is falling, and the actual/instantaneous Pa is lower than the mean Pa
dPR (diastolic pressure ratio)	Pd/Pa measured during the whole diastolic phase

1.1.1 Hyperemic functional index (fractional flow reserve)

The “gold standard” of invasive functional testing is fractional flow reserve (FFR) with its introduction around three decades ago [3]. Fractional flow reserve in a given coronary vessel is the ratio of maximal flow (Qsmax) measured during hyperemia compared to the theoretical maximal flow (Qnmax) under normal conditions (no disease present). The normal value is 1.0. Since in general, the measurement of flow is technically demanding and time-consuming in humans, fractional flow reserve measurement is achieved with simultaneous recording of pressure in the aorta and distal part of the coronary vessel with the help of a pressure wire which has a sensor close to the tip. Maximal hyperemia would minimize resistance and as such, the flow will be proportional to perfusion pressure. The validity, reproducibility, and good correlation with non-invasive investigations of ischemia as well as clinical benefit of applying FFR-guidance in multivessel percutaneous coronary intervention (PCI) have been investigated and verified in several studies (DEFER, FAME, FAME 2) [4, 5, 6]. The DEFER trial has a follow-up period of up to 15 years showing no evidence of harm if functionally non-significant lesions were not revascularized based upon their FFR value and even signalled harm with a higher number of myocardial infarctions in patients who were revascularized despite a non-ischemic fractional flow reserve value compared to medical therapy alone.
Coronary revascularization is recommended if the value of FFR is ≤ 0.80 and medical therapy is indicated if it is >0.80 [7]. It has been shown that FFR-guided PCI compared to PCI by angiography alone can decrease the number of revascularizations significantly along with a lower rate of MACE [8, 9]. FFR measured immediately after PCI (post-PCI FFR) has a prognostic value – the higher the post-PCI value of fractional flow reserve, the better the outcome [10, 11].

FFR measurement has a Class I recommendation by the European Society of Cardiology in stable patients with angina to identify hemodynamic significance in intermediate lesions if evidence of ischemia is not available and should be utilized in multivessel disease in this patient population [12]. Despite the well-established evidence of using FFR in clinical decision-making during coronary angiography, there

is still a low rate of utilization of this technique [13]. Possible explanations include the longer duration of the examination, higher costs, possible – at times even severe – complications such as wire or guide-induced dissection resulting in acute ischemia as well as the possible side effects of adenosine including hypotension, dyspnea (especially in patients with underlying lung disease). It is worth mentioning that the measurement should be performed by knowing and avoiding the possible pitfalls and the FFR-value measured should be interpreted in the clinical context.

1.1.2 Non-hyperemic functional indexes

The other major group of functional invasive tests is the so-called non-hyperemic pressure ratios (NHPR) which have been examined in the last decade. During these measurements there is no need to administer vasodilating substances, therefore the duration of the study can potentially be shortened, cost is less, and the side effects of vasodilators can be avoided.
These functional indexes measure pressure at different parts of the cardiac cycle, taking into account the whole cycle (e.g., resting Pd/Pa, RFR) or the total or specific part of the diastolic phase (iFR, dPR, DFR).

1.1.2.1 Resting whole cycle Pd/Pa

Due to its simplicity resting whole-cycle Pd/Pa can be measured when determining any functional index with a pressure wire. In general, it has a diagnostic accuracy of around 80% compared to FFR when using a cut-off of ≤0.91 [14].

1.1.2.2 Instantaneous wave-free ratio (iFR)

The instantaneous wave-free ratio (iFR, Philips Volcano Corporation, San Diego, California, USA) was the first non-hyperemic pressure ratio that was introduced into

the market and became available for clinical use. It measures Pd/Pa ratio during a special part of diastole, the so-called wave-free period (starting at 25% of the whole diastolic cycle after the beginning diastole and ending 5 ms before the end of diastole) when theoretically forward and backward waves are minimal and microvascular resistance is stable and theoretically comparable to hyperemia induced minimal microvascular resistance [14, 15]. During ventricular contraction early in systole, there is a forward flow generated in the coronary vessels which is attenuated by the compression of the microvasculature. In diastole, there is a "suction" wave moving backward through the heart vessels which is the most important wave in the initiation of forward coronary blood flow [16]. There have been studies to show a good correlation with fractional flow reserve with a cut-off of ≤0.89 corresponding to a fractional flow reserve value of ≤0.80 [17]. Compared to fractional flow reserve, diagnostic accuracy is around 80% (similar to resting Pd/Pa) and as mentioned earlier, a specific phase of the diastolic cycle is needed for measurement along with proprietary software [18, 19].

Two major clinical studies verified the practical utility, non-inferiority compared to fractional flow reserve guided percutaneous coronary intervention in mostly stable patients with intermediate coronary artery disease with regards to major adverse cardiovascular events in 1 year using a cut-off of 0.89 (IFR-SWEDEHEART, DEFINE-FLAIR). In these studies, procedure time and vasodilator-induced, procedure-related side effects/symptoms were significantly higher in the fractional flow reserve guided arms [20, 21].

In the 2019 Guideline of the European Society of Cardiology in patients with chronic coronary syndrome, the assessment of 50-90% coronary stenoses by instantaneous wave-free ratio or fractional flow reserve are both recommended in symptomatic patients or in case of high event risk [22].

Besides instantaneous wave-free ratio, there have been other non-hyperemic pressure ratios developed and introduced that measure pressure during specific periods including the whole cardiac cycle, as well as the whole period or part of the diastolic cycle.

1.1.2.3 Resting full-cycle ratio (RFR)

The resting full-cycle ratio (RFR) is the lowest instantaneous filtered Pd/Pa measured during the whole cardiac cycle (over 5 beats). When compared to the instantaneous wave-free ratio in a validation study, it was almost identical in diagnostic performance (97.4%). However, it was detected outside diastole in about 12% of all measurements; this finding was around 32% if measured in the right coronary artery [23]. This might explain the finding that the sensitivity of instantaneous wave-free ratio is significantly decreased if measurements are performed in the right coronary artery compared to the left (40.6% vs. 73.2%, $P<0.001$). Therefore, the validity of non-hyperemic pressure index evaluation of the RCA might be questionable [24].

1.1.2.4 Diastolic pressure ratio (dPR), diastolic hyperemia free ratio (DFR)

Diastolic pressure ratio (dPR) measures average Pd/Pa during the whole diastolic cycle over 5 beats. Diastolic hyperemia free ratio (DFR; Boston Scientific, Natick, Massachusetts, USA) measures mean Pd/Pa during diastole when actual Pa is lower than mean Pa and constantly decreasing over 5 beats (resulting in easier identification of the diastolic cycle if the dicrotic notch is not visible well enough due to dampened pressure tracings).

Studies verified the good correlation of these indexes with instantaneous wave-free ratio (cut-off ≤ 0.89) and the general perception is that these non-hyperemic indexes are interchangeable, however, clinical outcome studies are lacking except for iFR [25].

1.2 Other indexes of coronary physiology

These are used to assess global blood supply or the microvasculature, but mainly for investigational purposes.

CFR - coronary flow reserve is the maximal coronary flow compared to resting flow; in essence, gives us an index of stress-related coronary flow. It is normal if above 2. Epicardial vessels, microvasculature, contractility, and preload all affect its value. It cannot differentiate between epicardial and distal, microvascular disease in the case of ischemia.

IMR - index of microcirculatory resistance can be measured with a wire capable of simultaneous pressure and temperature recordings; it can be defined from distal coronary pressure and mean hyperemic transit time (which is related to absolute flow). Epicardial disease and hemodynamic changes (e.g., blood pressure and heart rate) would not affect it significantly. It is considered abnormal if above 25.

RRR - resistive reserve ratio records the ability of the microvascular resistance to change after a vasodilating, hyperemic agent (ratio of microvascular resistance at rest and after hyperemia).

1.3 Discrepancy between hyperemic and non-hyperemic functional indexes

These two types of measurements (hyperemic vs. non-hyperemic index, e.g., fractional flow reserve vs. instantaneous wave-free ratio) used simultaneously show different values in a given lesion or vessel in approximately 20% of cases. In a study, this difference reached 40% (albeit there the instantaneous wave-free ratio cut-off for significance was ≤0.83) [26]. There was also a significant change in iFR after adenosine administration which questions its true independence from hyperemia (wave-free period being a period of minimal resistance similar to hyperemia-induced states). Not only these differences were examined, but also the concept of true replacement of the hyperemic functional indexes by non-hyperemic ones was questioned since it seems more logical to assess blood supply under hyperemia which resembles the physiological condition of exertion (similarly to the non-invasive tests to assess ischemia) and therefore the ability to predict changes under stress can be better estimated by hyperemic functional indexes.

There have been several investigations performed to try to explain these differences.

The location of the stenosis can have an impact on the diagnostic accuracy when comparing the instantaneous wave-free ratio or Pd/Pa to fractional flow reserve (≤0.80 as a reference standard). When investigating measurements in the left main or proximal LAD compared to other vessels, non-hyperemic indexes (Pd/Pa or iFR) had a lower accuracy. This was mainly driven by a higher incidence of false-negative values in both cases. This difference in measurement is likely related to the larger myocardial area supplied by the left main and proximal left anterior descending artery compared to the left circumflex and right coronary artery. This leads to a higher rise in coronary blood flow from baseline during maximal hyperemia and therefore resulting in an increased pressure gradient and lower fractional flow reserve value [27].

On the contrary to this finding, in a substudy of the DEFINE–FLAIR population, instantaneous wave-free ratio guided deferral of percutaneous coronary intervention was similar in outcome compared to fractional flow reserve guided deferral when measured in lesions of coronary vessels excluding the left anterior descending artery. In lesions of the left anterior descending artery, the authors claimed better outcomes if the intervention was deferred using instantaneous wave-free ratio compared to fractional flow reserve [28].

Reaction to hyperemic agents and microvascular disease might also explain these differences between hyperemic and non-hyperemic pressure indexes. The loss of pressure (ΔP) and its relation to flow velocity (V) secondary to stenosis can be described by the equation of $\Delta P = FV + SV^2$. S is the flow separation pressure loss coefficient while F is the viscous friction pressure loss coefficient. If flow is massively increased by the induction of hyperemia, the drop in distal coronary pressure will be significant and FFR will be recorded as low in spite of a low resting gradient (resulting in normal resting indexes). On the other hand, in long moderate lesions, high resting gradients may change only minimally during hyperemia. Therefore, two different stenoses with similar resting gradients (equal iFRs) can show completely different responses to hyperemia (low or high FFRs).

This difference was shown in a post hoc analysis which was performed of the largest combined pressure and Doppler flow velocity registry (IDEAL [Iberian-Dutch-English] collaborators study) investigating intermediate stenoses comparing baseline (iFR) and hyperemic measurements (FFR) including coronary flow reserve (CFR - whole cycle

hyperemic flow velocity/whole cycle baseline flow velocity) in concordant and discordant iFR/FFR groups as well as unobstructed vessels [29]. CFR was significantly higher in the FFR positive and iFR negative (negative discordant) group compared to the FFR negative/iFR positive (positive discordant) group. The former was similar to the concordant iFR negative/FFR negative as well as an unobstructed vessel reference group, whereas the latter was similar to the concordant FFR positive/iFR positive group. Hyperemic coronary flow velocity differences explained the disagreement between these groups. Also, when comparing the discordant groups there was a higher prevalence of diabetes in the FFR negative/iFR positive group likely reflecting the higher likelihood of microvascular disease causing a decreased response to vasodilation resulting in higher FFR values.

Left ventricular end diastolic pressure (LVEDP) and diastolic dysfunction might also play a role in the discordance between iFR and FFR. A significantly higher iFR and FFR discordance were found in patients with an elevated LVEDP and diastolic dysfunction compared to normal [30, 31].

When investigating the difference between the two physiologic indexes several clinical as well as angiographic factors have been identified. It was found that diabetes, smaller vessels, female gender, and higher grade of stenosis were significantly associated with low iFR among high FFR groups (positive discordance likely secondary to microvascular disease causing an impaired response to vasodilation) whereas male gender and lower grade of stenosis were seen in the high iFR low FFR group (negative discordance) [32]. The presence of end-stage renal disease with hemodialysis as well as valvular heart disease influences iFR and FFR measurements.

These observations were confirmed in other studies and other factors have also been investigated. Younger age is associated with low FFR and high iFR, whereas older age is the opposite [33]. Left main or LAD location of the stenosis showed negative discordance in studies [27, 33]. Another resting index, the RFR was compared to FFR in these stenosis locations and an opposite result was found showing positive RFR values in negative FFR cases which underlines the role of complex factors contributing to differences in coronary physiology [34].

Not only location but also the distribution of coronary artery disease can affect iFR/FFR discordance. Focal disease more often causes negative discordance whereas diffuse disease is associated with positive discordance [35].

Technical considerations should also be taken into account when comparing these functional indexes. During hyperemia-induced vasodilation, trans-stenotic gradients are higher, and therefore technical errors causing a pressure drift might have a lower relative effect on a given measurement, whereas when using non-hyperemic ratios, smaller pressure changes might have a more significant effect and even lead to lesion over- or underestimation if the absolute number is close to the cut-off value. There is a higher likelihood of discrepant values also if the measurements are around the prespecified cut-off values (borderline lesions).

When comparing invasive physiological indexes, iFR, FFR, and Pd/P had similar diagnostic accuracy compared to PET-derived coronary flow reserve (CFR: ratio of stress myocardial blood flow to resting myocardial blood flow in target segments), but for relative flow reserve (ratio of stress myocardial blood flow after a stenosis compared to stress myocardial blood flow in normal segments) FFR had better discrimination ability [36].

1.4 Prognosis in case of discrepant functional indexes

It is not clear completely, how this discrepancy in resting and hyperemic indexes would affect prognosis but there are some data regarding the potential prognostic value if these two indexes are not concordant. In a study of 596 patients and 840 vessels, FFR and iFR were measured at the same time. The patients investigated were mostly stable (around 80% with chronic coronary syndrome (CCS) and 20% with acute coronary syndrome (ACS)). Vasodilating capacity was lowest in the low iFR/high FFR group, whereas the highest capacity was recorded in the high iFR/low FFR group. There was no significant difference in outcome in these groups with discordant resting and hyperemic values in 5 years (high iFR/lowFFR or low iFR/high FFR) compared to the high iFR/high FFR group. On the other hand, the concordant low iFR/low FFR group had the worst prognosis [37].

Similarly to the previous study, despite the differences mentioned in these two physiologic indexes in the diabetic population, a substudy of the diabetic patients of the DEFINE-FLAIR study showed that the two types of guidance (iFR vs. FFR to decide to revascularize or not) resulted in no major difference in terms of major adverse cardiovascular events and safety was comparable at one year. Patients with diabetes had a significantly higher risk of major adverse cardiovascular events compared to the non-diabetic patient group [38].

1.5 Combined functional testing

We can change the cut-off values of iFR and thereby can decrease the need for hyperemic testing using a hybrid algorythm. If we change the cut-off of iFR to ≤0.85 (positive) and ≥0.94 (negative) and perform hyperemic testing only in the 0.86-0.93 (grey) zone, the diagnosis will be correct in 95% of the cases using FFR as the gold standard and almost 2/3 of the cases would not need hyperemic testing. On the other hand, the two new cut-off values would need to be tested by other methods of ischemia detection to see if we can clearly define a functionally significant lesion or not using these thresholds [39].

Similar results were found in another study; iFR (≤0.90) and Pd/Pa (≤0.92) were the cut-off values used. The grey zone was 0.86 to 0.93 for iFR and 0.87 to 0.94 for Pd/Pa where hyperemic testing was performed. Around 50% of cases did not need adenosine, but still, around 10% were misclassified if compared to an FFR ≤80. There was a higher rate of misclassification in proximal vessels [40].

1.6 Revascularization of non-culprit vessels in ACS

In acute coronary syndrome, culprit lesions should be revascularized according to the latest guidelines. There is still some uncertainty regarding revascularization decisions in non-culprit vessels in ACS in our everyday practice.

Complete revascularization is recommended in STEMI prior to discharge according to the ESC (Class IIa; Level of evidence A); complete revascularization is recommended in NSTE-ACS (Class IIa; Level of evidence C) and non-culprit lesions can be intervened upon during the index PCI with the use of fractional flow reserve (Class IIb; Level of evidence B) [12, 41]. Prior to complete revascularization, we should consider co-morbidities, the angiographic picture, patient preference, and the actual clinical context (routine non-infarct-related artery intervention is not recommended in cardiogenic shock in the same setting). Non-culprit vessels can be assessed by angiography, by using functional indexes, or with the help of intracoronary imaging. Non-invasive functional indexes (e.g., nuclear imaging, stress echocardiography, or MRI) do not have a role in the acute setting but might be utilized in the subacute or chronic phase.

1.6.1 Angiographic assessment of non-culprit vessels in ACS

During coronary angiography, lesion assessment is performed by visual assessment or software-aided quantitative coronary angiography. There is substantial variability among observers as to lesion classification; a disagreement is found in around 30% [42]. This led to the introduction of contour detection algorithms in the ’70s, later with digital computation [43] which was further improved in the ’80s by the DICOM system (Digital Imaging and Communications in Medicine) as well as densitometry and 3D QCA.

Coronary angiography - even if supported by quantitative assessment - has certain limitations. Besides the above-mentioned inter-observer variability, due to eccentricity, vessel overlap, or inadequate filling by contrast the severity of a certain lesion can be under- or overestimated.

Despite these limitations, there are several studies that investigated the usefulness of angiography to find significant non-culprit vessels and to decide whether revascularization is beneficial. In an observational cohort study of 21857 patients with NSTE-ACS, complete revascularization with choosing angiographically significant

non-culprit lesions (≥75% diameter stenosis) resulted in a better long-term outcome with decreased total mortality compared to culprit-only intervention (22.5% complete revascularization vs. 25.9% culprit vessel intervention; P= 0.0005) with a mean follow-up of 4.1 years, although initial in-hospital mortality was increased [44].

Similar results were seen in STEMI patients with multivessel disease. The PRAMI study (2013) randomizing ~500 patients showed a significantly better outcome with a mean follow-up of 23 months in terms of combined MACE (a composite of cardiovascular mortality, non-fatal myocardial infarction, and revascularization for refractory angina with confirmed ischemia), but also in terms of cardiovascular mortality and myocardial infarction combined when non-culprit vessels were revascularized based upon angiographic assessment (a significant lesion was defined as ≥50% diameter stenosis) compared to the culprit–only intervention [45]. Long-term follow-up of the CvLPRIT study (2019) randomizing ~300 patients showed a significantly better outcome in terms of combined MACE (a composite of all-cause mortality, heart failure, revascularization for angina with confirmed ischemia, and myocardial infarction) with a mean follow-up of 5.6 years, but also in terms of all-cause mortality and myocardial infarction when non-culprit vessels were revascularized based upon angiographic assessment (significance defined as ≥70% diameter stenosis) compared to culprit only intervention [46].

The COMPLETE trial (2019) assigned ~4000 patients with STEMI and multivessel coronary artery disease randomly to culprit-lesion only PCI or complete revascularization (within 45 days) mainly by angiographic assessment. Lesion significance was defined as ≥70% diameter stenosis or FFR ≤0.80 if the diameter stenosis was 40-69% (this was the case in less than 1% of the lesions in both study groups). There was a 26% risk reduction in cardiovascular mortality and myocardial infarction over approximately 3 years of follow-up. In two-thirds of the cases, completion of revascularization was performed during the initial hospitalization (median 1 day) whereas in one-third, within 45 days (median 23 days), a difference that did not affect the outcome [47].

It is worth mentioning that in acute cases angiographic assessment might overestimate the significance of a non-culprit lesion in a substantial number of cases (10-20%) when compared to follow-up angiography at a later stage. A potential explanation of an

overestimated non-culprit stenosis severity during the acute phase is vasoconstriction, but also the presence of thrombus, the effect of statin therapy, relative vasodilation of normal segments, or a change in hemodynamics might have a role [48, 49].

1.6.2 Invasive functional testing in ACS

1.6.2.1 Hyperemic test/fractional flow reserve

Most of the information on the benefit of using functional indexes to guide revascularization derives from stable patients and data is limited regarding ACS cases. There is uncertainty because of possible interference caused by transient microvascular dysfunction. In general, it is not recommended to measure fractional flow reserve in culprit vessels, since we might underestimate the significance of the lesion due to a decreased response to adenosine caused by microvascular injury (inadequate vasodilation). This can be secondary to vasoconstriction caused by increased α-adrenergic stimulation and endothelin-1 effect; endothelial dysfunction caused by inflammation, elevated CRP; distal embolization; vessel compression by myocardial edema or hemorrhage and elevated left ventricular diastolic pressure (LVEDP). These changes lead to a higher FFR, lower CFR, and increased IMR in the culprit vessels [50].

Not only the infarct-related territories are involved during an acute coronary syndrome, but in animal experiments, non-ischemic territories showed evidence of focal infarction along with functional derangement [51].

Similar findings were observed in human studies showing dysfunctional microcirculation in the non-culprit vessels as well likely caused by an elevated LVEDP and increased vasoconstriction. This leads to impaired vasodilation (defined as the ratio of maximal to basal coronary blood flow) during the acute phase which could potentially interfere with hyperemic functional assessment [52].

In the majority of investigations however, these microvascular changes have not resulted in a major influence on FFR measurement in human studies or animal models.

In the FISIOIAM study, 93% of STEMI patients had microvascular and endothelial dysfunction in the non-culprit areas assessed by detailed physiologic assessment. The investigators found no significant effect or attenuated response to hyperemia on FFR measurements despite these microvascular changes [53].

In a porcine acute myocardial infarction model MI was provoked by selective balloon occlusion of the Lcx (left circumflex artery) for 30 minutes and a non-IRA lesion was created by bare-metal stent implantation in the LAD (left anterior descending coronary artery) 4 weeks prior to the experiment. Functional testing was performed at baseline, during balloon occlusion as well as after 15 minutes of reperfusion. The resting trans-stenotic gradient was significantly higher, and the resting microvascular resistance was significantly lower after reperfusion compared to baseline whereas these indexes (trans-stenotic gradient and microvascular resistance) during hyperemia have not changed significantly. Similarly, fractional flow reserve has not changed significantly after reperfusion while CFR and iFR were significantly lower compared to baseline [54].

In the WAVE study, FFR was measured at the index procedure in non-culprit vessels of STEMI patients and then 5-8 days later with the finding of stable values, however, this might be related to the fact that the changes in circulation and microvasculature described above have not resolved yet [55].

Despite the theoretical obstacles mentioned above, fractional flow reserve measurement in non-culprit vessels of ACS patients has not changed significantly in two other studies with a longer follow-up test if performed in 35 +/- 4 or 41.8 +/- 10.2 days [56, 57]. Microvascular dysfunction was assessed in a subgroup of one of these studies [56] with the measurement of IMR in non-culprit regions and it was found that it was normal in 79% of patients without a significant change during follow-up.

A good correlation of FFR measurement was also observed in NSTE-ACS patients compared to stress cardiac MRI if the latter was performed 6+/- 3 days after PCI [58].

In the REDUCE-MVI study, fractional flow reserve, instantaneous wave-free ratio, coronary flow reserve, and index of microcirculatory resistance were measured in 73 STEMI patients at the time of the acute event and at 1 month. Compared to the initial measurement, FFR and CFR showed significant changes at 1-month; fractional flow reserve decreased, and coronary flow reserve increased. In the acute phase, microcirculatory response to adenosine was decreased. These changes were seen more

likely in larger infarcts, low left ventricular ejection fraction, and microvascular injury [59].

The present approach is that fractional flow reserve can be reliably measured in non-culprit vessels during an acute coronary syndrome reflected in the ACS guidelines by the ESC keeping in mind that there is some chance of underestimating the significance of the non-culprit vessels in the acute phase, especially with large infarcts.

1.6.2.2. Non-hyperemic testing: iFR and Pd/Pa

Less is known about non-hyperemic testing of non-culprit vessels/lesions in acute coronary syndrome.

In the REDUCE-MVI study, iFR and Pd/Pa both increased but did not significantly change at 1-month. The lower initial non-hyperemic index was explained by a slightly increased rest flow during the acute event [59].

The iSTEMI study investigated iFR during the acute phase and follow-up (median 16 days) in 120 STEMI patients/157 non-culprit lesions after successful primary PCI. 89% of measurements were similar within 5 days whereas only 70% ≥16 days (median increase of 0.03). After at least 16 days, iFR was higher which raises the possibility of overestimation of the functional significance of the non-culprit lesion during the acute phase by iFR. On the other hand, non-significant lesions can be predicted with good certainty (negative predictive value of 89%) [60].

The WAVE study (observational registry of 50 patients with 66 non-culprit lesions) showed that iFR measurements in non-culprit vessels of STEMI patients at the acute phase compared with the subacute phase (5-8 days) were stable [55].

The negative predictive value was 89% and 91%, the positive predictive value was 68% and 53% in iSTEMI and REDUCE-MVI, respectively using the follow-up iFR as reference. Of note, the patient characteristics (e.g., prevalence of significant non-culprit lesions 52% vs. 23%) and the timing of follow-up measurement (median 16 days in iSTEMI and 31 days in REDUCE-MVI) differed between these studies.

These investigations suggest that iFR (and likely Pd/Pa) can reliably rule out significant disease in the acute phase whereas there is a chance of overestimation of the significance of non-culprit lesions (both REDUCE-MVI and iSTEMI showed an increase in iFR in the subacute state).

1.6.3. Revascularization guided by functional testing in ACS patients

Since there has been abundant evidence of the benefit of revascularization guided by functional testing compared to angiographic assessment in chronic coronary syndrome, prospective studies were designed to assess the feasibility of FFR guidance in the revascularization of non-culprit vessels in acute cases. The Compare-Acute trial randomized 895 patients with STEMI and multi-vessel disease with a follow-up of 12 months to compare FFR-guided complete revascularization of acute patients to IRA-only treatment (in this group elective PCI within 45 days was not considered to be an endpoint). The primary endpoints were all-cause mortality, myocardial infarction, cerebrovascular event, or any revascularization. There was a significant difference in primary outcome: 7.8% in the FFR-guided (complete group) versus 20.5% in the IRA-only group ($p<0.001$). By FFR, around 50% of angiographically significant lesions were found to be non-significant [61].

In the Danami3-Primulti study (Complete Revascularisation versus Treatment of the Culprit Lesion Only in Patients with ST-Segment Elevation Myocardial Infarction and Multivessel Disease), 627 patients with STEMI and multi-vessel disease were followed up for 27 months the primary endpoint being MACE (all-cause mortality, myocardial infarction, ischemia-driven revascularization of non-IRA lesions). The FFR-guided interventions of non-culprit vessels were performed at a median of 2 days after the index procedure. FFR-guided complete revascularization was better than IRA-only treatment with a MACE of 13% vs. 22%, respectively ($p=0.004$). There was also a significant proportion of lesions found to be non-significant by functional testing compared to angiographic assessment (around 30%) [62].

In both trials, the benefit was mainly driven by a lower number of urgent revascularizations. There was no benefit in terms of mortality or myocardial infarction alone in either of these studies.

In large meta-analyses of several studies, complete revascularization compared to culprit-only was better in terms of all aspects of MACE (including CV death and recurrent MI) regardless of angiography or FFR guidance with no major difference between the two approaches [63, 64].

The Flower-MI study compared FFR-guided total revascularization with angiography-guided total revascularization with respect to MACE at 1 year (mortality, myocardial infarction, or urgent revascularization) in 1171 patients. There was no benefit of FFR-guidance, however, due to wide confidence intervals, it was not possible to have firm conclusions drawn. There was a much lower event rate in the trial population compared to what was expected and the cause of death was different in the two groups. There was a higher rate of non-cardiac death in the FFR-guided group compared to the angiography-guided patients (approximately 80% versus 30%). Since patients were included with severe non-culprit disease, the number of patients with intermediate stenosis range (<70%) was low (less than 50%) and therefore the benefit of FFR-guidance relied on a relatively small number of patients (198 of 586). FFR-guidance resulted in less interventions (like other studies) still resulting in similar outcomes [65, 66].

On the other hand, FRAME-AMI, a recently presented study at the ESC Congress 2022 investigating approximately 600 patients with myocardial infarction (STEMI or NSTEMI) found that FFR-guided revascularization of non-culprit vessels compared to angiographic guidance (during index hospitalization with 60% immediate and 40% staged) with a median follow-up of 3.5 years resulted in a significantly decreased rate of myocardial infarction or death, whereas unplanned revascularization was not significantly different. The primary endpoint (a composite of death, myocardial infarction, or revascularization) occurred in 7.4% (FFR-guided group) versus 19.7% (angiography-guided group) of patients (p=0.003) [67].

This concept has not been proved in a recent large-meta-analysis of around 9000 patients with STEMI and multivessel disease. Angiography-guided complete revascularization was better compared to culprit-only treatment in terms of

cardiovascular death, all-cause death and myocardial infarction, whereas FFR-guided approach was not [68].

In a pooled analysis of 5 large studies (approximately 9000 patients), deferral of revascularization of non-culprit vessels based upon FFR resulted in a higher risk of major adverse cardiovascular events at 1 year in ACS patients compared to stable coronary artery disease (SCD) mainly related to unplanned revascularization. The prognosis was similar, however in treated patients guided by FFR [69]. Similar results were found in a meta-analysis showing a higher MACE risk in ACS patients with FFR-guided revascularization of non-culprit vessels compared to stable angina [70]. It is not known whether this increased risk is due to possible underestimation of risk by physiologic indexes in ACS cases or the inherently higher risk of future events in ACS patients due to the more widespread disease of the coronary vessels along with more vulnerable plaques compared to chronic coronary syndromes or a combination of both.

2. OBJECTIVES

There is evidence mostly from stable patients that FFR guidance improves clinical outcomes compared to angiography-guided revascularization. In ACS patients there is also evidence that FFR (hyperemic) guidance of revascularization in non-culprit vessels can improve clinical outcomes mainly driven by a decreased need for urgent revascularization later. On the other hand, there is limited and equivocal data regarding the use of resting indexes in non-culprit vessels of ACS cases to predict outcomes. Therefore, we compared FFR and resting Pd/Pa in the non-culprit vessels of patients in the Compare-Acute trial and their respective power to predict 3-year MACE [71].

3. METHODS

3.1. Patients

The Compare-Acute trial enrolled STEMI patients with multivessel disease within 12 hours of symptom onset. Two groups were randomized in a 1:2 fashion to infarct-related artery only (IRA-only) and FFR-guided complete revascularization, immediately after the successful and uncomplicated primary percutaneous intervention of the infarct-related artery. Resting Pd/Pa and FFR of all non-culprit vessels (with at least 50% diameter stenosis) were measured in all patients. In the complete revascularization group, non-culprit revascularization was decided by FFR (cut-off ≤0.80), whereas in the other arm, resting Pd/Pa and FFR values were measured but concealed and all non-culprit lesions were left without intervention. FFR and resting Pd/Pa were measured using commercially available pressure wires (St. Jude Medical, now Abbott). Intravenous infusion or intracoronary boluses of adenosine at standard doses were used to achieve hyperemia. A total of 885 patients were randomized in the study, 295 to the FFR-guided complete revascularization arm and 590 to the IRA-only group. To assess the relative prognostic power of FFR and resting Pd/Pa to predict 3-year MACE, we included only patients from the IRA-only group (n=517) who had both FFR and resting Pd/Pa measured in the non-culprit vessels (target vessels in this evaluation) [71].

3.2. Endpoints

Target vessel-related MACE included target vessel myocardial infarction (TVMI) and target vessel revascularization (TVR) at 36 months in this analysis. Cardiovascular death was not included as an endpoint, because it is hard to relate it to a specific vessel. We compared the respective power of FFR and resting Pd/Pa in predicting target vessel-related MACE with special attention to cases with discrepant FFR and Pd/Pa values. The Clinical Event Committee reviewed all reported non-fatal myocardial infarction (MI) events. These were assigned to a target or a non-target vessel. In case

the event (non-fatal MI or non-target vessel revascularization) was related to a non-target vessel, it was not counted as an event [71].

3.3. Statistical analysis

Categorical variables were presented as counts and percentages. Continuous patient- and vessel-level variables were presented as mean (±SD) or median (interquartile range) depending on their distribution. The correlation of FFR and resting Pd/Pa on a target-vessel-level was assessed by Pearson coefficient of determination (R2). Receiver-operating characteristic (ROC) analysis was performed to examine the concordance of Pd/Pa and FFR≤0.80. Concordance was assessed using Harrell C in a univariate frailty model, taking also the hierarchical nature of the data into account. Optimal cut-off for Pd/Pa was determined using Youden's index. Diagnostic inter-testagreement between FFR≤0.80 and Pd/Pa≤0.91 was tested by Cohen's kappa statistic. Agreement between the methods was assessed by Bland-Altman plots with corresponding 95% limits of agreement. Discrepant pairs and their relation to TV-related MACE at 36 months were assessed using the $\chi 2$ test. A frailty model (cox regression mixed model) with a gamma distribution was used to construct a prediction-model for the endpoint TVR and/or TVMI on a vessel-level. This analysis takes both time and the multilevel structure of the data (the clustering of vessels in one patient) into account. For each of the independent variables, hazard ratio (HR) and its 95% CI are presented. For predictor selection in the final model, we used backward selection. To check if the assumption of a constant hazard over time was met for the included variables, the backward selection plots produced in R were eyeballed. R version 3.6.2 and SPSS version 27 were used for the analysis [71].

4. RESULTS

4.1. Patients, vessels, and physiology parameters

517 patients and 665 target vessels were included [**Figure 1**]. 282 (42.4%) were left anterior descending (LAD), 221 (33.2%) were left circumflex (Lcx) and 162 (24.4%) were right coronary artery (RCA). The majority, 371 patients had one, 144 had two, and 2 had three target vessels. The distribution of FFR and resting Pd/Pa values are shown in **Figure 2**. Median FFR was 0.83 (interquartile range, 0.14), and median resting Pd/Pa was 0.92 (interquartile range, 0.10) [71].

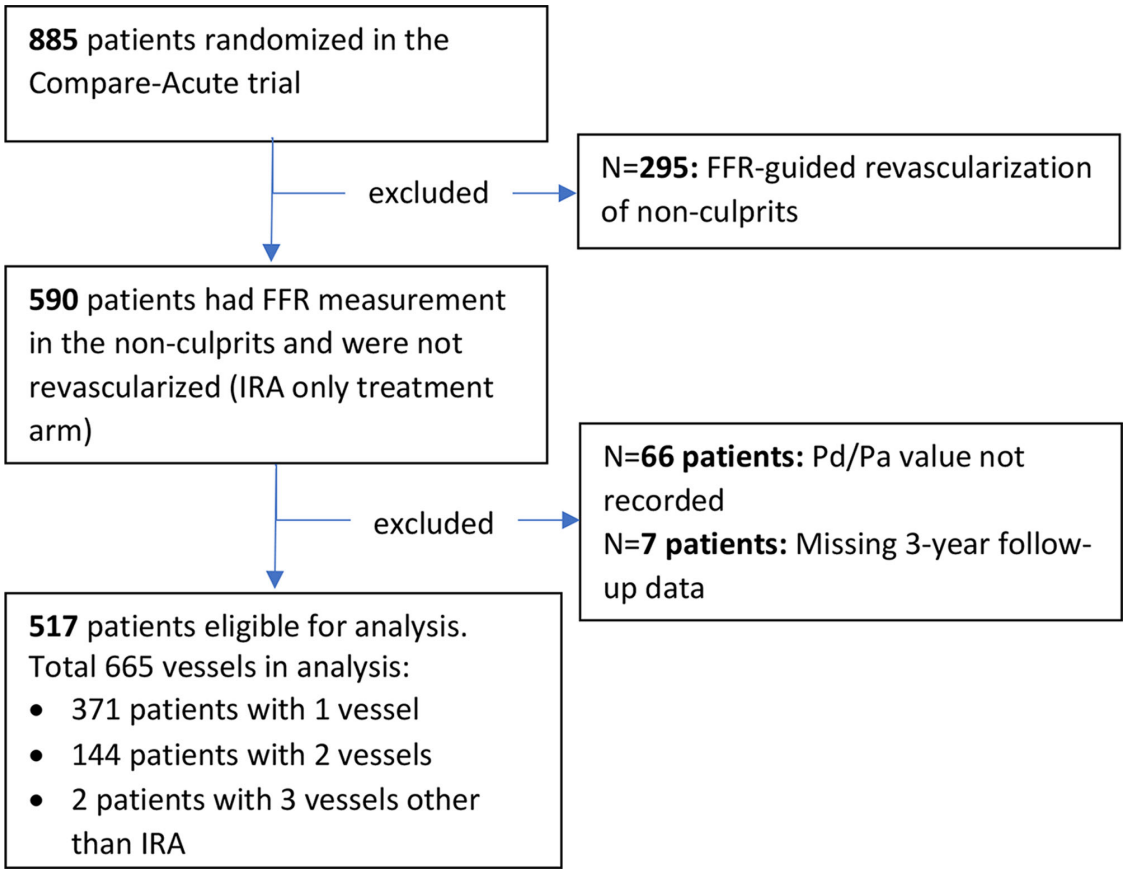


Figure 1. Patient flow chart. FFR indicates fractional flow reserve; IRA, infarct-related artery; and Pd/Pa, resting full cycle distal coronary to aortic pressure ratio. (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional

Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 3) [71].

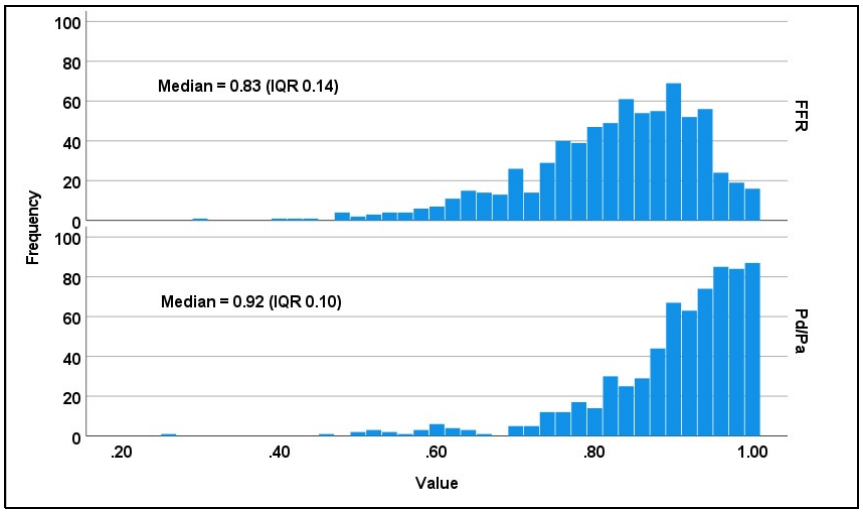


Figure 2. Distribution of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa) values. IQR indicates interquartile range. (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 5) [71].

4.2 Correlation of FFR and resting Pd/Pa

The scatter plot of FFR and resting Pd/Pa are shown in **Figure 3**. There was a linear correlation between FFR and resting Pd/Pa with a Pearson R^2 of 0.84 ($p<0.01$). The area under the ROC curve (C statistic) to predict an FFR≤0.80 was 0.894 for resting Pd/Pa indicating a good correlation [**Figure 4**].

Based on ROC curve analysis, the optimal cut-off value of resting Pd/Pa to predict an FFR≤0.80 was 0.905 (Youden index 0.620). 301 vessels (45%) had an FFR >0.80 and a resting Pd/Pa >0.91 [true negatives, **Figure 3**, quadrant B], 232 (35%) had an FFR≤0.80 and a resting Pd/Pa≤0.91 [true positives, **Figure 3**, quadrant C]). 85 (13%)

had an FFR >0.80 and a resting Pd/Pa≤0.91 [false positives, **Figure 3**, quadrant D] and 47 (7%) had an FFR≤0.80 and a resting Pd/Pa>0.91 [false negatives, **Figure 3**, quadrant A]. Altogether 132 vessels (20%) had discrepant FFR and resting Pd/Pa values. The overall sensitivity, specificity, positive and negative predictive value of Pd/Pa≤0.91 versus FFR≤0.80 were 83.15%, 77.98%, 73.19%, and 86.49%, respectively, and the overall diagnostic accuracy was 80.15%.

To achieve a diagnostic accuracy of 90%, 95%, and 99%, adenosine was needed in 24.1%, 31.4%, and 74.9% of the lesions, respectively [**Figure 5**].

Of the 132 vessels with discrepant FFR and resting Pd/Pa, 57 (43%) were left anterior descending, 34 (26%) were left circumflex and 41 (31%) were right coronary arteries. Resting and hyperemic measurements of coronary physiology of the target vessels were discrepant in 20% in the left anterior descending (57/282), 15% in the left circumflex (34/221), and 25% in the right coronary artery (41/162). The level of diagnostic agreement between FFR≤0.80 and resting Pd/Pa≤0.91 had a kappa of 0.60 (SE 0.031, p<0.001), indicating a moderate level of agreement [71].

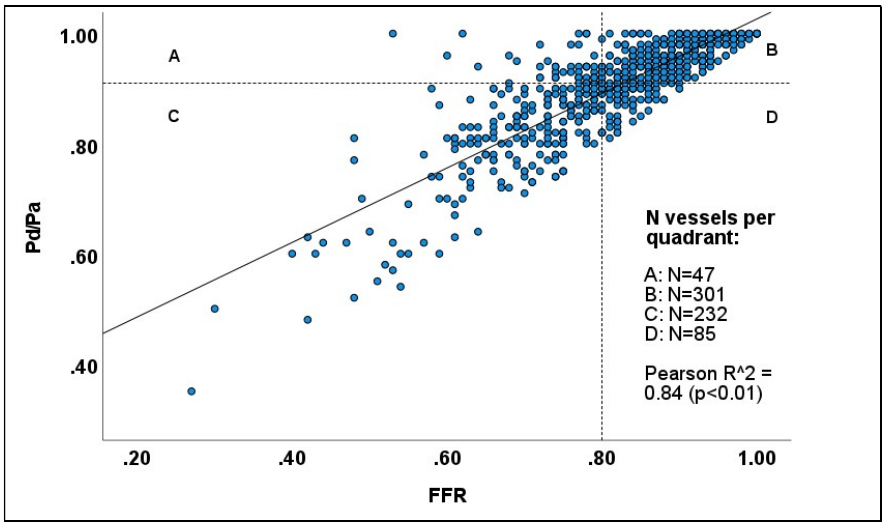


Figure 3. Scatter plot of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa). (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of

Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 5) [71].

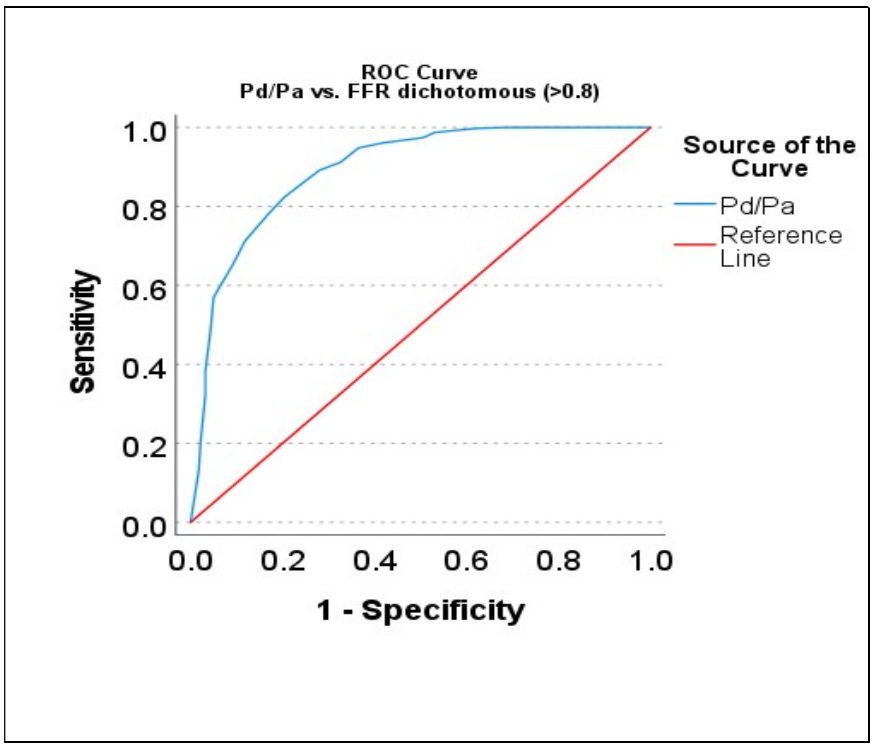


Figure 4. Receiver-operating characteristic (ROC) curve for resting full cycle distal coronary to aortic pressure ratio (Pd/Pa). FFR indicates fractional flow reserve. (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 6) [71].

4.3 Endpoints, the predictive power of FFR versus resting Pd/Pa

130 target vessel revascularizations (57 LAD, 43 Lcx, and 30 RCA) and 14 target vessel-related myocardial infarctions (4 LAD, 7 Lcx, and 3 RCA) occurred in 36 months. 132 vessels were related to an endpoint (TVR and/or TVMI). 82 of the 279

(29.4%) target vessels with an FFR≤0.80 had an endpoint compared with 50 of 386 (13.0%) with an FFR >0.80. FFR had a sensitivity, specificity, and overall diagnostic accuracy of 62%, 63%, and 63%, respectively. 81 of the 317 (25.6%) target vessels with a resting Pd/Pa ≤0.91 had an endpoint compared with 51 of 348 (14.7%) with a resting Pd/Pa of >0.91. Resting Pd/Pa had a sensitivity, specificity, and overall diagnostic accuracy of 61%, 56%, and 57%, respectively.

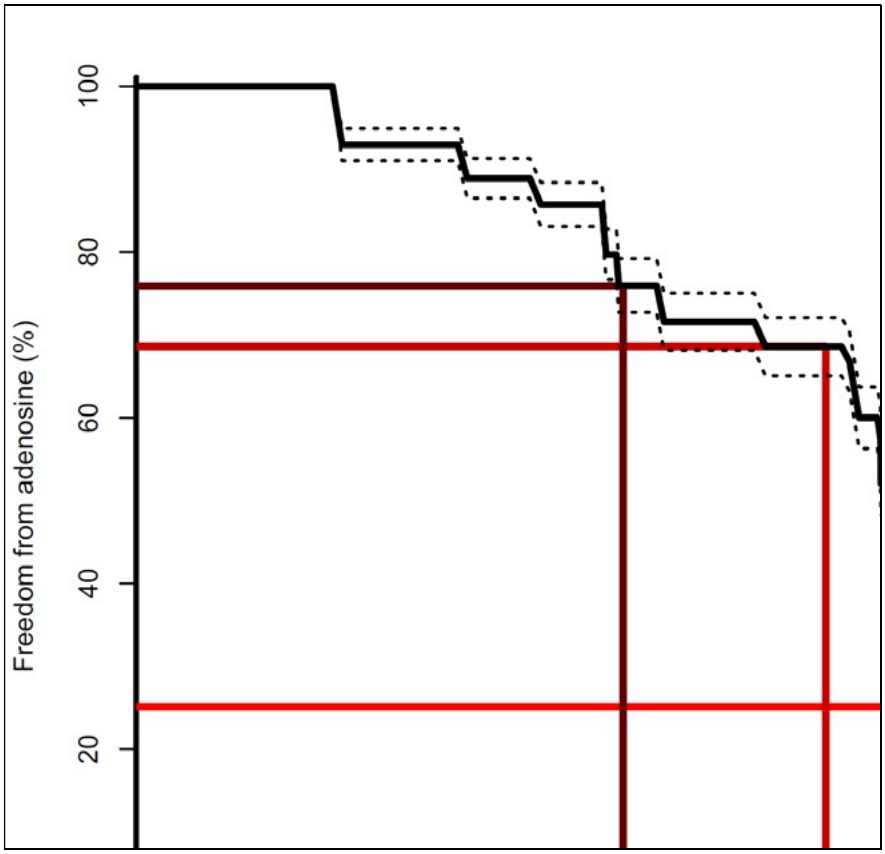


Figure 5. Association between the freedom from adenosine and the diagnostic accuracy of resting full cycle distal coronary to aortic pressure ratio. The 95% confidence interval is indicated by dashed lines. (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, Supplemental Material) [71].

The ROC curves of FFR and resting Pd/Pa in predicting 36-month TVMI and/or TVR are shown in **Figure 6**. The AUC for FFR and resting Pd/Pa were 0.630 (95% CI, 0.578–0.682) and 0.608 (95% CI, 0.556–0.661), respectively (p=0.20). Based on ROC analysis, the best cut-off values of FFR and resting Pd/Pa to predict 36-month TVMI and/or TVR were 0.815 and 0.935, respectively [71].

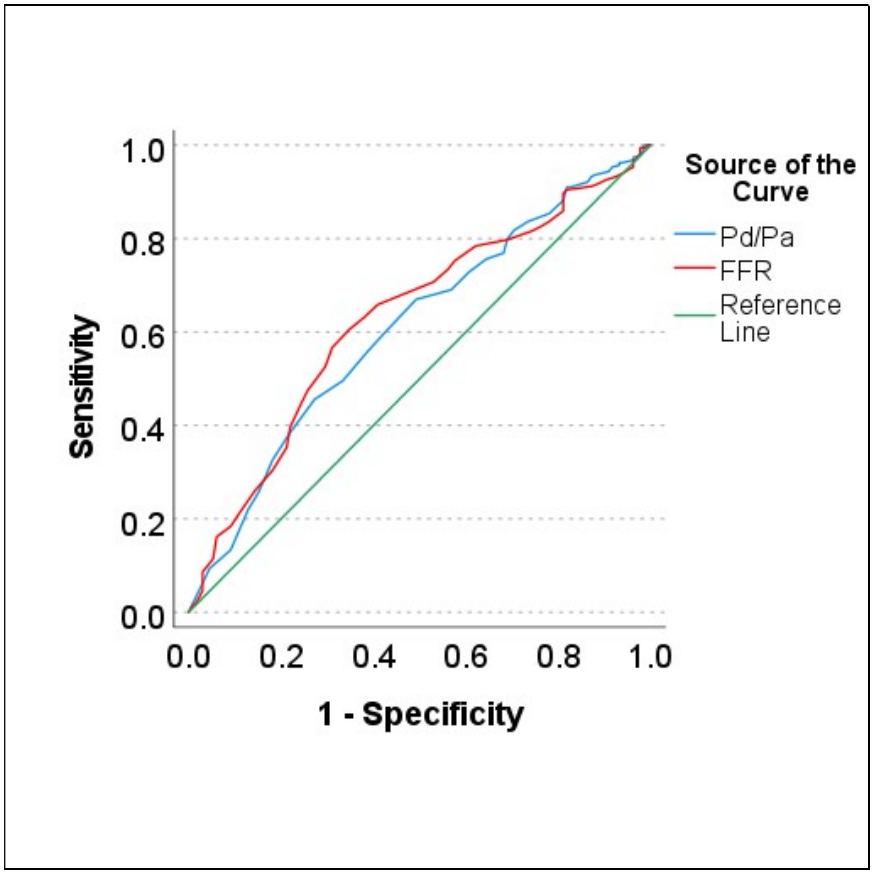


Figure 6. Receiver-operating characteristic curves of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa) in predicting 36-month target vessel myocardial infarction and/or target vessel revascularization. (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 8) [71].

4.4 Outcome of vessels with discrepant FFR and resting Pd/Pa values

The outcome was analyzed in vessels with discrepant Pd/Pa and FFR (i.e., FFR≤0.80 and Pd/Pa>0.91 or FFR>0.80 and Pd/Pd≤0.91) [quadrants A and D in Figure 3]. In these cases, revascularization decisions of non-culprit vessels would have been different. There was a discrepancy in the resting (Pd/Pa) and hyperemic (FFR) measurements in 132 of the 665 vessels (20%). In 105, no TVMI or TVR occurred, of these, 72 had negative FFR and positive Pd/Pa, and 33 had positive FFR and negative Pd/Pa [**Figure 7a**]. In 27, TVMI and/or TVR occurred, of these 13 had negative FFR and positive Pd/Pa and 14 had positive FFR and negative Pd/Pa [**Figure 7b**]). FFR was better than resting Pd/Pa (P=0.048) to identify which nIRA could be safely deferred. The event-free survival curves of the 4 concordant and discordant groups are shown in **Figure 8** [71].

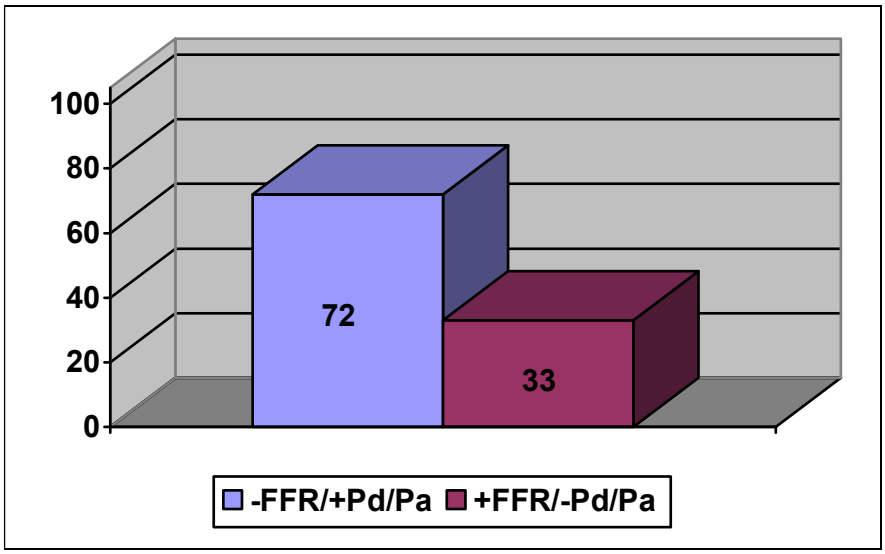


Figure 7a. Non-culprit vessels with discrepant functional indexes and no target vessel myocardial infarction (TVMI) and/or target vessel revascularization (TVR).

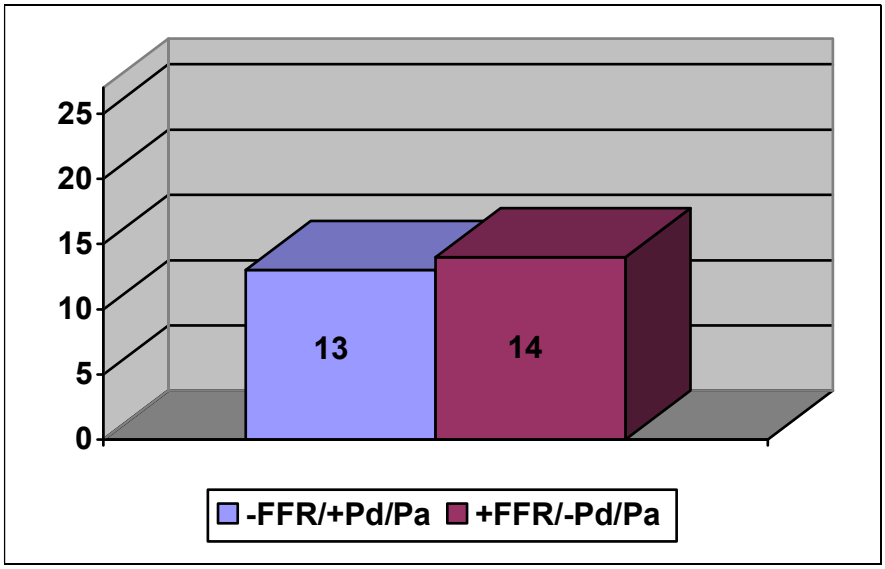
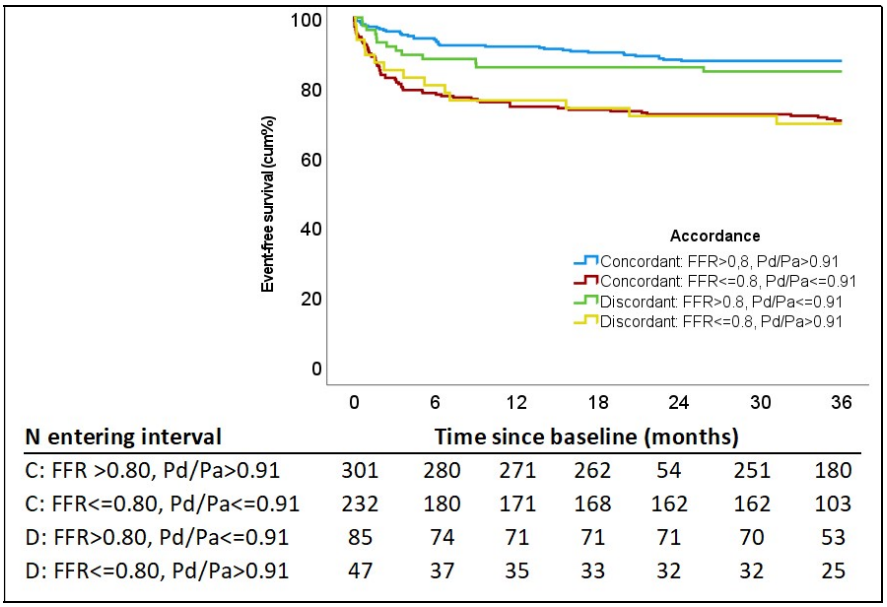


Figure 7b. Non-culprit vessels with discrepant functional indexes with target vessel myocardial infarction (TVMI) and/or target vessel revascularization (TVR).



N entering interval							
C: FFR >0.80, Pd/Pa>0.91	301	280	271	262	54	251	180
C: FFR<=0.80, Pd/Pa<=0.91	232	180	171	168	162	162	103
D: FFR>0.80, Pd/Pa<=0.91	85	74	71	71	71	70	53
D: FFR<=0.80, Pd/Pa>0.91	47	37	35	33	32	32	25

Figure 8. Event-free survival curves of the 4 groups according to the concordance of fractional flow reserve (FFR) and resting full cycle distal coronary to aortic pressure ratio (Pd/Pa). (Adapted from Piróth Z, Fülöp G et al. Correlation and Relative Prognostic Value of Fractional Flow Reserve and Pd/Pa of Nonculprit Lesions in ST-

Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv, 2022; 15(2): e010796, p. 8) [71].

5. DISCUSSION

The European guidelines recommend complete revascularization in hemodynamically stable ACS cases with the potential use of FFR. At present, there is some uncertainty and a non-uniform approach in everyday practice on when and how to choose lesions to intervene upon despite the recommendation.

If we consider the studies based upon angiographic assessment only, non-culprit lesions should be intervened if the stenosis diameter is ≥70% (data with one smaller trial showing benefit ≥50%) [45]. There is a possibility of overestimating lesion severity in the acute or early subacute setting.

Functional assessment of non-culprit lesions by FFR compared to angiographic assessment (≥50% stenosis) showed a benefit mostly related to a lower rate of urgent revascularization in randomized studies [61, 62]. The FRAME-AMI study showed a benefit in hard endpoints (death or myocardial infarction) with FFR-guided complete revascularization. In studies applying FFR-guidance for non-culprit revascularization, 30-50% of angiographically significant (DS >50%) lesions proved to be FFR-negative. Similarly, a high rate of functionally non-significant lesions was found in another ongoing study of FFR-guided revascularization versus initial conservative treatment in ACS patients (STEMI and high-risk NSTEMI) with approximately 20% rate of non-significant lesions by FFR in the angiographic range 90-99% and 50% in the 70-89% range [72]. In the first two studies using a hyperemic index to define significant non-culprit lesions, FFR-guidance resulted in no worsening in major outcomes compared to angiographic assessment only despite a lower number of interventions, and no late catch-up was noticed.

It stands to reason that risk is not only related to a specific ischemic threshold but rather it is related inversely to the absolute value of a functional index [73], whereas local plaque vulnerability also plays a role in future MACE. The latter can be assessed by intracoronary imaging (IVUS, OCT). Risk factors can be identified which can increase vulnerability (thin cap fibroatheroma, high atherosclerotic load, presence of

macrophages, and small luminal area) [74, 75]. Trials have been performed and are also underway incorporating that into the decision-making process. The intervention of angiographically mild lesions in MI patients showing the above high-risk characteristics was associated with better vessel-related outcomes [76].

The investigations assessing the repeatability of hyperaemic and non-hyperemic indexes in the acute and subacute settings show an opposite direction. FFR might under-, resting indexes might overestimate lesion severity in the non-culprit vessels in the acute setting.

At present there is a question regarding the timing of non-culprit revascularization although the guidelines recommend in-hospital complete revascularization in these patients. No harm was seen in the COMPLETE trial if non-culprit lesions were intervened upon at a later stage (mean delay of 23 days) [77]. Similar finding of no major difference between acute and staged non-culprit PCI was noted in meta-analyses. Combined and individual endpoints of cardiovascular death and/or new myocardial infarction were not significantly different [64] and 30-day and 1-year mortality were similar [78]. There are ongoing trials investigating this, BIOVASC (NCT03621501), iMODERN (NCT03298659), and MULTISTARS AMI (NCT03135275) [79, 80].

In our analysis, the correlation and respective power to predict vessel-related outcomes of FFR and resting Pd/Pa were evaluated in non-culprit arteries of patients with STEMI and primary PCI. There was a linear and good correlation between FFR and resting Pd/Pa (R^2, 0.84). The optimal cut-off of resting Pd/Pa to predict an FFR≤0.80 was 0.905. The diagnostic accuracy of Pd/Pa≤0.91 was approximately 80%, similar to the results of other studies in patients with stable angina [18, 19]. The level of diagnostic agreement between FFR≤0.80 and resting Pa/Pd≤0.91 was moderate. The two indexes (FFR and Pd/Pa) predicted future target-vessel-related events (TVMI and TVR) with similar diagnostic accuracy at 36 months (63% vs. 57%, p=0.20). In case the two functional (hyperemic and resting) values were discrepant, FFR was significantly better in defining which vessel could be deferred. Our results are in line with another analysis in which resting Pd/Pa was shown to be less important prognostically compared with

FFR in patients primarily with stable angina [81]. Similar finding was recorded in post-PCI patients when Pd/Pa and FFR were measured. About 50% of patients had discrepant values, but low Pd/Pa and high FFR patients had similar outcomes compared to concordant negative cases (high iFR and high FFR) [82].

The dilemma is whether or not we could replace hyperemic testing with easier-to-obtain resting indexes to assess the functional severity of non-culprit lesions and to decide whether or not revascularization is necessary. This could potentially lead to shorter procedure time as well as lower costs and avoidance of potential side effects of adenosine.

The reason why resting indexes might not be a good option according to our data is the following. The diagnostic accuracy of Pd/Pa compared with FFR in this analysis was 80%. This is similar to the findings of resting index evaluation compared to hyperemic testing in stable patients. Although in general, the two indexes were similar in predicting adverse outcomes, FFR was better to defer revascularization of non-culprits than resting Pd/Pa (in cases with discrepant FFR and resting Pd/Pa). Since adenosine is a medication that can be used to treat no-reflow in ACS cases, it is not contraindicated in this setting and therefore could help us to better evaluate risk.

There are limitations of this analysis which are in general related to the fact that some patients were excluded from the main trial e.g., patients with failed primary PCI, left main disease, or significant valve disease. Relating non-fatal MI events to a specific vessel by the blinded clinical events committee was not possible in all cases and some of the patients had >1 target vessel included. Other resting indexes were not measured, although in general, they are equal in diagnostic performance. The indexes were measured on-site (no core laboratory analysis was used).

6. CONCLUSIONS

In STEMI patients and multivessel disease, the functional assessment of non-culprit vessels immediately after successful primary PCI showed that resting Pd/Pa had an 80% diagnostic accuracy compared with FFR. In this analysis, the best cut-off value of resting Pd/Pa to predict an FFR≤0.80 was 0.905. FFR was not significantly better than resting Pd/Pa to predict major adverse cardiovascular events, but in case the two indexes were discrepant, FFR was superior in identifying which non-culprit lesions could be safely deferred.

7. SUMMARY

Functional assessment of coronary lesions has been extensively investigated and proved to be beneficial in chronic coronary syndrome. There is a recommendation from the guidelines to perform complete revascularization in ACS cases during the index hospitalization. Still, it is not completely clarified how to define significance of non-culprit lesions and how to safely defer intervention.

In our study we investigated the correlation and prognostic power of resting Pd/Pa and FFR to predict outcomes in 3 years in non-culprit vessels of STEMI patients of the COMPARE-Acute trial who had successful primary PCI.

We found that the resting Pd/Pa had approximately 80% diagnostic accuracy when compared to fractional flow reserve. In case the two indexes were discrepant (approximately 20% of the cases), FFR had better ability to indicate which lesions could be deferred safely.

Our analysis indicates that deferral of an intervention of non-culprit vessels in the acute phase seems to be better aided by FFR compared to resting indexes. Further studies are needed to clarify the optimal approach for these patients.

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