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Review article

Functional assessment of coronary stenosis: alternative hyperemic, nonhyperemic, and angiographic indexes

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ABSTRACT

Assessment of the functional significance of coronary artery stenoses to guide percutaneous coronary intervention is widely performed using pressure wire fractional flow reserve during adenosine- or adenosine triphosphate-induced hyperemia. However, the use of fractional flow reserve may be limited by the contraindications and adverse effects of this hyperemic stimulus, as well as the potential risk of vessel damage from the pressure wire. This review will discuss alternative evaluation methods, including various hyperemic agents, nonhyperemic pressure ratios, and angiography-based indices.

Keywords: Angiography. Fractional flow reserve. Hyperemia. Percutaneous coronary intervention.

Evaluación funcional de las estenosis coronarias: índices hiperémicos alternativos, no hiperémicos y angiográficos

RESUMEN

La evaluación funcional de las estenosis coronarias para guiar los procedimientos de intervencionismo coronario percutáneo se realiza frecuentemente midiendo la reserva fraccional de flujo durante la hiperemia inducida por adenosina o trifosfato de adenosina. Las contraindicaciones de estos estímulos hiperémicos y la posibilidad de que se produzca daño vascular con la guía de presión pueden limitar la utilización de la reserva fraccional de flujo. Esta revisión discute los métodos alternativos de evaluación funcional: diferentes agentes hiperémicos, índices no hiperémicos e índices angiográficos.

Palabras clave: Angiografía. Reserva fraccional de flujo. Hiperemia. Intervención coronaria percutánea.

Abbreviations

FFR: fractional flow reserve. **iFR:** instantaneous wave-free ratio. **NHPR:** nonhyperemic pressure ratio. **PCI:** percutaneous coronary intervention. **PW:** pressure wire. **QFR:** quantitative flow ratio.

INTRODUCTION

The functional significance of coronary artery stenoses is widely assessed using fractional flow reserve (FFR), which is based on measurement of the pressure beyond the stenosis that is usually obtained with a pressure wire (PW) during adenosine- or adenosine triphosphate (ATP)-induced hyperemia. The use of FFR may be limited by the contraindications and adverse effects of this hyperemic stimulus and the possibility of damaging the vessel with the PW, despite its Class 1 recommendation to guide the revascularization of chronic coronary syndromes.[1] Consequently, various hyperemic drugs and alternative methods have been introduced overtime. This review will focus on: *a)* the relevant characteristics of hyperemic agents, and *b)* the diagnostic accuracy and outcome data of nonhyperemic pressure ratios (NHPRs) and angiography-derived indices.

HYPEREMIC AGENTS

Coronary flow is the critical determinant of ischemia and at rest is controlled to match myocardial oxygen demand and to counteract variations in coronary perfusion pressure by parallel changes in

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microvascular resistance, resulting in an autoregulatory plateau. Under maximal hyperemia, the relationship between coronary flow and pressure becomes curvilinear: it is straight within the physiological pressure range, but curves toward the pressure axis at lower pressures.[2]

Given this relationship, the ratio between mean distal coronary pressure and mean aortic pressure during maximal hyperemia (FFR) is used to estimate the ratio between maximum flow in stenosed coronary arteries and maximum flow in healthy arteries.

In animal studies, papaverine was the most potent pharmacologic vasodilator and this finding was also confirmed in humans, but given its adverse effects adenosine was validated.[3] Subsequently, adenosine or ATP became widely used in clinical studies evaluating the usefulness of FFR (eg, DEFER, FAME, FAME-2 trials).

Consequently, the use of adenosine or ATP is recommended unless patients consume caffeine (a competitive antagonist of all adenosine receptor subtypes) within 24 hours or have contraindications (eg, asthma and atrioventricular or sinus node dysfunction)[4]; in such cases, other drugs or a NHPR are particularly useful. The relevant characteristics of the hyperemic agents investigated to calculate FFR are shown in table 1 and below.

Papaverine

Efficacy

Although an overall comparison of hyperemic agents overall is lacking, papaverine (used at standard or higher doses) has been shown to be the most potent vasodilator compared with ATP or nicorandil; the FFR mean difference was 0.01 (P = .01, n = 50)[11] and 0.016 (P < .001, n = 40),[4] respectively.

In a group of 115 patients, FFR values after using the standard and higher doses of papaverine showed no significant difference.[5]

Adverse effects

The main adverse effect of papaverine, ventricular tachyarrhythmia, is linked to prolongation of the QTU interval. Risk factors for its development are sex (female), hypokalemia, and alkalosis.[5]

Hyperemia characteristics

The characteristics of hyperemia were evaluated in 46 patients without comparison with other agents: papaverine showed a time to achieve 90% of the hyperemic onset of 12 seconds, but about 50 seconds to achieve the maximum onset.[6]

Adenosine

In vascular smooth muscle, adenosine binds to purinergic type 1 receptors (subtype A2A), which are coupled to Gs-proteins. This coupling results in a subsequent increase in cyclic adenosine monophosphate, activation of protein kinase and inwardly rectifying potassium (K_{ir}) channels, leading to vasodilatation.

Adenosine is commercially available in 6 and 30 mg vials. Compared with the intracoronary (IC) route, the use of the intravenous (IV) route requires higher doses and consequently higher costs[8]; moreover, its preparation takes longer.

Efficacy

In a meta-analysis of 11 studies (n = 587), when high (120-600 µg) IC doses of adenosine were used, no significant FFR mean difference was observed compared with IV adenosine, which was infused between 140 µg/kg/min (the most widely used infusion rate) and 200 µg/kg/min.[8]

There is uncertainty regarding the optimal dose needed to achieve maximal hyperemia with IC adenosine: for instance, Leone et al.[13] and De Luca et al.[20] showed a dose-response relationship between FFR values and IC adenosine up to 600 µg and 720 µg, respectively.

Adjedj et al.[7] suggested a lower range of IC dose, allowing up to 98% of maximum hyperemia, which might represent the best compromise between diagnostic accuracy and safety (see "Standard dose" in table 1).

Adverse effects

Complete AV block, although transient, is more common with a high (> 100 µg) IC dose of adenosine is used than with IV infusion.[8] On the other hand, systemic adverse effects are more frequent with IV adenosine.[8]

Hyperemia characteristics

The times to achieve 100% hyperemia with adenosine (IC and IV), papaverine and ATP were evaluated in a study by De Bruyne et al.[9] (n = 21) and IV adenosine had the longest time, while the plateau phase of hyperemia was short for the IC route, making this route unsuitable to perform pressure pullback maneuvers. The latter are important to assess the presence of tandem stenoses or focal vs diffuse coronary artery atherosclerosis (diffuse disease is associated with suboptimal postpercutaneous coronary intervention [PCI] outcomes and more angina) and consequently to take PCI decisions.[21]

Adenosine triphosphate

ATP is a nucleoside triphosphate consisting of adenosine (formed by the nitrogenous base adenine and a ribose sugar) and 3 serially bonded phosphate groups. ATP binds to purinergic type 2 receptors and determines increased intracellular calcium in vascular endothelium, which indirectly leads to stimulation of smooth muscle K_{ir} channels. ATP is commercially available in 100 mg vials, which can facilitate its administration and may reduce costs compared with adenosine.

Efficacy

As shown, IV ATP has been demonstrated to be less potent than papaverine.[11] IV ATP efficacy was similar to that of IV adenosine[9] and lower or similar compared with nicorandil[10,17] (see "Nicorandil" section).

Adverse effects, hyperemia characteristics

They are similar to those of IV adenosine.[9,11]

Sodium nitroprusside

Efficacy

In a meta-analysis of 7 studies (n = 342), sodium nitroprusside (NPS) produced similar FFR measurements (weighted mean difference:

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Table 1. Characteristics of hyperemic agents

Type of agent	Mechanism of action	Need to discontinue caffeine ≃ 24 h before	Standard dose	Route of administration	Vasodilatory efficacy	Main adverse effects	Time to achieve maximal hyperemia (sec)*	Plateau phase of hyperemia (sec)*	Reversing agent
Papaverine	Blocking of cAMP and cGMP phosphodiesterase	No	[12 mg (LCA), 8 mg (RCA)][5]	IC	>	Ventricular tachyarrhythmia (ventricular fibrillation 1.7%)[5]	Slightly less than 50 [referred to a dose of 12 to 16 mg (LCA), 8 to 12 mg (RCA)][6]	44 [referred to a dose of 12 to 16 mg (LCA), 8 to 12 mg (RCA)][6]	No
Adenosine	Nonselective stimulation of P1 (A1, A2A, A2B and A3) receptors	Yes	160 to 200 µg (LCA), 60 to 100 µg (RCA)][7]	IC	≃	AV block transient (complete 11.6%)[8]	15 [referred to a dose of 20 or 40 µg][9]	21 [referred to a dose of 200 ug (LCA)][7] 12 [referred to a dose of 100 µg (RCA)][7]	No
			140 µg/kg/min[8]	IV	≃	[AV block transient (complete 4.4%) Chest discomfort Dyspnea Flushing Nausea][8]	[80 (FV), 112 (PV)][9]	Depending on infusion duration	
Adenosine triphosphate	Stimulation of P2 receptors	Yes	150 µg/kg/min[10]	IV	≃	AV block transient Chest discomfort Dyspnea Flushing][11]	[76 (FV), 104 (PV) (referred to a dose of 140 µg/kg/min)][9]	Depending on infusion duration	No
Sodium nitroprusside	Induction of nitric oxide	No	[50 or 100 ug or 0.6 µg/kg][12]	IC	≃	Symptomatic hypotension (4%)[13]	About 15 [referred to a dose of 0.6 µg/kg][14]	51 [referred to a dose of 0.6 µg/kg][14]	No
Regadenoson	Selective stimulation of P1 A2A receptor	Yes	400 µg[15]	IV	≃	[Chest discomfort (20%) Flushing (16%) Headache (16%) Dyspnea (4%)][16]	34-59[15]	10-600[15]	Yes (150 mg aminophylline IV bolus)
Nicorandil	Opening of ATP-sensitive potassium channel Induction of nitric oxide	No	2 mg[4]	IC	≃	Chest discomfort/ dyspnea (5%)[10]	17-18[17,18]	27-32[17,18]	No
Nicardipine	Calcium channel blocker	No	200 µg[19]	IC	≃	[Chest discomfort (10%) Flushing (4%)][19]	13[19]	143[19]	No

ATP, adenosine triphosphate; AV, atrioventricular; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; FV, femoral vein; IC, intracoronary; IV, intravenous; LCA, left coronary artery; P, purinergic; PV, peripheral vein; RCA, righy coronary artery.

* When not specified, the characteristics of hyperemia refer to the standard dose of the hyperemic agent.

0.00) compared with IC adenosine (dose of 50 to 300 µg) or IV adenosine (standard dose); in the included studies, NPS was also administered in different doses (see "Standard dose" in table 1), which may have influenced its efficacy.[12]

Adverse effects

In the meta-analysis, NPS showed a significant reduction in adverse effects.[12]

Hyperemia characteristics

In 40 patients, the mean duration of the plateau phase was longer for 0.6 µg/kg NPS (51 seconds) compared with 60 ug adenosine (28 seconds).[14]

Regadenoson

Efficacy

In a meta-analysis of 5 studies (248 patients undergoing elective angiography) that compared regadenoson with IV adenosine (usually

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at standard dose), the mean difference between FFR measurements was 0.001.[15]

Adverse effects

Transient AV conduction block, chest discomfort, shortness of breath, hypotension, flushing, and headache were higher with adenosine.[15] When regadenoson was reversed using intravenous aminophylline, no adverse effects were observed.[22]

Hyperemia characteristics

Compared with IV adenosine, IV regadenoson achieved maximal hyperemia in an interval that was approximately 30 seconds shorter. The shorter time to FFR in patients receiving regadenoson can potentially be explained by the nonweight-based dose of intravenous regadenoson and by its longer half-life (2-4 minutes).[15]

On the other hand, the length of the plateau phase of regadenoson varies, probably because of drug metabolism, which represents a limitation (together with its high cost).[15]

Nicorandil

Efficacy

In a pooled cohort of 429 patients, the hyperemic efficacy of an IC bolus of nicorandil 2 mg was similar to IV infusion of adenosine 140 µg/kg/min or ATP 150 µg/kg/min: the FFR mean difference was 0.002.[17]

In a single center study (n = 207), nicorandil 2 mg was even more effective in achieving maximum hyperemia than ATP 150 µg/kg/min; a potential reason could be ATP administration via a peripheral IV line.[10]

Adverse effects

Nicorandil caused no AV block and less chest discomfort than adenosine or ATP.[17,18]

Hyperemia characteristics

The time to the lowest FFR was lower than with IV adenosine or ATP.[17]

Nicardipine

Efficacy

When nicardipine was compared with a standard dose of IC adenosine in 159 patients, the FFR was slightly higher with nicardipine (median difference 0.02, P = .246) and the number of vessels with FFR < .80 was 28.5% with nicardipine and 32.1% with adenosine (P = .016).[19]

Adverse effects

Nicardipine produced less chest pain and flushing compared with adenosine and no AV block.[19]

Hyperemia characteristics

The time to the lowest FFR was similar for the 2 drugs, while the plateau time of an IC bolus of nicardipine was significantly longer than with IC adenosine.[19]

Summary

IC vasodilator administration requires lower doses (and costs) and shorter times for preparation and to reach maximal efficacy compared with IV administration; in contrast, it has the disadvantage of being harder to maintain maximum hyperemia, which is important for pullback maneuvers.

A suggested strategy to accurately assess functional significance is to use adenosine or ATP or nicorandil (in the event of caffeine intake within 24 hours or adenosine or ATP contraindications) as the first-line drugs and to reserve papaverine for doubtful cases (ie, FFR, 0.81-0.85).[4] However, nicorandil has the limitation of low availability.[17]

Nicorandil and NPS are valid first-line alternatives to adenosine or ATP on the basis of their safety, efficacy, and characteristics of maximal induced hyperemia. NPS has a longer hyperemia plateau phase than nicorandil (even if there is no a direct comparison). Moreover, the appropriate dose of NPS has not been well established.

Papaverine has high efficacy but an unfavorable safety profile and consequently it is useful especially in doubtful cases (FFR, 0.81-0.85) when there are no risk factors for ventricular tachyarrhythmia.

Regadenoson (due to variable duration of maximal hyperemia and cost) and nicardipine (due to its slightly lower efficacy) seem to be less valid alternatives.

NONHYPEREMIC PRESSURE RATIOS

NHPRs are evaluated with a 0.014″ PW or a pressure microcatheter (PMC) and various pieces of software without using hyperemic agents. Because they are independent of a steady-state hyperemia, they are useful in performing pullback maneuvers.

The definitions of NHPRs and some characteristics of the devices used to calculate them are shown in table 2.

The instantaneous wave-free ratio (iFR) is the most widely investigated and a value of 0.89 matched best with an FFR ≤ 0.80.[30] Its diagnostic accuracy compared with PW FFR will be discussed in the "Instantaneous wave-free ratio" section.

The resting distal coronary pressure to aortic pressure ratio (P_d/P_a) has a cutoff of 0.91 to predict functional significance, while the other NHPRs have the same cutoff as iFR (0.89); in a post-hoc analysis studies, these values were the best predictors of PW iFR, usually with very high diagnostic accuracy (which was somewhat lower for the diastolic pressure ratio $[dPR]_{micro}$), as shown in the "Resting P_d/P_a" to "Constant resistance ratio" sections.

Instantaneous wave-free ratio

When compared with adenosine FFR, iFR showed significantly less adverse procedural signs and symptoms (30.8% vs 3.1%), mainly chest pain and/or dyspnea,[31] as well as shorter procedural times (about 2-4 minutes of difference).[31,32]

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Table 2. Definitions of NHPRs and characteristics of devices

Type of NHPR	Definition	Calculation period	Device (last version)	Manufacturer	Site of sensor (from the tip)*	Type of sensor	Coregistration (angiography and IVUS)
iFR	Average P_d/P_a[23]	Diastolic sub-cycle (wave-free period) that begins at the point 25% into diastole and ends 5 ms before end of diastole[23]	PW: OmniWire	Philips (the Netherlands)	3 cm	Piezoelectric (with conductive bands)	Yes (for IntraSight 7 Platform via SyncVision)
Resting P_d/P_a	Average P_d/P_a[24]	Whole cardiac cycle[24]	PW/PMC	Not proprietary technology	NA	NA	NA
dPR	Average P_d/P_a[25]	Whole-diastole that begins at the nadir of the dicrotic notch until 50 ms before the upstroke of the next heartbeat[25]	PW: OptoWire Deux	OpSens Medical (Canada)	3.5 cm	Optical	No
RFR	Lowest filtered P_d/P_a[26]	Whole cardiac cycle[26]	PW: PressureWire X	Abbott (United States)	3 cm	Piezoelectric	No
DFR	Average P_d/P_a (on 5 beats)[27]	Diastolic sub-cycle that begins when the P_a is less than the mean P_a and there is a down-sloping P_a[27]	PW: Comet II	Boston Scientific (United States)	3 cm	Optical	No
dPR_{micro}	Average P_d/P_a (on 5 beats)[28]	Diastolic point within diastole halfway between the peak of one waveform and the peak of the next waveform[28]	PMC: Navvus II	ACIST (United States)	5 mm	Optical	No
cRR	Average P_d/P_a[29]	Diastolic sub-cycle (wave-free period) identified by calculating the time derivative of P_d/P_a and finding the longest period when it equals zero[29]	PMC: TruePhysio	Insight Lifetech (China)	~2.5 mm	Piezoresistive microelectro mechanical system	No

cRR, constant resistance ratio; DFR, diastolic hyperemia-free ratio; dPR, diastolic pressure ratio; iFR, instantaneous wave-free ratio; IVUS, intravascular ultrasound; NA, not applicable; NHPR, nonhyperemic pressure ratio; P_a, aortic pressure; P_d, distal coronary pressure; PMC, pressure microcatheter; PW, pressure wire; RFR, resting full-cycle ratio.
* For PWs the sensor is just proximal to the radiopaque part.

iFR is the only index with the option of angio and intravascular ultrasound (IVUS) co-registration, which can favor evaluation of stenoses.

Diagnostic accuracy

Concordant results between iFR and FFR ranged from 79.4% to 88.2% in 3 studies (total n = 1259).[33-35]

Both hyperemic (FFR) and resting (NHPRs) measurements can be used to evaluate the significance of stenoses, even if FFR is evaluated during hyperemic flow, which falls with progressive stenosis severity with a consequent increase in transstenotic pressure gradient (TPG) and a decrease in FFR, while the NHPRs are evaluated during resting coronary flow, which is maintained in progressively worse stenoses (beyond a critical point of stenosis, resting flow is also expected to fall).[36] The maintenance of resting flow, however, is due to a compensatory reduction in microvascular resistance at the expense of distal coronary pressure, which falls with widening TPG; therefore, TPG increases with progressive stenosis severity in both hyperemic and resting measurements.[36]

Some factors may influence hyperemic and/or resting flow and explain the observed discordances, at least partly. Discordance between FFR and NHPRs (FFR high and iFR or resting full-cycle ratio (RFR) low) was seen in conditions that may give higher FFR values because of reduced vasodilation ability due to microvascular dysfunction (MVD): insulin-treated diabetes mellitus, lower estimated glomerular filtration rate, advanced age (because of its association with the latter comorbidities), atrial fibrillation (due to its association with advanced age and/or higher heart rate).[33] A similar discordance (FFR high and iFR low), as resting coronary flow increases with heart rate, was seen with elevated heart rate and/or absence of beta-blocker use,[34] which may therefore give lower iFR values. Other causes of FFR high and iFR low discrepancy may be severe aortic stenosis and myocardial infarction (MI).

The other kind of discordance (FFR low and iFR high) is affected by potentially high coronary flow reserve (CFR): indeed, left main (LM), proximal left anterior descending artery stenosis and male sex could result in greater coronary flow variation between resting and hyperemic conditions and consequently in greater discordance.[34,35]

Both kinds of discordance are more frequent among intermediate stenoses (41%-70%) than among mild or severe stenoses.[34,35]

Evaluation in specific clinical or angiographic conditions

Aortic stenosis: in patients with a severe defect, a blunted response to hyperemia is possible due to myocardial hypertrophy, elevated left ventricular diastolic filling pressure, and MVD. iFR seems more reliable in this context, although it might be reduced by increased oxygen demand and resting coronary flow due to hypertrophy.[33]

Diabetes mellitus: this condition is associated with MVD which may affect the reliability of FFR, and consequently NHPRs might be preferred in these patients.[33] On the other hand, in diabetic patients in the DEFINE-FLAIR trial, iFR- and FFR-guided revascularization had a comparable risk of adverse events.

LM disease: discordance was even higher (25.0%) in a recent study in patients with isolated LM disease or with LM and concomitant downstream disease (36.2%); previous data suggest that both FFR and iFR can guide the decision to revascularize or defer LM lesions; if there are discordant results, performing IVUS and deferring the LM lesion can be considered only when the minimal lumen area is above 6 mm squared.[37]

MI: compared with stable angina patients, noninfarct-related arteries (non-IRA) of subacute non-ST-elevation MI/ST-elevation MI (NSTEMI/STEMI) showed increased resting flow and reduced CFR, while hyperemic flow was preserved. Moreover, the index of microcirculatory resistance (IMR), derived from pressure-temperature guidewires, was not increased and consequently the higher resting coronary flow in MI patients may have been the result of neurohumoral compensatory mechanisms triggered by the acute myocardial damage.[38]

According to the 1st study, these findings support the use of FFR in subacute MI,[38] but another study reported a significant FFR decrease in non-IRA in STEMI from the acute phase to the 1-month follow-up (mean difference 0.02, P = .001), together with an increased acute IMR.[39] In the same setting, iFR increased over time, although without significance (mean difference 0.01, P = .12).[39]

Eventually, both methods may be altered in patients with STEMI since lesion severity can be underestimated by FFR and overestimated by iFR. The 2023 European Guidelines recommended that PCI of non-IRA in STEMI patients be based on angiographic severity because the FFR-guided strategy does not usually reduce the risk of adverse events, whereas in patients with NSTE-acute coronary syndrome (ACS), the FFR-guided strategy has more favorable data compared with STEMI, and functional invasive assessment of non-IRA may be considered during the index procedure.[40]

Tandem lesions: these lesions are another cause of discordance between NHPRs and FFR, which can both be used for this evaluation; FFR may estimate TPG better in distinct lesions, while NHPRs may be less influenced by the interplay between serial stenoses.[21] Pullback can give a TPG for each lesion constituting tandem lesions and treating the lesion with the greatest TPG first and then reevaluating the other lesion is a reasonable approach.[21]

Outcome data

Two large randomized trials (DEFINE-FLAIR, n = 2492; iFR-SWEDEHEART, n = 2037) showed the noninferiority of an iFR vs an FFR-guided PCI strategy during follow-up at 1 year and 5 years, although iFR showed lower revascularization rates with almost significant P values.[31,32]

The rate of major adverse cardiac events (MACE) were 18.6% (iFR) vs 16.8% (FFR) (P = .63) after 5 years in deferred patients who presented with stable angina (n = 611) or nonculprit lesions of ACS (unstable angina and NSTEMI, n = 297). Moreover, there have been no significant differences in long-term event rates between stable angina and ACS.[41]

As regards deferred lesions with iFR-FFR discordance, they did not show an increased risk of adverse events at 5 years.[42]

Similarly, deferred lesions with discordant results between NHPRs (iFR, dPR, RFR) and FFR had a higher risk of vessel-related events at 5 years than those with concordant negative results but did not have a higher risk than revascularized lesions.[43] In patients with discordant results, meticulous follow-up was recommended with intensive medical treatment.[43]

Post-PCI: iFR ≥ 0.95 (n = 500) after successful stenting was associated with a significant reduction in the composite endpoint of cardiac death, spontaneous MI, or clinically-driven target vessel revascularization at 1 year compared with lower iFR.[44]

Resting P_d/P_a

Diagnostic accuracy

Resting P_d/P_a is evaluated throughout the cardiac cycle, which provides higher microvascular resistance and consequently a lower pressure gradient and potentially lower sensitivity than the diastolic wave-free period of iFR.[36] However, its diagnostic accuracy was high (93.0%) when compared with that of iFR (n = 627).[24]

Outcome data

Resting P_d/P_a and iFR showed similar associations with the risk of MACE at 2 years (1.5% for negative P_d/P_a vs 1.6% for negative iFR values; n = 375).[45]

Post-PCI: P_d/P_a ≤ 0.96 poststenting was the best predictor of MACE at 30 months (n = 574).[46]

Diastolic pressure ratio (pressure wire)

Diagnostic accuracy

Diagnostic accuracy was approximately 97.0% in a study by Van't Veer et al. (n = 197).[25]

Outcome data

In the study by Lee et al.,[43] a sample of 435 patients showed similar vessel-related events at 5 years for negative dPR (7.9%), iFR (8.0%), and FFR (7.7%) values.

Post-PCI: not available.

Resting full-cycle ratio

Diagnostic accuracy

As shown in table 2, the RFR is calculated over the whole cardiac cycle. It was detected outside diastole in 12.2% of cases and consequently, according to the authors, lesions of potential significance might be missed by NHPR measured only during diastole.[26] However, the diagnostic accuracy of the RFR compared with iFR was 97.4% in the VALIDATE-RFR trial (n = 504),[26] and was therefore similar to that of diastolic NHPRs such as dPR and the diastolic hyperemia-free ratio.

Outcome data

In the same study conducted by Lee et al.,[43] negative RFR showed a similar percentage (8.1%) of adverse events.

Post-PCI: no data are available; the ongoing "PICIO (NCT04417634)" trial will evaluate the RFR in this setting.

Diastolic hyperemia-free ratio

Diagnostic accuracy

Diagnostic accuracy was 97.6% in the study by Johnson et al. (n = 833).[27]

Outcome data

In 926 patients, deferred lesion failure (cardiac death, MI, repeated revascularization) after 3 years was similar for negative diastolic hyperemia-free ratio (6.8%), iFR (6.9%), dPR (6.9%), RFR (7.1%) and FFR (5.9%).[47]

Post-PCI: not available.

Diastolic pressure ratio measured using a microcatheter (dPR_{micro})

Diagnostic accuracy

In a study by Arashi et al.[28] (n = 161), dPR_{micro} showed a mean bias of −0.028 and a diagnostic accuracy of 82.2% compared with PW iFR; this reduced value compared with the other NHPRs may have been influenced by the cross-sectional area at the lesion site of Navvus PMC, which is larger than the PW (and also compared with TruePhysio PMC) and this may have overestimated the stenoses.

Outcome data

Data are only available in the setting of post-PCI: dPR_{micro} ≤ 0.89 was associated with significantly higher cardiac mortality at 2 years in 735 patients (of note due to the limited number of events, receiver operating characteristics analysis was not able to identify an optimal cutoff value and therefore the authors deliberately took the accepted ischemic threshold of 0.89).[48]

Constant resistance ratio

Diagnostic accuracy

Diagnostic accuracy was 97% with a mean bias of −0.0001 compared with PW iFR in an abstract by Li et al. (n = 86).[29]

Outcome data

No outcome data are available yet. The ongoing trial, SUPREME II (NCT05417763) will evaluate the implications of post-PCI constant resistance ratio.

Summary

Among NHPRs, iFR has the largest amount of evidence and showed noninferiority vs a FFR-guided PCI strategy over a long follow-up with less adverse procedural symptoms and procedural times. However resting P_d/P_a, dPR (PW), RFR, the diastolic hyperemia-free ratio and the constant resistance ratio showed very high diagnostic accuracy compared with iFR, and consequently they may be used to replace iFR.

In contrast, discordance results between NHPRs and FFR have been shown in a nontrivial percentage of cases. Patients with discordant results showed a worst outcome than those with concordant negative results and a meticulous follow-up with intensive medical treatment has been recommended, while revascularization of discordant lesions is uncertain.

ANGIOGRAPHY-DERIVED INDICES

Angiography-derived indices do not need PW or PMC use or drug-induced hyperemia, thus avoiding the potential risks of coronary injury and adverse effects. Moreover, they are not limited by pressure drift (the difference between initial pressure equalization and final check), which can be related to alterations in the pressure sensor (eg, due to temperature variations) and may lead to the need to repeat the measurements with both PW and PMC systems.

Angiography-derived indices share the same FFR cutoff value (0.80); a virtual pullback trace, which shows values along the interrogated vessel/vessels, is provided by all the systems.

Currently, the following indices have been evaluated: vessel fractional flow reserve (vFFR), quantitative flow ratio (QFR), coronary angiography-derived FFR (FFR_{angio}), computational pressure-flow dynamics-derived FFR (caFFR), angiography-based FFR ($accuFFR_{angio}$), and Murray law-based QFR (μQFR).

These indices are calculated using various softwares through 3 dimensional (3D) reconstruction of the coronary artery based on 1 or more angiographic projections and estimated coronary flow velocity based on aortic pressure and/or frame count analysis. Aortic pressure measurement is needed for vFFR, FFR_{angio}, $accuFFR_{angio}$ and caFFR; in the latter case, a specialized pressure transducer (FlashPressure, RainMed Medical, China) connected to the guiding catheter is needed. Other details are reported in table 3. Diagnostic accuracy (compared with PW FFR) and outcome data are shown below.

Aortic-ostial lesions and significant vessel overlap are exclusion criteria for all the indices because they hamper software analysis.

Vessel fractional flow reserve

Diagnostic accuracy

In the multicenter FAST II study (n = 334, 39 NSTEMI), diagnostic accuracy was 90% compared with FFR ≤ 0.80 by a blinded independent core laboratory.[58]

Accuracy was maintained in specific subgroups such as patients with diabetes, bifurcations, moderate or severe calcifications, and tortuous lesions (NSTEMI subanalysis is not available).[58] The diagnostic accuracy of vFFR ≤ 0.80 in identifying LM lesions with IVUS minimal lumen area < 6.0 mm^2 was good (sensitivity 98%, specificity 71.4%).[59]

Outcome data

Outcome data are available only in post-PCI: lower (≤ 0.93) vFFR values were associated with a significantly increased risk of target vessel failure (TVF) at 5 years of follow-up (n = 748).[60]

Quantitative flow ratio

QFR is currently the index with the largest amount of evidence.

Table 3. Characteristics of angiography-derived indices

Type of index*	Software provider	Base of 3D reconstruction	Frame count analysis needed	Need for aortic pressure input	Type of 3D reconstruction	Simultaneous analysis of main vessel and side branches	Time to calculation (minutes)	Verification of an index to analyze microcirculation*	Verification of an index to differentiate focal and diffuse disease (quantitative method)*
vFFR	Pie Medical Imaging (the Netherlands)	2 projections at least 30° apart at 15 frames/s (eventually 7.5)[49,50]	No	Yes	Single-vessel	No	Not reported	No	No
QFR	Medis Medical Imaging (the Netherlands)/ Pulse Medical Imaging Technology (China)	2 projections at least 25° apart at 15 frames/s (eventually 7.5)[49,51]	Yes (for cQFR)	No	Single-vessel	No	5[52]	Yes: – IMR_{angio} – angio-IMR – A-IMR – nonhyperemic IMR_{angio}	Yes: – QVP – QFR-PPG
FFR_{angio}	CathWorks (Israel)	≥ 2 projections at least 30° apart at 10 frames/s[53]	No	Yes	Multi-vessel	Yes	9.6[54]	No	No
caFFR	RainMed Medical (China)	≥ 2 projections at least 30° apart at 15 frames/s[55]	Yes	Yes (with specialized pressure transducer)	Single-vessel	No	4.5[55]	Yes: – caIMR	Yes: – angio-FFR based PPG
$accuFFR_{angio}$	ArteryFlow Technology (China)	2 projections at least 25° apart at 15 frames/s[56]	Yes	Yes	Single-vessel	No	4.3[56]	Yes: – accuIMR	No
μQFR	Pulse Medical Imaging Technology (China)	1 projection at 15 frames/s[57]	Yes	No	Single-vessel	Yes	1.1[57]	Yes: – AMR	No

$accuFFR_{angio}$, angiography-based FFR; AMR, angiographic microvascular resistance; caFFR, computational pressure-flow dynamics-derived fractional flow reserve; FFR_{angio}, coronary angiography-derived fractional flow reserve; IMR, index of microcirculatory resistance; PPG, pullback pressure gradient; μQFR, Murray law-based QFR; QFR, quantitative flow ratio; QFR-PPG, QFR derived pullback pressure gradient; QVP, QFR virtual pullback; vFFR, vessel fractional flow reserve.
* All the listed indices are guidewire-free.

QFR was calculated from 3 models, obtaining fixed-flow QFR (fQFR), adenosine-flow QFR (aQFR), and contrast-flow QFR (cQFR), respectively; the latter is derived without induction of hyperemia using contrast flow velocity through the stenosis estimated using frame count analysis,[51] which is automatic in the latest software.

Diagnostic accuracy

cQFR and aQFR showed similar agreement with FFR and higher accuracy than fQFR.[51] The overall diagnostic accuracy was 87% in the meta-analysis by Westra et al.[61] (n = 819).

In the multicenter registry of Choi et al.[62] (n = 452), the diagnostic accuracy of cQFR was not reduced in nonculprit vessels in ACS (n = 153), while in the registry of Lee et al.[63] (n = 915), it was lower in nonculprit vessels in the acute MI group (n = 103) compared with the angina group (92.4% vs 96%), although without significance. A possible explanation is that its calculation is based on frame count analysis, which may be affected by transient MVD of infarct-related and noninfarct-related arteries.[63]

In the meta-analysis by Westra et al.,[61] diabetes, which may also cause MVD, showed a statistically significant ability to predict QFR values at least 0.10 lower than the corresponding FFR measurement, but the diagnostic accuracy of cQFR was not different in the diabetes subgroup in the registry by Choi et al.[62]

Accuracy was preserved in bifurcations and calcified and tortuous lesions,[63] but was reduced or preserved in tandem lesions in 2 different studies.[63,52]

Concordance was acceptable (90.7%) in intermediate LM lesions.[64]

The numerical agreement of QFR to FFR was negatively affected by low FFR[61]; similarly, in the case of $0.75 < FFR \leq 0.85$ QFR accuracy was reduced (91.2%) in the registry by Lee et al.[63] This could indicate difficulties in contouring more severe lesions with QFR.[61]

Outcome data

In a large (n = 3825) multicenter randomized trial (FAVOR III China) among patients undergoing PCI (ACS 63.5%), the composite endpoint of death from any cause, MI, or ischemia-driven revascularization at 1-year was significantly reduced in the QFR-guided group compared with the angiography-guided group (5.8% vs 8.8%).[65]

Post-PCI: the cutoff values of post-PCI QFR to predict the 1- to 3-year vessel-oriented composite endpoint ranged from 0.89 to 0.94 in a recent systematic review.[66]

Coronary angiography-derived FFR

In coronary angiography-derived FFR, the entire coronary tree including side branches (SBs) is evaluated, allowing FFR values to be obtained along each vessel. However, this may prolong computation times compared with indices with a per vessel approach (table 3).

Diagnostic accuracy

In a pooled analysis of 5 studies (n = 588, 59 NSTEMI), diagnostic accuracy was 93% by blinded operators and was consistent across nonculprit lesions of NSTEMI, diabetic patients, bifurcations, moderately/severely calcified or tortuous vessels, and tandem lesions.[67]

For lesions with FFR between 0.75 and 0.85, accuracy was somewhat lower (85.5%).[67]

Outcome data

In a cohort of 536 patients (approximately 50% with ACS), FFR_{angio}-guided treatment in the deferral group showed 2.5% of 1-year MACE, a rate consistent with previously reported data using FFR.[68]

Post-PCI: not available.

Computational pressure-flow dynamics-derived FFR

Diagnostic accuracy

In a multicenter trial (FLASH-FFR) in patients with stable or unstable angina pectoris (n = 328), diagnostic accuracy was 95.7% by an independent blinded core laboratory.[55]

The caFFR diagnostic accuracy was lower (89.9%) in 119 vessels with FFR between 0.75 and 0.85.[55]

Outcome data

In a small single-center study (n = 69), the 12-month outcome showed that caFFR-guided PCI deferral is safe (3.4% of patients had target vessel revascularization) and comparable to previous data on FFR-guided PCI deferral.[69]

Post-PCI: in a group of 136 patients, lower post-PCI caFFR (< 0.90) was associated with a higher rate of 9-month TVF.[70]

Angiography-based FFR

Diagnostic accuracy

In a single-center observational study of 300 patients with stable angina pectoris, the accuracy of $accuFFR_{angio}$ was 93.7%.[56]

Outcome data

Not available (ongoing trials).

Murray law-based quantitative flow ratio

The µQFR uses Murray bifurcation fractal law to reconstruct reference vessel size and a single angiographic projection (with a consequent time saving) to produce values along the main vessel and its SBs.

Diagnostic accuracy

The vessel-level diagnostic accuracy for µQFR to identify FFR ≤ 0.80 lesions was 93.0% in 330 main vessels in 306 patients (main presentation: stable/unstable angina pectoris); diagnostic accuracy was not evaluated in SBs.[57]

Outcome data

In 288 patients with true coronary bifurcations who underwent a provisional approach without SB treatment, after 3 years, TVF was 29.2% in the SB µQFR < 0.8 group vs 10.8% in the SB µQFR ≥ 0.8 group (P < .05).[71]

Post-PCI: in a group of 169 patients, µQFR ≤ 0.89 after treatment of in-stent restenosis with a drug-coated balloon was the best cutoff to predict the 1-year vessel-oriented composite endpoint and was associated with a 6-fold higher risk.[66]

Summary

Angiography-derived indices are a valid alternative to FFR in terms of clinical agreement. However, some angiographic characteristics have not been investigated. Diagnostic accuracy compared with FFR was good but was generally reduced at the borderline FFR zone. Direct comparison with FFR-guided treatment on outcomes is lacking, and reproducibility was variable.

Regarding the latter, QFR inter- and intraobserver reproducibility ranged from high to poor among trained operators and there was significant variability in vFFR values between nonexpert and expert operators; conversely, repeated FFR could be performed with close to zero imprecision in previous studies.[72]

The authors highlighted the importance of adherence to standard operating procedures and continuous feedback and training to achieve accurate computation.[72]

FUTURE PROSPECTS

In our opinion, the most important issues requiring clarification concern the need for PCI in lesions with discordant NHPR/FFR values and the comparison of angiography-derived indices vs FFR in guiding treatment. The value of these indices will be further established by the ongoing trials FAST III (NCT04931771), LIPSIASTRATEGY (NCT03497637), FAVOR III Europe Japan trial (NCT03729739), FLASH-FFR II (NCT04575207), NCT05209503 and NCT05202041, and ALL-RISE (NCT05893498), which will evaluate the risk of adverse events with vFFR, QFR, caFFR, $accuFFR_{angio}$, and FFR_{angio} vs FFR-guided revascularization.

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial Intelligence was not used in the preparation of this work.

AUTHORS' CONTRIBUTIONS

F. Vergni, G. Fiore, F. Pellone, and M. Luzi contributed to the design of the work. F. Vergni drafted and edited the work. F. Vergni, G. Fiore, F. Pellone, and M. Luzi revised the work and approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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