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Non-hyperemic pressure ratios – theoretical basis, clinical applications, and limitations

Índices fisiológicos não hiperêmicos – base teórica, aplicações clínicas e limitações

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ABSTRACT – Coronary physiology has become the standard of care to assess the functional significance of coronary atherosclerotic disease. It allows for identification of myocardial ischemia on a vessel level, discrimination of the functional patterns of atherosclerotic disease, guidance for the need of revascularization, complements the planning of percutaneous coronary intervention and verification of the functional success of percutaneous coronary intervention. On a previous issue of the Journal of Transcatheter Interventions, we presented a comprehensive review about fractional flow reserve. Despite the robust body of evidence supporting its use, the clinical use of fractional flow reserve is variable, and unreasonably low in many areas around the globe. The perceived increase in procedure time, the use of hyperemic agents with its related costs and patient discomfort, and difficulty in interpreting results in certain anatomical scenarios have contributed to the limited adoption of fractional flow reserve. The introduction of instantaneous wave-free ratio overcame most of these limitations. Supported by sound technical validation, and clinical outcomes data, instantaneous wave-free ratio received the same clinical indications as fractional flow reserve in the most recent guidelines recommendations. This was followed by the introduction of other non-hyperemic pressure ratios for commercial use. In the current manuscript we review the physiological basis that supports the use of non-hyperemic pressure ratios, their technical and clinical validation, clinical outcomes data, and discuss its applications on specific anatomic scenarios, with examples of cases from the authors, whenever applicable.

Keywords: Fractional flow reserve, myocardial; Standard of care; Percutaneous coronary intervention

RESUMO – A fisiologia coronariana tornou-se o padrão de tratamento para avaliar o significado funcional da doença aterosclerótica coronariana. Ela permite identificar isquemia miocárdica em nível de vaso, discriminar os padrões funcionais da doença aterosclerótica e orientar a necessidade de revascularização; complementar o planejamento da intervenção coronária percutânea e confirmar o sucesso funcional dessa última. Em uma edição anterior do *Journal of Transcatheter Interventions*, apresentamos uma revisão abrangente sobre o fluxo fracionado de reserva do miocárdio. Apesar do robusto corpo de evidências que apoiam seu uso, a aceitação clínica do fluxo fracionado de reserva é variável e excessivamente baixa em muitas áreas do mundo. O aumento percebido no tempo do procedimento, o uso de agentes hiperêmicos com seus correspondentes custos e desconforto do paciente, e a dificuldade de interpretação dos resultados em determinadas situações anatômicas contribuíram para a adoção limitada do método. A introdução do índice de fluxo instantâneo no período livre de ondas superou a maioria dessas limitações. Apoiada por uma validação técnica sólida e dados de desfechos clínicos, o índice de fluxo instantâneo no período livre de ondas recebeu as mesmas indicações clínicas que o fluxo fracionado de reserva nas recomendações mais recentes das diretrizes. Isso foi seguido pela introdução de outros índices pressóricos não hiperêmicos, já comercialmente disponíveis. Neste artigo, revisamos as bases fisiológicas que justificam o uso de índices pressóricos não hiperêmicos, sua validação técnica e clínica e dados de desfechos clínicos, além de discutirmos suas aplicações em situações anatômicas específicas, com exemplos de casos dos autores, sempre que aplicável.

Descritores: Fluxo fracionado de reserva do miocárdico; Padrão de cuidado; Intervenção coronária percutânea

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INTRODUCTION

Due to the well-known association between myocardial perfusion and angina, ischemia-guided revascularization is a central component of evidence-based treatment algorithms for management of stable coronary artery disease (CAD).[1] By offering a real-time assessment of ischemia in a vessel- and lesion-specific manner, invasive physiology identifies patients (and lesions) who can benefit from revascularization.

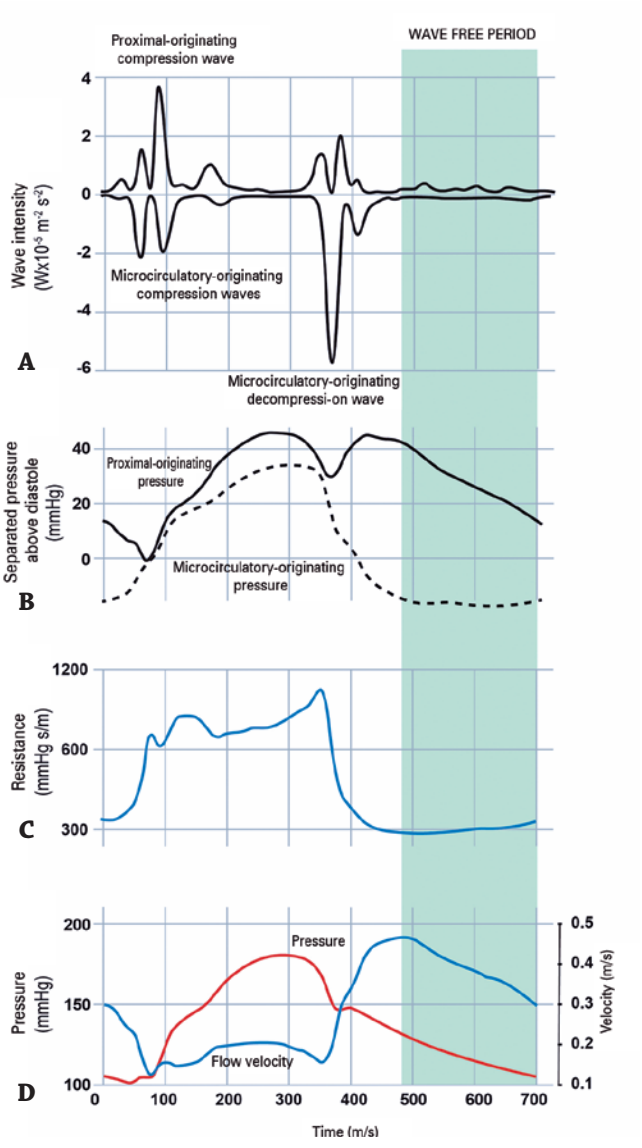
In a previous issue of the Journal of Transcatheter Interventions, we reviewed the concepts and clinical applications of fractional flow reserve (FFR).[2] Despite the robust body of evidence and undeniable cost-effective data, clinical use of FFR remains low and highly variable across health care systems.[3] Added time, cost, discomfort to patients, lack of familiarity with the technique, and difficult interpretation of results in certain anatomical scenarios are reported barriers to FFR use.[4]

The development of non-hyperemic pressure ratios (NHPRs) carries the potential to circumvent most of these barriers and to increase the use of coronary physiology. In the second part of this physiology series, we discuss the physiological basis of NHPRs, describe the available indices, their technical and clinical validation, and discuss their application in specific clinical and anatomical scenarios.

PHYSIOLOGICAL BASIS OF RESTING INDICES – WAVE INTENSITY ANALYSIS AND THE CONCEPT OF INSTANTANEOUS WAVE-FREE RATIO

Fractional flow reserve fundamentals rely on the principle that pressure assumes a linear relationship with flow when microvascular resistance is minimal and stable; this is a condition achieved with the administration of hyperemic agents such as adenosine. Therefore, FFR theory has led to the misleading assumption that translesional pressure gradient can only serve as a surrogate for coronary flow in the setting of induced hyperemia.

Coronary microvascular resistance has a phasic pattern, rising in systole and decreasing in diastole due to compression and decompression of the microvasculature during the cardiac cycle.[5,6] A seminal work by Gould et al.[7] demonstrated the most appropriate period for assessment of coronary stenosis is when intracoronary pressure is not confounded by the contraction and relaxation of the myocardium, during a phase when the myocardium is passive, and intracoronary pressure and flow velocity have an almost linear relation. This approach had limited clinical applicability because could only be identified from simultaneous pressure and flow velocity recordings. More recently, wave-intensity analysis characterizing the relation between coronary pressure and flow during the cardiac cycle identified a period where transmission of pressure and flow waves is quiescent – the wave-free period (WFP). The WFP starts 25% of the way into the diastole and ends 5 milliseconds before starting the next systole. During the WFP, flow velocity is approximately 30% higher than whole-cycle resting flow velocity; intracoronary pressure and flow decline together in a linear fashion, and microvascular resistance is significantly more stable and lower (not necessarily minimal) than over the rest of the cardiac cycle.[8] These features offer optimal conditions for the assessment of the physiological significance of epicardial coronary stenoses, with no need for pharmacological hyperemia (Figure 1).



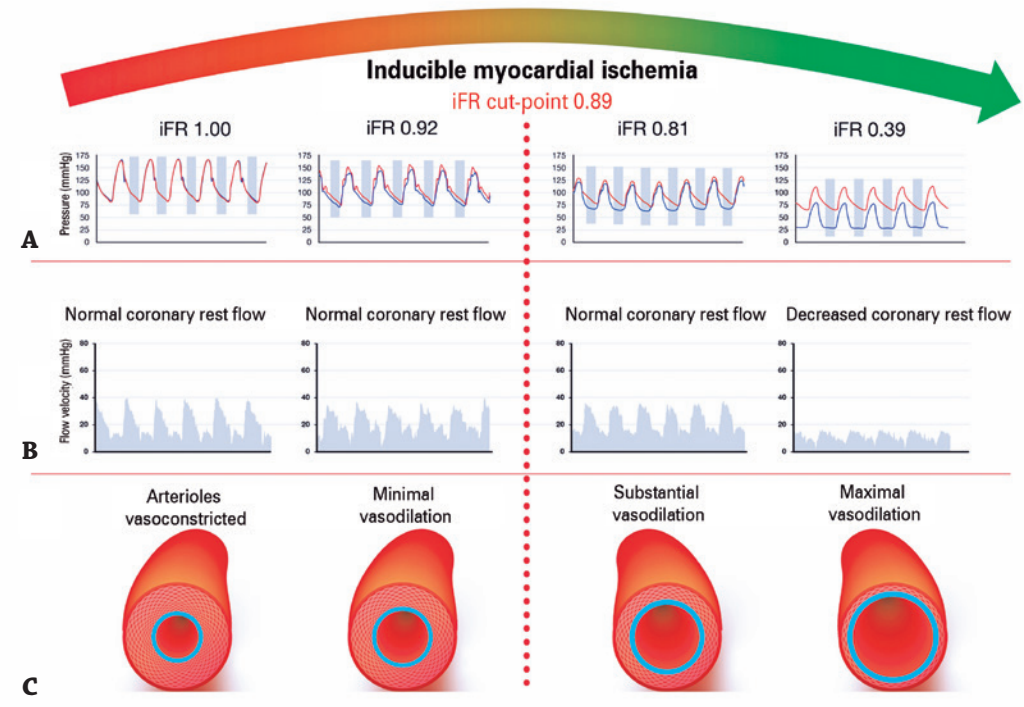
Source: adapted from Sen et al.[8]

Figure 1. The physiological derivation of the wave-free period. (A) Wave intensity analysis shows the wave-free period in diastole (green) where there is minimal transmission of antegrade and retrograde pressure waves, there is minimal microcirculatory originating pressure (B), and the resistance is minimal and constant (C). During the wave-free period, the coronary flow (blue) and pressure (red) are linearly related (D), offering a unique intrinsic window during cardiac cycle, where a translesional pressure gradient can serve as surrogate for coronary flow with no need for pharmacological hyperemia.

INSTANTANEOUS WAVE-FREE RATIO – DESCRIPTION, MEANING, AND VALIDATION

Following the identification of the WFP, Sen et al.[8] introduced the instantaneous wave-free ratio (iFR), which is measured using a pressure-sensor tipped guidewire and calculated as the ratio between the distal coronary and aortic pressures during the WFP. Unlike FFR – which estimates the maximum achievable myocardial blood flow in the presence of coronary stenosis as a percentage of the hypothetical maximum blood flow, as if the same vessel was free from stenoses – iFR better estimates the autoregulation capacity of the microcirculation. The IDEAL study demonstrated that with increasing stenosis severity, resting coronary flow velocity is maintained stable by compensatory vasodilating changes in the microvascular resistance.[9,10] The magnitude of microvascular dilation regulates the trans-stenotic pressure gradient at rest. Because iFR is a continuous index, measured from 0.01 to 1.00, lower values correspond to an increased compensatory arteriolar vasodilation and, thus, higher functional severity of the stenosis (Figure 2).

The technical validation of iFR was based on several studies comparing iFR and FFR (Table 1). An iFR cutoff ≤0.89 better predicted an FFR ≤0.80. Overall, iFR presented a mean diagnostic agreement of 81% with FFR. In an analysis of 339 stenoses, Petraco *et al*.[11] showed an excellent (100%) concordance between iFR and FFR in extreme values of FFR. This agreement significantly fell to less than 50% when iFR and FFR values were close to the cutoff of each method. This level of agreement was similar to the agreement of approximately 50% between two repetitive FFR measurements when the FFR value is close to its cutoff.[11] Thus, the intrinsic variability of FFR by itself prevents a perfect agreement between iFR and FFR measurements. When compared against other reference standards, iFR and FFR presented similar diagnostic accuracies to detect myocardial ischemia, and iFR was as accurate or superior to FFR when compared with coronary flow reserve (CFR)[12,13] and hyperemic stenosis resistance (HSR).[14] Coronary flow reserve – defined as the ratio of hyperemic to resting flow – expresses the capacity of the coronary bed to increase flow in response to a vasodilatory agent. Coronary flow reserve can be reduced by both an increase in functional stenosis severity and by a decreased ability of the microcirculation to respond to vasodilating stimuli (microvascular dysfunction). Because CFR accounts for the microcirculation autoregulatory reserve, the better correlation between iFR and CFR supports the idea that iFR informs on the downstream effect a stenosis has on the autoregulatory capacity of the microcirculation.



Source: adapted from de Waard et al.[10].
iFR: instantaneous wave-free.
Figure 2. Rationale of instantaneous wave-free ratio measurement. (A) shows the aortic (red lines) and distal coronary pressures (blue lines). The shaded gray areas represent the wave-free period when instantaneous wave-free is calculated. As stenosis severity increases, instantaneous wave-free worsens. (B) shows that coronary flow is maintained at a stable level despite increased stenosis severity. If the stenosis becomes functionally severe and the autoregulatory reserve is almost depleted however, resting flow starts to fall. (C) depicts that with increased stenosis severity, the arterioles progressively vasodilate keeping resting flow stable until autoregulation is depleted.

Table 1. Comparative studies between instantaneous wave-free ratio and fractional flow reserve

Reference	Patients	Lesions	Diagnostic agreement (%)	Pearson r	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	C statistics	iFR cutoff
Sen et al.[8]	-	157	88*	0.90	85	91	91	85	0.93	0.83
Petraco et al.[11]	312	339	80	-	-	-	-	-	0.86	0.89
Park et al.[15]	238	243	82	0.77	76	86	80	82	0.90	0.90
Johnson et al.[16]	-	1.129	78†	0.82	-	-	-	-	0.86	0.89
Berry et al.[17‡]	206	206	60*	0.79	40	99	98	47	0.87	-
Berry et al.[17‡]	500	500	59*	0.79	40	99	99	44	-	-
Petraco et al.[18]	313	392	80	-	81	79	71	87	0.87	0.89
Jeremias et al.[19]	1.768	1.593§	80	0.81	79	82	85	73.3	0.81	0.90
Härle et al.[20]	108	151	83	0.81	80	85.9	-	-	0.91	0.90
Fede et al.[21]	54	89	85	0.83	100	87	78	100	0.96	0.89
Escaned et al.[22]	598	690§	83	0.81	73	88	77	85.3	0.90	0.89
Indolfi et al.[23]	82	123	81	-	76	84	67	89	0.87	0.92
Mean	418	468	78	0.81	73	88	84	74	0.89	0.89
Weighted mean based on number of stenoses¶	434	453	81	0.81	78	84	80	79	0.85	0.90

* Berry et al.[17] and Sen et al.[8] used iFR cutoff point of 0.83. All other studies used iFR cutoff point of 0.89 or 0.90; † data were manually extrapolated from a manuscript figure; ‡ Berry et al.[17] reported two cohorts in the same manuscript (one prospective and another retrospective); they are presented separately in this table; § data included in the final analysis; ¶ Berry et al.,[17] Johnson et al.,[16] and Sen et al.[8] were also considered in the article by Jeremias et al.;[19] therefore, they were not included in the weighted analysis of means based on number of stenoses per study. In the studies by Jeremias et al.;[19] and Escaned et al.,[22] 381 and 229 lesions, respectively, did not reach the quality standards predetermined by the core laboratories and, thus, were not used in the original analyses.

PPV: positive predictive value; NPV: negative predictive value; iFR: instantaneous wave-free ratio.

INSTANTANEOUS WAVE-FREE RATIO: CLINICAL DATA

Two large trials evaluated the clinical use of iFR to guide coronary revascularization. The DEFINE-FLAIR[24] is a conventional prospective, multicenter, double-blind, controlled trial, while the iFR SWEEDEHEART[25] is a randomized clinical study that used the open registry SCAAR (Swedish Coronary Angiography and Angioplasty Registry) for patient inclusion. Both studies included patients with stable ischemic heart disease (SIHD) or non-culprit lesions in acute coronary syndrome (ACS), with intermediate angiographic stenoses (40% to 70% stenosis in DEFINE-FLAIR and 40-80% in iFR SWEEDEHEART). Patients were randomized 1:1 to iFR- or FFR-guided percutaneous coronary intervention (PCI). The primary endpoint was 1-year major adverse cardiac events (MACE), defined as the composite of all-cause death, non-fatal myocardial infarction (MI), or unplanned revascularization. DEFINE-FLAIR had 90% power to detect non-inferiority of iFR to FFR, with a non-inferiority margin of 3.4% in MACE. iFR SWEEDHEART had 85% power to detect non-inferiority between iFR and FFR with a non-inferiority margin of 3.2% in MACE.

DEFINE-FLAIR RESULTS

A total of 2,492 patients were included in this study. One-year MACE occurred in 6.8% in the iFR-guided group, and in 7.0% in the FFR-guided group (risk difference in MACE: -0.2%; 95%CI -2.3%-1.8%; p<0.001 for non-inferiority; hazard ratio – HR – of 0.95; 95%CI 0.68-1.33; p=0.78).[24]

Significantly less patients in the iFR group experienced procedure-related adverse symptoms (3.1% *versus* 30.8%; p<0.001). Median duration of procedures were significantly shorter in the iFR group (40.5 minutes *versus* 45.0 minutes; p=0.001).[25]

At 2 years, MACE rate was 11.8% in the iFR group, and 10.5% in the FFR group (HR: 1.15; 95%CI 0.91-1.45; p=0.25).[26]

IFR SWEEDEHEART RESULTS

Among the 2,037 patients included, 1-year MACE occurred in 6.7% in the iFR group, and 6.1% in the FFR group (risk difference in MACE: 0.7%; 95%CI -1.5%-2.8%; p=0.007 for non-inferiority; HR: 1.12. 95%CI 0.79-1.58; p=0.53). Chest discomfort was significantly less reported in the iFR group (3.0% *versus* 68.3%; p<0.001).[25]

At 5 years, MACE occurred in 21.5% in the iFR group, and 19.9% in the FFR group (HR: 1.09; 95%CI 0.90-1.33).[27]

META-ANALYSIS OF DEFINE-FLAIR AND IFR SWEEDEHEART

The combination of the DEFINE-FLAIR and iFR SWEEDEHEART trials provided outcomes data for 4,529 patients with intermediate coronary stenoses guided by coronary physiology. Beyond the proven non-inferiority of iFR to FFR, this meta-analysis demonstrated that iFR guidance indicates less revascularization than FFR guidance. Defer-

ral from revascularization occurred in 50% of the pooled iFR population and 45% of the pooled FFR group (p<0.01). Importantly, low MACE rates at 1 year were seen, regardless of iFR- or FFR-based deferrals[28] (Figure 3).

NOVEL NON-HYPEREMIC PRESSURE RATIOS

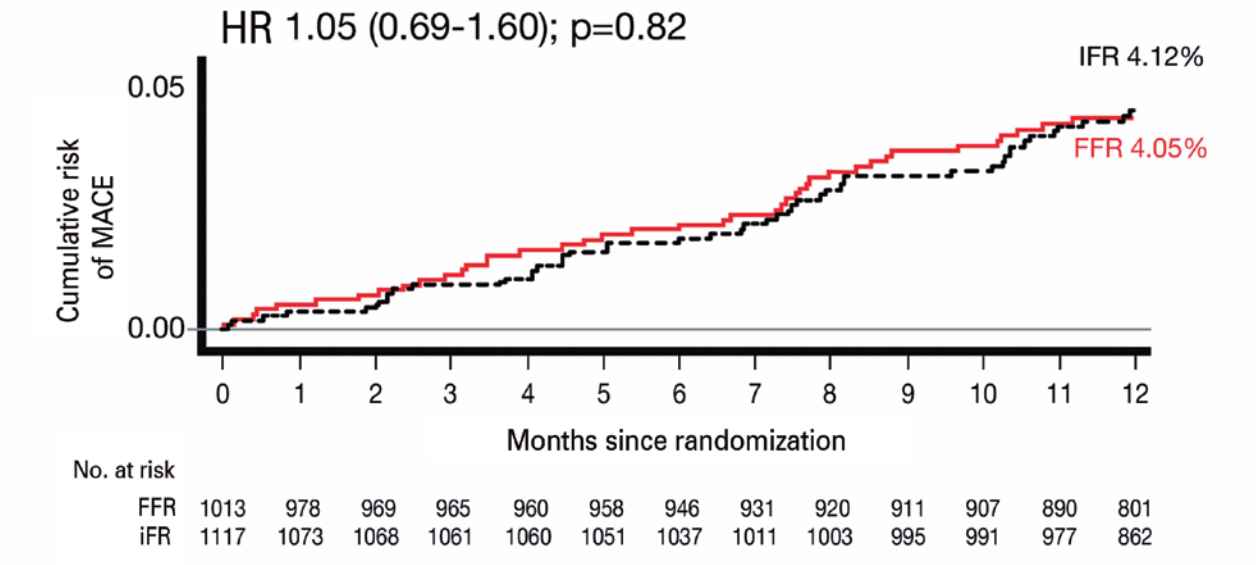
Following the successful validation and clinical outcomes data of iFR, several alternative NHPRs have emerged. In a recent *post-hoc* analysis of the VERIFY2 study, iFR was compared with the ratio of resting distal coronary pressure (Pd) and aortic pressure (Pa) in the complete duration of diastole (dPR), 25% to 75% of diastole (dPR_{25-75}), midpoint of diastole (dPR_{mid}), with Matlab calculated iFR (iFR_{matlab}), and iFR-like indexes shortening the length of the WFP by 50 and 100 ms (iFR_{50ms} and iFR 100_{ms}), respectively. Spearman correlations were >0.99 (p<0.001) for all indices with iFR, as were the values from areas under the receiver-operating curve characteristic analyses (>0.99 for all).[29] These results support the idea that a class effect should be considered among all NHPRs. As such, all NHPRs share the same threshold value as iFR.

At the time of this writing, beyond iFR, there are three commercially available NHPRs in Brazil (Figure 4). These include the resting full-cycle ratio (RFR, Abbott Vascular), diastolic hyperemia-free ratio (DFR, Boston Scientific), and diastolic pressure ratio (DPR, ACIST). Resting full-cycle ratio is derived from an average of five consecutive beats by calculating the minimum Pd/Pa within the cardiac cycle, after smoothing the instantaneous Pd/Pa tracing. This can happen in systole or diastole (wherever the minimum Pd/Pa occurs). In the VALIDATE RFR study, the minimum Pd/Pa was in diastole in 88% of cases.[30] Diastolic hyperemia-free ratio is calculated when the mean Pd/Pa in diastole satisfies two premises: aortic pressure (Pa) is below the mean arterial pressure; the Pa tracing has a down-sloping morphology.[31] Diastolic pressure ratio is calculated as the Pd/Pa ratio at the midpoint of peak-to-peak Pa pressures of two adjacent cardiac cycles, and is presented as an average of five consecutive cycles.[32]

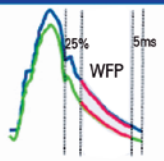
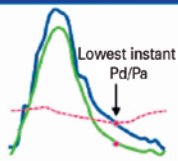
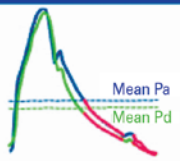
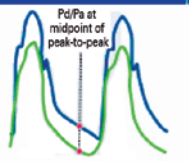
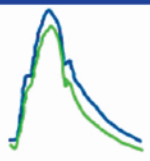
APPLICATIONS OF NON-HYPEREMIC PRESSURE RATIOS IN SPECIFIC SCENARIOS

Multivessel disease

The ability to perform multiple measurements and pressure wire pullback without hyperemia quickly and safely make NHPRs an attractive and more economical alternative for the assessment of patients with multivessel disease (MVD). Approximately 40% of patients included in the iFR SWEDEHEART and DEFINE-FLAIR trials had MVD, and a substudy of iFR-SWEDEHEART demonstrated no significant difference between FFR- and iFR-guided revascularization for 1-year MACE in patients with MVD or single-vessel disease.[33] Importantly, most reclassifications were the conversion of PCI to optimal medical treatment in the iFR/FFR groups (31.4%/29.0%). Reclassification increased with the increasing number of lesions evaluated (odds ratio per evaluated lesion for FFR: 1.46 *versus* iFR 1.37). Reclassification rates for patients with one, two, and



Source: adapted from Escaned et al.[22]
HR: hazard ratio; iFR: instantaneous wave-free ratio; FFR: fractional flow reserve.
Figure 3. Clinical outcomes of deferred lesions by instantaneous wave-free and fractional flow reserve. One-year cumulative risk for the composite of death from any cause, non-fatal myocardial infarction, or unplanned revascularization for patients with lesions deferred based on instantaneous wave-free (dashed black line) or fractional flow reserve (solid red line) measurements.

NHPR	iFR	RFR	DFR	DPR	Resting Pd/Pa
					
Manufacturer	Philips/Volcano	Abbott Vascular	Boston Scientific	ACIST	Not proprietary
Calculation	Pd/Pa ratio during the WFP	Lowest Pd/Pa ratio over the entire cardiac cycle	Average Pd/Pa ratio when Pa < Mean Pa, and down sloping Pa	Pd/Pa ratio at midpoint of peak to peak	Ratio of average Pd/Pa over the entire cardiac cycle at rest
Period in the cardiac cycle	Diastole	Lowest Pd/Pa at any point in the cardiac cycle	Diastole	Diastole	Entire cardiac cycle
Sampling	Mean of 5 cycles; beat-to-beat for pull-back curve	Mean of 5 cycles; beat-to-beat for pull-back curve	Mean of 5 cycles	Mean of 5 cycles	Single cycle
Additional features	Pullback curve; angiographic co-registration	Pullback curve available	...	...	...
Threshold	≤0.89	≤0.89	≤0.89	≤0.89	≤0.91
Summary of Evidence	Clinical validation from the prospective randomized trials DEFINE-FLAIR and iFR SWEEDEHEART; iFR non-inferior to FFR for MACE at 1 year	Diagnostic equivalence between RFR and iFR in a retrospective analysis of the VAL-IDATE RFR and RE-VALIDATE RFR studies	Diagnosis equivalence between DFR and iFR in a retrospective analysis of the VER-IFY 2 and CONTRAST studies	Diagnostic equivalence between DPR and iFR in a retrospective analysis of the ACIST FFR study	Excellent agreement with iFR and FFR. Resting Pd/Pa has slightly lower sensitivity to stenosis severity than iFR

Source: authors.

NHPR: non-hyperemic pressure ratio; iFR: instantaneous wave-free; RFR: resting full-cycle ratio; DFR: diastolic hyperemia-free ratio; DPR: diastolic pressure ratio; Pd: distal coronary pressure; Pa: aortic pressure; WFP: wave-free period; FFR: fractional flow reserve; MACE: major adverse cardiac events.

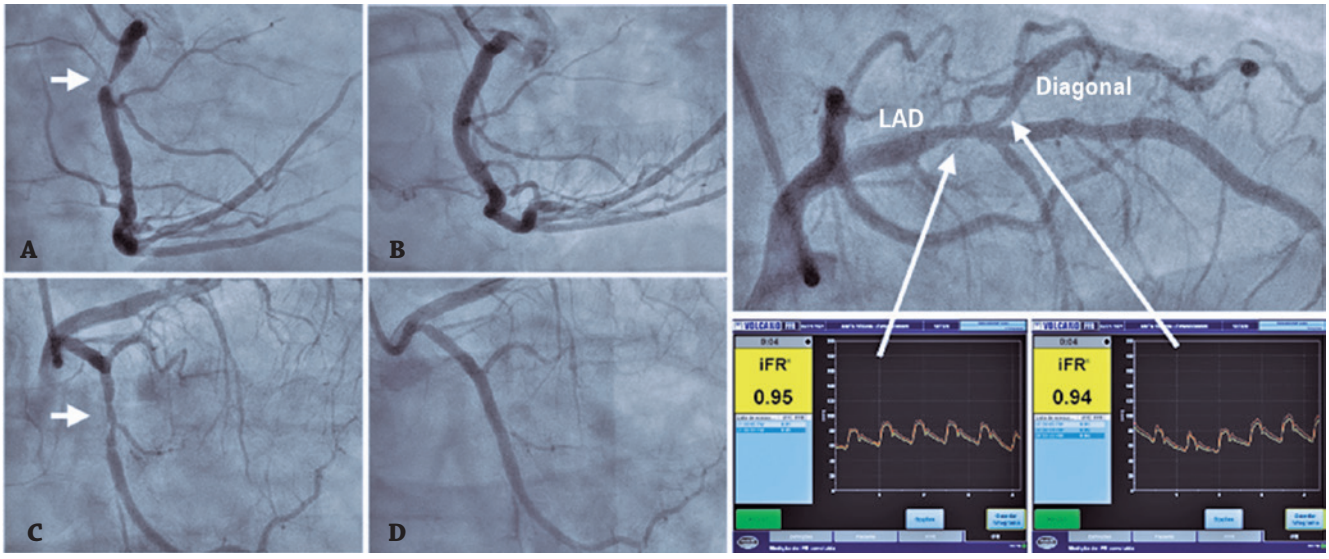
Figure 4. Description, calculation, characteristics, thresholds, and summary evidence of the currently available non-hyperemic pressure ratios.

three assessed vessels were 36%, 52%, and 53% (p<0.01), respectively. Figure 5 shows an example of functional MVD patient reclassification based on iFR evaluation.

The SYNTAX II[34-36] study was a multicenter, all-comers, open-label, single-arm study that investigated the impact of a contemporary PCI strategy on clinical outcomes in 454 patients with *de novo* three-vessel CAD, with no left main disease. The SYNTAX II strategy included heart-team decision-making utilizing the SYNTAX Score II, coronary physiology-guided revascularization, implantation of thin-strut bioresorbable-polymer drug-eluting stents, intravascular ultrasound (IVUS)-guided stent implantation, contemporary chronic total occlusion revascularization techniques, and guideline-directed medical therapy. A hybrid approach was used in all lesions; initially, iFR was performed, and lesions were revascularized if iFR <0.86, or deferred if iFR >0.93. In the 0.86-0.93 iFR range, FFR was used for decision-making. The rate of major adverse cardiac and cerebrovascular events (MACCE; composite of all-cause death, cerebrovascular event, any MI, and any revascularization) at 1 year was compared to a predefined PCI cohort from the original SYNTAX-I trial, selected based on equipoise 4-year mortality between coronary artery bypass graft (CABG) and PCI. As an exploratory endpoint, comparisons were made with the historical CABG cohort of the original SYNTAX-I trial. At 1 year, the SYNTAX-II strategy was superior to the SYNTAX-I PCI cohort (MACCE SYNTAX-II 10.6% *versus* SYNTAX-I 17.4%; HR 0.58, 95%CI 0.39-0.85; p=0.006). This difference was driven by a significant reduction in the incidence of MI (HR 0.27, 95%CI 0.11-0.70; p=0.007) and revascularization (HR 0.57, 95%CI 0.37-0.9, p=0.015).[34] The proportion of initially deferred lesions requiring revascularization between 1- and 2-year follow-up was low (14%, 3/22 lesions). Notably, no MI in the territory of the initially deferred lesions occurred.[35] At 5 years, MACCE rate in SYNTAX II was significantly lower than in the SYNTAX I PCI cohort (21.5% *versus* 36.4%; p<0.001), reflected by lower rates of revascularization (13.8% *versus* 23.8%; p<0.001), and MI (2.7% *versus* 10.4%; p<0.001). All-cause mortality was lower in SYNTAX II (8.1% *versus* 13.8%; p=0.013), reflecting a lower rate of cardiac death (2.8% *versus* 8.4%; p<0.001). MACCE at 5 years among patients in SYNTAX II and predefined patients in the SYNTAX I CABG cohort was similar (21.5% *versus* 24.6%; p=0.35).[36]

SERIAL STENOSES AND DIFFUSE DISEASE

Serial lesions are defined as two or more stenoses separated by angiographically normal segments. Nonetheless, atherosclerosis is often diffusely present in normal angiographic regions.[37] Aiming to unmask functionally significant coronary segments, we recommend starting the physiological assessment with the pressure wire positioned more distally as possible in the target vessel, and performing a pressure wire pullback meticulously and constantly. Pressure wire pullback allows identifying lesions with the highest-pressure gradients and, therefore, the most favorable PCI targets. It also enables operators to discriminate



Source: courtesy of Adriano Caixeta.
LAD: left anterior descending artery; iFR: instantaneous wave-free.
Figure 5. Non-hyperemic pressure ratio application in a patient with multivessel disease. A 60-year-old patient presented with non-ST elevation myocardial infarction and three-vessel disease by coronary angiography. Percutaneous coronary intervention with drug-eluting stent was performed in the right coronary artery (culprit lesion) (A and B) and left circumflex (C and D), which had severe lesions by visual assessment. Moderate lesions in the proximal left anterior descending artery and diagonal branch ostium were evaluated by instantaneous wave-free period index showing values of 0.95 and 0.94, respectively. Based upon these instantaneous wave-free results, these lesions were managed clinically with no intervention. Physiology assessment reclassified this three-vessel disease to a two-vessel disease patient.

between focal stenoses (amenable to PCI) and diffuse disease, which may result in abnormal distal vessel physiology, but may not be suitable for PCI.

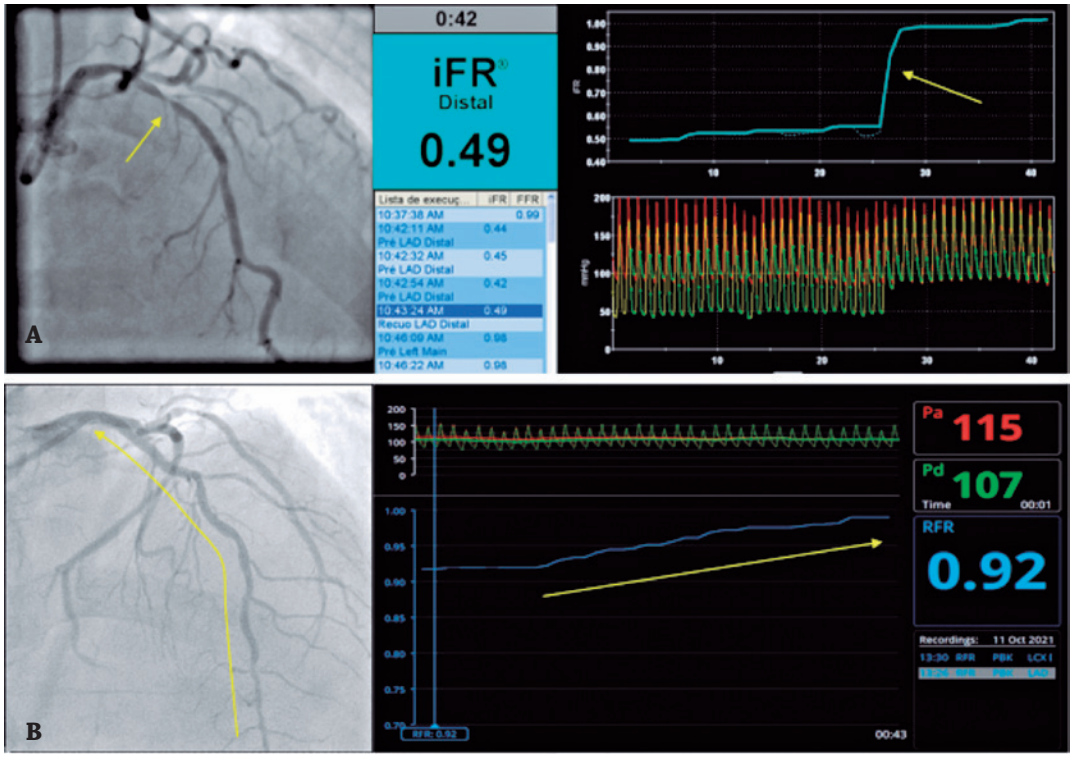
It is widely recognized that assessing the physiological severity of individual stenosis under hyperemia in vessels with serial and/or diffuse disease is clinically challenging.[38] This limitation is caused by the phenomenon of hemodynamic interdependency.[38-40] Hyperemic flow through one stenosis is limited by the presence of another stenosis, and vice versa.[40,41] In contrast, autoregulatory mechanisms ensure resting flow is stable across almost the entire range of stenosis severity, making the baseline state uniquely suited to the assessment of vessels with diffuse or tandem lesions.[42] iFR and RFR provide beat-by-beat measurements allowing the generation of a high-fidelity resting pullback tracing where the hemodynamic significance of each stenosis can be accurately mapped and quantified (Figure 6).

The utility of iFR for assessment of serial lesions was first demonstrated by Nijjer et al.,[40] in 2014. In this pilot study, motorized iFR pullbacks were performed in 32 coronary arteries with serial or diffuse disease. Decreases of iFR in every millimeter of the vessel were calculated offline, plotted, and overlaid onto a time-stamped fluoroscopic run of the pullback recording to create a co-registered physiological map. "Virtual PCI" was then performed using computer simulations to model the hemodynamic effect of removing stenosis on the iFR pullback trace to estimate a post-PCI iFR value. There was a small mean difference and strong correlation between the expected and observed post-PCI iFR (r=0.97; p<0.001).

This concept was clinically evaluated in the international, multicenter iFR-GRADIENT registry.[43] Among 134 vessels with serial or diffuse disease, the mean difference between the predicted and actual post-PCI iFR values was 0.011±0.004, with a strong correlation (r=0.73; p<0.001). Additionally, the ability of iFR pullback to detect the individual contribution of each stenosis to the distal iFR changed the angiography-based PCI strategy in 31% of vessels.

The GIFT (Pressure Gradient of hyperemic-iFR in Tandem Lesions) Registry[44] included 70 consecutive patients (88 vessels) with angiographically serial lesions. The physiological lesion predominance was defined according to the pressure gradient along the vessels on a pressure wire-pullback trace. Resting iFR was used as the reference standard and compared to FFR-based and hyperemic-iFR-based lesion predominance. The physiological lesion predominance changed by 22.7% in FFR and 20.5% in hyperemic-iFR, in comparison with resting iFR pullbacks. These results suggest potential advantages of resting pullback beyond hyperemic pullback, with a diagnostic performance difference of approximately 20% in tandem coronary artery lesions. Figure 7 illustrates the clinical use of resting pullback in serial/diffuse lesions.

Physiological-anatomical co-registration by real-time tracking of pressure wire movement along the vessel under continuous fluoroscopy enables operators to locate regions



Source: courtesy of Daniel Chamié and Júlio Maia.
iFR: instantaneous wave-free ratio; RFR: resting full-cycle ratio.
Figure 6. Non-hyperemic pressure ratio pullbacks of focal and diffuse atherosclerotic lesions. In (A), an instantaneous wave-free pullback discriminating a focal stenosis, characterized by a sharp and localized step-up in the pressure pullback curve. In (B), a resting full-cycle ratio pullback showing a diffuse disease, characterized by a ramp-like gradual recovery in pressure during pullback.

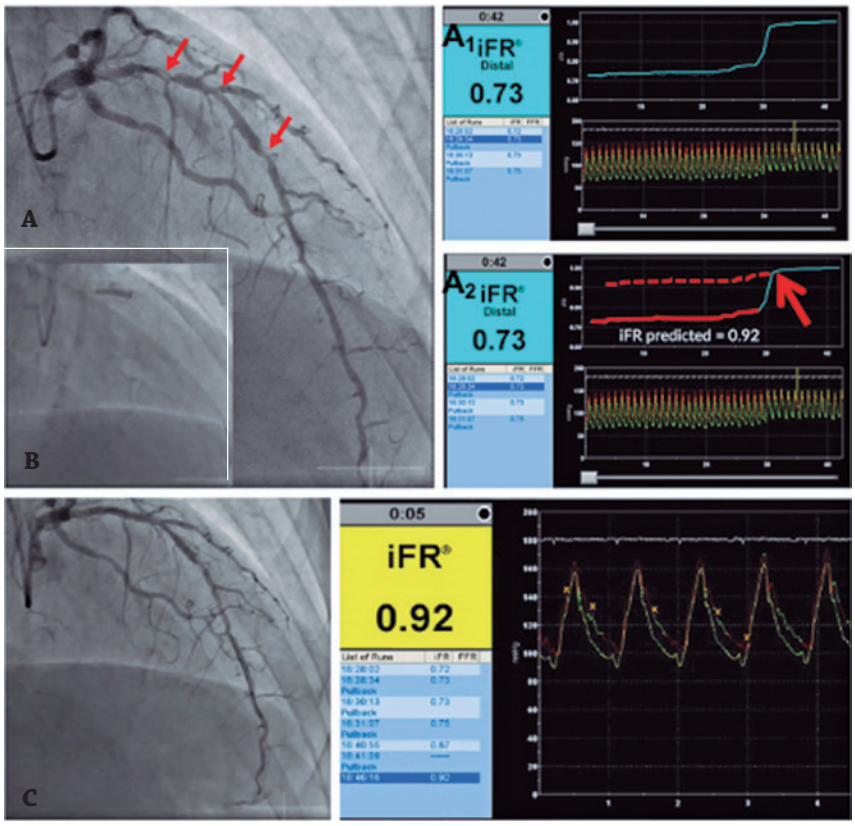
and magnitude of pressure loss, its distribution pattern and to plan their preferred stenting strategy (Figure 8).

LEFT MAIN CORONARY ARTERY LESIONS

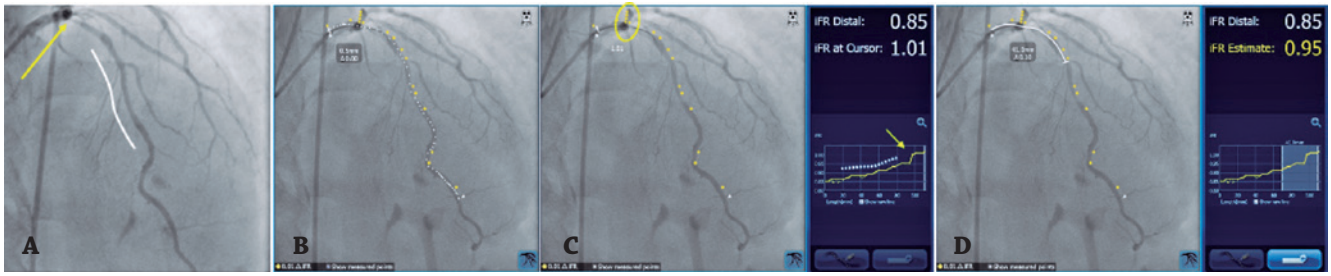
The LMCA is the coronary segment with the greatest degree of interobserver variability for angiographic stenosis assessment and well-recognized visual-functional mismatch.[45] Due to the potentially harmful consequences of revascularization procedures for non-significant LMCA lesions, or deferral of significant LMCA lesions from revascularization, accurate assessment of LMCA lesions is crucial for decision-making.

Left main coronary artery stenoses are usually accompanied by additional lesions in the downstream vessels. The hemodynamic interdependence of serial lesions poses significant difficulty in assessing the functional contribution of individual stenoses under hyperemia. In the presence of an intermediate LMCA lesion and concomitant downstream lesion, the blood flow across the LMCA will be reduced because of the distal lesion, and its FFR value underestimated. This magnitude of influence is related to severity of the distal lesion and its proximity to the LMCA. Likewise, treatment of the downstream lesion increases blood flow across the LMCA, potentially unmasking a clinically significant LMCA stenosis. In this scenario, NHPR appears as a suitable alternative.

An assessment of 91 intermediate LMCA stenoses revealed a significant correlation (r=0.67; p<0.001) between iFR and FFR, with a classification agreement of 81% between the two indices.[46] A multicenter and observational study included 314 patients with LMCA stenoses, of which 163 (51.8%) were deferred, and 151 (48.1%) revascularized according to the iFR cutoff ≤0.89. At a mean follow-up of 30 months, the primary endpoint (a composite of cardiac death, non-fatal MI, and ischemia-driven target lesion revascularization – TLR) occurred in 9.2% and 14.6% of the deferred and revascularized patients, respectively (HR 1.45; 95%CI 0.75-2.81), suggesting deferral of LMCA stenosis based on iFR appears safe, with a similar long-term outcome to those in whom the LMCA lesion was revascularized.[47] Another multicenter and observational study explored the diagnostic ability of iFR to identify significant LMCA lesions in 125 patients. The minimum lumen area (MLA) cutoff ≤6.0mm^2 by IVUS was the criterium for a significant LMCA lesion. Receiver operating curve analysis showed that an iFR of ≤0.89 identified MLA <6.0mm^2, with an area under the curve (AUC) of 0.77 (77% sensitivity and 66% specificity; p<0.0001). Among a subgroup of 69



Source: courtesy of Ricardo Petraco and Fernando Sant'Anna.
iFR: instantaneous wave-free ratio.
Figure 7. Practical management of a patient with serial lesions. This is a case of an 85-year-old male, with unstable angina and normal ventricular function. (A) Left anterior descending artery with diffuse atherosclerotic disease and serial lesions; (A1) Pullback curve shows a steep and focal gradient across the proximal left anterior descending artery stenosis and diffuse disease pattern with small gradients in the remaining vessel. Non-hyperemic pressure ratio allows predicting the outcome of stent implantation; in this case, an instantaneous wave-free ratio of 0.92 if the proximal lesion is treated (A2). (B) Stent implantation in proximal lesion. (C) Final angiographic and physiological result confirming the predicted instantaneous wave-free ratio and avoiding placement of additional stents in other lesions that were not functionally important.



Source: courtesy of Daniel Chamié.
iFR: instantaneous wave-free ratio.
Figure 8. Clinical application of instantaneous wave-free ratio co-registration. In (A), a severe stenosis in the ostium of the left anterior descending artery (yellow arrow) followed by a segment of mild disease in the mid segment (dashed while line). In (B), automatic tracking (white dots) of the manual pullback of the pressure sensor from the distal left anterior descending artery to guiding catheter. In (C), the physiological results presented. The instantaneous wave-free ratio in the distal left anterior descending artery position is 0.85. A pullback curve is presented in the bottom of the result tab, showing a diffuse disease in the mid left anterior descending artery (dashed white line) and focal gradient across the ostial left anterior descending artery lesion (yellow arrow). Each 0.01 unit of pressure loss is presented in the angiography image by the overlayed yellow dots. Note the diffuse distribution of dots in the mid left anterior descending artery, and a focal concentration of dots at the left anterior descending artery ostium (yellow circle). In (D), percutaneous coronary intervention simulation is possible by dragging the cursor at the desired vessel segment. The chosen segment is indicated by a white line drawn onto the angiography and by the highlight overlayed onto the instantaneous wave-free ratio pullback curve. In this case, treating from the left main coronary artery (LMCA) ostium up to the proximal left anterior descending artery would require 41mm of stent, and would recover 0.10 unit of instantaneous wave-free ratio, with a final instantaneous wave-free of 0.95.

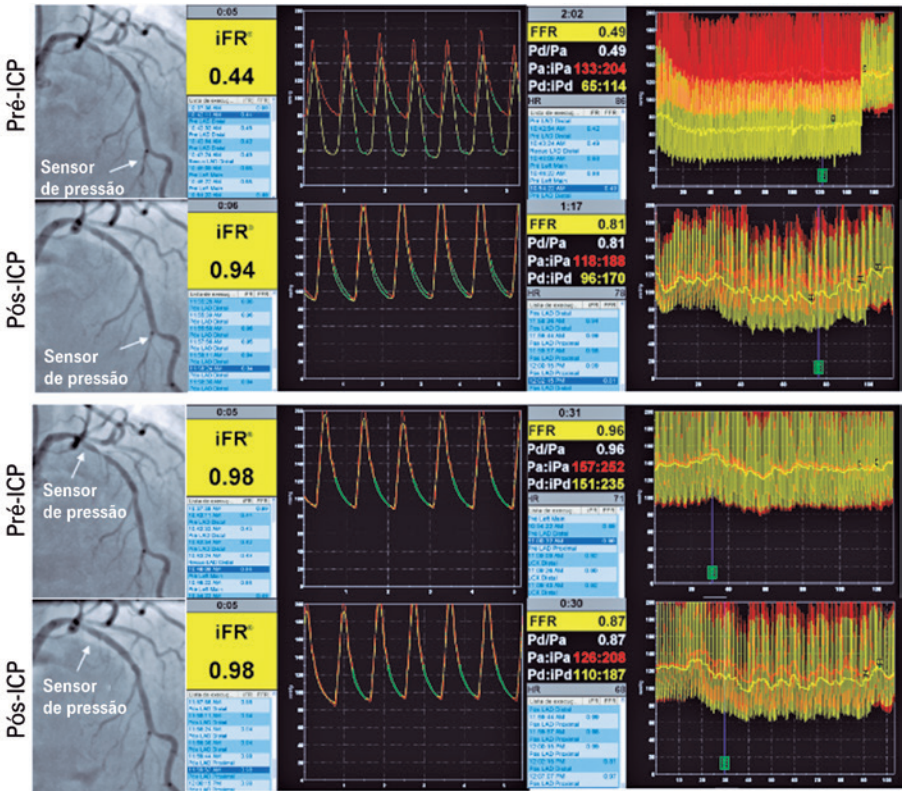
patients without ostial left anterior descending artery or left circumflex artery disease, the AUC increased to 0.84 (70% sensitivity, 84% specificity; p<0.0001). iFR correlated with IVUS MLA regardless of the body surface area.[48] Figure 9 illustrates the resting and hyperemic assessment of a LMCA lesion followed by a severe downstream lesion.

In the VIP-LMS (NCT04531007) we are investigating the hemodynamic effects of severe downstream lesions on the FFR and iFR values of an intermediate LMCA lesion, before and after treatment of the downstream lesion, and establishing the MLA cutoffs derived from IVUS and optical coherence tomography to predict functionally significant lesions. The iLITRO study (NCT03767621) will investigate the concordance of FFR and iFR in LMCA lesions as well as compare the clinical outcomes between patients who have FFR-guided and iFR-guided revascularization.

ACUTE CORONARY SYNDROME

In contrast to stable angina, an acute coronary syndrome (ACS) can unpredictably alter the microvascular milieu by a variety of mechanisms, including intramyocardial hemorrhage and microvascular obstruction. These factors can limit attaining maximum hyperemia, ultimately underestimating the true hemodynamic significance of stenosis by FFR.

The role of hemodynamic indices in non-culprit vessels in patients with ST-segment elevation myocardial infarction was assessed in a subgroup of 73 patients from the REDUCE-MVI study. After successful primary PCI, non-culprit intracoronary hemodynamic measurements were performed and repeated after 1 month. iFR did not change significantly from the acute moment to 1 month (0.93±0.07 *versus* 0.94±0.06; p=0.12), while FFR experienced a signi-



Source: courtesy of Daniel Chamié.

PCI: percutaneous coronary intervention; iFR: instantaneous wave-free ratio; FFR: fractional flow reserve; Pd: distal coronary pressure; Pa: aortic pressure.

Figure 9. Non-hyperemic pressure ratio and fractional flow reserve use in serial lesions involving the left main and a downstream vessel. Physiology assessment of a patient with intermediate lesion in the distal left main, followed by a severe lesion in the proximal left anterior descending artery. The top panel presents the instantaneous wave-free ratio and fractional flow reserve measurements pre- and post-percutaneous coronary intervention of the left anterior descending artery lesion. Note the significant improvement of both indices (instantaneous wave-free ratio from 0.44 to 0.94 and fractional flow reserve from 0.49 to 0.81). The lower panel presents the instantaneous wave-free ratio and fractional flow reserve measurements in the proximal left anterior descending artery, between the left main and the left anterior descending artery lesion, before and after treatment of the proximal left anterior descending artery lesion. The initial instantaneous wave-free ratio between the left main and left anterior descending artery lesions was 0.98 and remained unchanged after treatment of the left anterior descending artery lesion. Conversely, the initial fractional flow reserve between the left main and left anterior descending artery lesions was 0.96. Treatment of the left anterior descending artery lesion significantly increased hyperemic flow across the left main, which significantly reduced the initial fractional flow reserve to 0.87 (reduction of 0.09 fractional flow reserve unit). This case illustrates the stability of resting flow and non-hyperemic pressure ratio in the presence of serial lesions, and the significant crosstalk experienced by hyperemic flow and fractional flow reserve.

ficant reduction (0.88±0.07 *versus* 0.86±0.09; p=0.001). Over 1 month, the hyperemic index of microvascular resistance decreased, and the resting microcirculatory resistance increased. The resultant effect was a significant increase in CFR after 1 month (2.9±1.4 *versus* 4.1±2.2; p<0.001). Collectively these changes indicate increased hyperemic microvascular resistance and a blunted adenosine responsiveness in the non-culprit territory in the acute moment, which was correlated with the final infarct size, as quantified by cardiac magnetic resonance (r: -0.29; p=0.02).[49]

In a pooled analysis of the DEFINE-FLAIR and iFR SWEEDEHEART studies for assessment of non-culprit lesions in 440 patients with ACS, deferral with FFR had a higher rate of clinical events compared with FFR deferral in stable CAD (HR of 0.52, 95%CI 0.27-1.00; p<0.05). Conversely, deferral based on iFR guidance yielded similar outcomes, regardless of clinical presentation (HR of 0.74, 95%CI 0.38-1.43; p=0.37).[28] Although this data might suggest iFR is a better prognostic tool for deferring non-culprit lesions in ACS, the inherent limitations of a subgroup analysis of studies where superiority between iFR and FFR was not shown, prevent definitive conclusions to be drawn. The ongoing prospective, multicenter, randomized iMODERN (iFR-Guided Multi-Vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction; NCT03298659) study will provide further insights into the clinical value of iFR-guided revascularization in ACS.

AORTIC STENOSIS

Coronary artery disease frequently coexists in patients with severe aortic stenosis (AS).[50] The increasing adoption of transcatheter aortic valve replacement (TAVR) raised the interest in the application of invasive physiology to identify ischemia-inducing lesions in AS patients.

In addition to functioning as a serial lesion (stenotic valve and coronary lesion), AS induces several physiological changes that affect the interpretation of hyperemic and non-hyperemic indices. Notably, AS decreases aortic and proximal coronary pressures and increases the left ventricular and intra-myocardial pressures, by compressing the microcirculation and altering left ventricular relaxation. Together, these changes can lead to hyperemic blunting, through which the effects of adenosine are attenuated. Furthermore, the greater oxygen demands by the hypertrophied left ventricle induce partial microcirculatory vasodilation and limit the additional vasodilation that could be achieved with adenosine. This partial microvascular vasodilation increases resting coronary flow and can also affect NHPR measurements. Data suggest that a lower iFR cutoff point (0.82 or 0.83) better predicts ischemia-inducing lesions in patients with severe AS.[51,52]

Several studies have demonstrated discrepancies between FFR and iFR in the same lesion immediately before and after TAVR. In a study of 28 patients with severe AS and CAD (30 lesions) intracoronary pressure and flow were assessed at rest and during hyperemia, immediately before and after TAVR. During the WFP, flow did not change post-TAVR (29.78±14.9cm/s *versus* 30.81±19.6cm/s; p=0.64), nor did iFR (0.88±0.09 pre-TAVR *versus* 0.88±0.09 post--TAVR; p=0.73). Conversely, whole-cycle hyperemic flow increased significantly (33.44±13.4cm/s pre-TAVR versus 40.33±17.4cm/s post-TAVR; p=0.006). This significantly decreased FFR from 0.87±0.08 pre-TAVR to 0.85±0.09 post-TAVR (p=0.001).[52] In another study on 13 patients followed-up to 6 months, FFR decreased from 0.85 (0.76 to 0.88) pre-TAVR to 0.79 (0.74 to 0.83) post-TAVR, and then to 0.71 (0.65 to 0.77) at 6 months (p<0.001 for all comparisons). Conversely, iFR was not significantly different: 0.82 (0.80 to 0.90) pre-TAVR, 0.83 (0.77 to 0.88) post-TAVR, and 0.83 (0.73 to 0.89) at 6 months (p=0.735).[53] The role of pressure-based physiological assessment of coronary stenoses in patients with severe AS is being further investigated in two large, randomized trials: NOTION-3 (Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation; NCT03058627) and FAITAVI (Functional Assessment In TAVI; NCT03360591) .

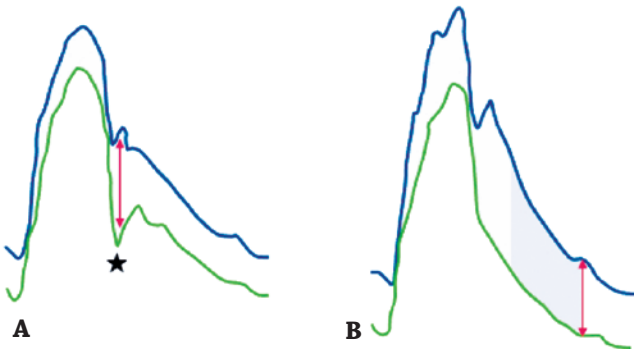
MYOCARDIAL BRIDGING

Unlike coronary atherosclerosis, myocardial bridge (MB) causes dynamic luminal narrowing due to cyclic systolic compression and diastolic relaxation. Therefore, MB has important implications in how pressure-based physiology indices are used to assess the functional significance of MB or fixed coronary stenoses, which coexist with MB.

Because these dynamic stenoses depend on the degree of extravascular compression and intramyocardial tension, and are unmasked by chronotropic and inotropic stimulation, their invasive assessment should not be limited to resting conditions or vasodilator-induced hyperemia. MB can cause significant diastolic pressure gradients and artificially normal or even negative systolic pressure gradients, as a result of systolic pressure overshooting. This is due to ventricularization of coronary pressure secondary to myocardial compression.[54] Accordingly, Escaned et al.[54] demonstrated that diastolic FFR during a dobutamine challenge is more suitable for unmasking ischemia associated with MB than the averaged whole cycle FFR. This led to speculations as to whether diastolic indices would be more reliable in assessing the hemodynamic significance of MB. Tarantini et al.[55] enrolled 20 patients with angina and/or positive noninvasive stress test, absence of significant coronary artery stenosis, and angiographic suspicion/evidence of MB in the left anterior descending artery. Fractional flow reserve and iFR were measured at rest and after dobutamine challenge. At baseline, no MB was hemodynamically significant according to FFR, whereas iFR was below the cutoff value in all, but 7 patients. During the inotropic challenge, median FFR

did not change significantly (0.87 to 0.86; p=0.59), while iFR significantly changed from 0.88 (interquartile range – IQR: 0.80-0.94) at rest to 0.79 (IQR: 0.65-0.93) after dobutamine (p<0.0001).

Intracoronary flow velocities measured by Doppler-tipped guidewires have revealed retrograde flow during systole immediately proximal to the MB, and an abrupt early diastolic flow acceleration described as the "fingertip phenomenon", rapid mid-diastolic flow deceleration, and mid-to-late diastolic plateau. In conjunction, this Doppler flow signal presents a characteristic "spike-and-dome" pattern.[56] As a result, MB has a pressure wave pattern distinct from fixed atherosclerotic stenoses (Figure 10). Because RFR measures the maximum filtered Pd/Pa during the entire cardiac cycle, including the early diastole, it has been speculated that RFR might be more useful than other diastolic indices (*e.g.*, iFR, DFR, DPR) for detection of MB-related ischemia – a concept that needs confirmation in comparative studies. On the other hand, when the goal is to assess the functional significance of fixed atherosclerotic stenoses that coexist in a vessel with MB, a diastolic index that excludes systole and the early diastolic phase seems more appropriate (*e.g.* iFR, DFR, DPR); again, this also needs confirmation.



Source: courtesy of Daniel Chamié.

Figure 10. Distal coronary pressure (green lines) and aortic pressure (blue lines) traces obtained in vessels with myocardial bridge (A) and fixed atherosclerotic stenosis (B). In myocardial bridge, a negative suction wave (black star in A) can occur early in diastole due to the vigorous decompression of the microcirculation. As a result, the largest distal coronary pressure/aortic pressure gradient (double red arrow in A) can be observed in the early diastolic phase, before the window of the wave-free period (shaded area). Therefore, if the goal of physiologic assessment is to investigate the hemodynamic impact of myocardial bridge in the downstream flow, an index that does not operate in a fixed time window could be theoretically more appropriate (e.g., resting full-cycle ratio). In fixed atherosclerotic lesions, the largest drop in distal coronary pressure usually occurs late in diastole and is usually captured in the wave-free period. Thus, if the goal of the physiological assessment is to investigate the hemodynamic impact of an atherosclerotic lesion in a vessel with myocardial bridge, a diastolic index that eliminates the early diastolic effects of the myocardial bridge (such as instantaneous wave-free, diastolic hyperemia-free ratio or diastolic pressure ratio) could theoretically be more appropriate.

POST-PERCUTANEOUS CORONARY INTERVENTION ASSESSMENT

An excellent final angiographic PCI result co-exists with residual ischemia in 18 to 25% of patients.[57,58] Post-PCI physiology is independently associated with target vessel failure.[57,59-62]

DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI) was a multicenter, prospective, observational study in which a blinded iFR pullback was performed after angiographically successful PCI in 562 vessels in 500 patients. Despite the angiographic success, 24% of patients had residual ischemia. Of these, 81.6% had one or more focal areas of pressure loss and only 18.4% of patients had diffuse disease. Among the focal lesions, 38.4% were located within the stent, while 31.5% were proximal and 30.1% were distal to the stent. These residual focal stenoses correlated poorly with the angiographic minimum lumen diameter or percent residual stenosis, highlighting the inability of coronary angiography to determine physiological lesion severity.[58] At 1 year, patients with post-PCI iFR ≥0.95 had lower rates of the composite of cardiac death, spontaneous MI, or clinically-driven TVR compared with patients with post-PCI iFR <0.95.[62]

LIMITATIONS OF NON-HYPEREMIC PRESSURE RATIOS

Several factors such as anxiety, pain, or prehydration can induce fluctuations in heart rate, blood pressure, contractility, and loading conditions, which can influence myocardial oxygen demand. Autoregulation adjusts to this metabolic demand to maintain coronary flow stable. Therefore, hemodynamic variability has been suggested as a potential source of error for NHPRs.[16,17] Although theoretically reasonable, evidence about the diagnostic impact of hemodynamic variability on NHPR results is conflicting. While the VERIFY study showed that the relative difference between iFR and FFR is significantly correlated with both resting heart rate and blood pressure,[17] the ADVISE study found iFR to be independent of heart rate and systolic or diastolic pressure.[8] Likewise, the CLARIFY study showed that heart rate variability does not significantly influence the relation between iFR and FFR or HSR.[63]

Some operators showed concern with NHPR measurement in patients with atrial fibrillation. In ADVISE, iFR was not affected by heart rate in the range of 46 to 120 bpm, and it was also stable in irregular rhythms.[8] Thus, provided the WFP can be identified, atrial fibrillation should not be a source of concern for iFR measurements. However, when the heart rate is not controlled, myocardial demand increases, resulting in a pseudo-hyperemic state that is not representative of true resting condition. Thus, NHPR results should be interpreted with caution in tachycardic patients, with heart rate above the upper limit of validation studies.

Still to this date, there is debate regarding the discordances between FFR and NHPR. Discrepancies between NHPR and FFR have been explained by sex, presence of diabetes, use of beta-blockers, and pattern of coronary disease distribution.[64-68] In an analysis of 360 intermediate coronary lesions, FFR disagreed with iFR in 22% (79 lesions). The physiological pattern of disease was the only factor that influenced FFR/iFR discordance. Predominantly focal lesions were significantly associated with FFR+/iFR- (58.5%; 24 of 41) while predominantly diffuse disease was significantly associated with FFR-/iFR+ (81.6%; 31 of 38).[69] This data led some operators to extrapolate that NHPRs are not suited to assess focal stenoses. However, the lack of combined measurements of coronary flow or documentation of the presence/absence of myocardial ischemia does not allow for such a definitive conclusion. At best, this assumption is only speculative and requires further investigation.

CONCLUSION

Non-hyperemic pressure ratio introduction completed a decade, with a great deal of controversy, particularly when non-hyperemic pressure ratio and fractional flow reserve disagreed. However, a large body of evidence regarding its theoretical description, technical validation, and sound clinical outcomes data support the clinical use of non-hyperemic pressure ratios, which have been endorsed by national and international guidelines. In addition, non-hyperemic pressure ratios are quicker and easier to perform than fractional flow reserve, have a lower incidence of patient-related discomfort, lower cost, and superior signal-to-noise ratio, allowing for precise assessment of serial lesions and prediction of post-percutaneous coronary intervention outcomes. Collectively, these aspects have ramped up the clinical uptake of non-hyperemic pressure ratio, making it the first-choice pressure-based physiology index in most catheterization laboratories around the world.

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CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: DC and FMS; data collection: DC, FMS, JPM, TR, LE, LBS and AC; data interpretation: DC and FMS; text writing: DC, FMS, JPM, TR, LE, LBS and AC; approval of the final version to be published: DC and FMS.

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