Coronary circulation: Pressure/flow parameters for assessment of ischemic heart disease

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Both invasive and non-invasive parameters have been reported for assessment of the physiological status of the coronary circulation. Fractional flow reserve and coronary (or myocardial) flow reserve may be obtained by invasive or non-invasive means. These metrics of coronary stenosis severity have achieved wide clinical acceptance for guiding revascularization decisions and risk stratification. Other indices are obtained invasively (e.g., instantaneous wave-free ratio, iFR; hyperemic stenosis resistance) or non-invasively (e.g., PET absolute myocardial blood flow (mL/min/g)) and have been used for the same purposes. Both iFR, and whole-cycle distal coronary to aortic mean pressure (Pd/Pa) are measured under basal condition and used for assessment of hemodynamic stenosis severity as is index of basal stenosis resistance (BSR). These metrics typically are dichotomized at an empirically derived cut point into ''normal'' and ''abnormal'' categories for purposes of clinical decision making and data analysis. Once dichotomized the indices do not always point in the same direction and so confusion may arise. This review, therefore, will present basic principles relevant to understanding commonly employed metrics of the physiological status of the coronary circulation, potential strengths and weaknesses, and hopefully an improved appreciation of the clinical information provided by each. (J Nucl Cardiol 2019;26:459–70.)

Key Words: Physiology of myocardial/coronary perfusion • Basic science, CAD • Diseases/processes, myocardial ischemia and infarction • Diseases/processes, PET • Modalities, FFR: fractional flow reserve • Modalities, Myocardial blood flow • Tests

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Abbreviations	
Pa	Mean aortic pressure
Pd	Mean pressure distal to coronary stenosis
CBF	Coronary blood flow
MBF	Myocardial blood flow
CBF	Thermodilution mean transit time ($T_m \simeq$ k/CBF) or Doppler flow velocity (cm/s)
MBF	PET (provides MBF as mL/min/g)
CCTA	Coronary computed tomographic angiography
CFR and MFR	Coronary or myocardial flow reserve: CBF or MBF with coronary vasodilator (e.g., adenosine)/CBF or MBF at rest. Defined as absolute flow reserve (see text) and differs from relative flow reserve (e.g., FFR and FFR_{PET})
FFR	Fractional flow reserve: Pd/Pa. Obtained with coronary vasodilator stimulus. Considered relative flow reserve (see text)
FFR_{CT}	FFR computed from modeled hyperemic pressure/flow CCTA data. CCTA obtained at rest
FFR_{PET}	MBF stenotic coronary artery/MBF normal coronary artery. Obtained with coronary vasodilator stimulus requires normal reference artery
iFR	Instantaneous wave-free ratio (Figure 2). Pd/Pa. Obtained at rest pressures measured during wave-free interval in mid to late diastole
BSR	Basal stenosis resistance (CBF at rest). Pa − Pd/CBF
HSR	Hyperemic stenosis resistance (CBF with coronary vasodilator). Pa − Pd/CBF
IMR	Index of microvascular resistance (CBF with coronary vasodilator). Pd/CBF

INTRODUCTION

The maximal flow capacity of a coronary vascular bed may be characterized in a variety of ways. Invasive methods employ pressure or flow (or both) measurements while non-invasive methods focus on flow. CCTA, however, combines anatomical data and fluid dynamic modeling to estimate pressure loss, at a modeled, patient-specific, maximal blood flow, to obtain a non-invasive estimate of a pressure parameter, FFR.[1-3] While invasive FFR is currently employed as the ''gold'' standard metric for assessing coronary stenosis severity and guiding revascularization,[4-6] more recently iFR has been shown to be non-inferior for this purpose.[7,8] Further, the ratio rest Pd/Pa correlates closely with iFR and in a small study was found to be of similar utility in guiding revascularization decision making.[9,10] The purpose of the current paper is to review essential physiological principles necessary to understanding strengths and limitations of these and other frequently employed parameters of coronary dilator capacity (e.g., IMR, CFR, maximal myocardial blood flow) and thereby gain a greater appreciation of each.

Physiology

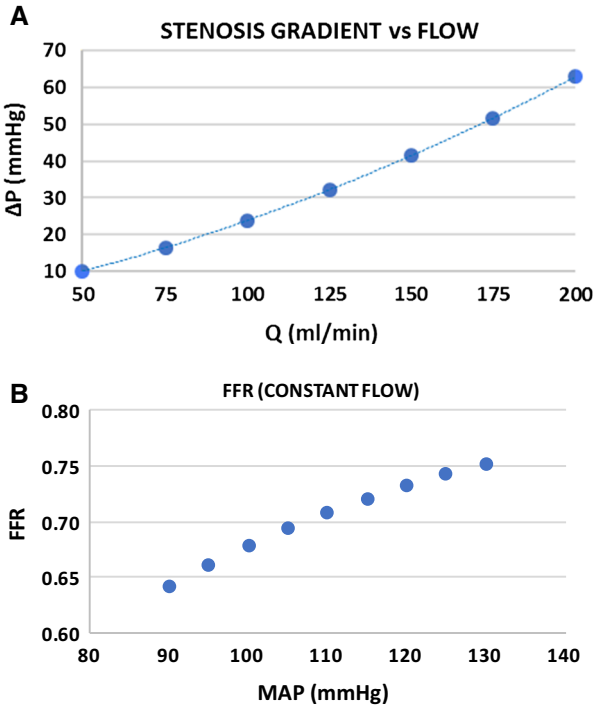
Since each of the commonly employed metrics assumes a simple model of the coronary circulation (FFR_{CT}, excluded), as with most endeavors, it's best to begin there. However, it is appreciated at the outset, in the setting of clinical coronary artery disease, the problem often is rendered more complex by factors such as (1) diffuse disease with only mild stenosis with or without additional superimposed hemodynamically significant lesion(s)[11,12] (2) collateral blood supply to an occluded or severely stenosis vessel[13] (3) serial lesions of variable hemodynamic severity in a given artery.[14] So, for the simple case of an otherwise normal coronary vessel from origin to micro-circulation and all levels in between, the pressure drop (ΔP) across an epicardial stenosis is given by the following equation[15-17]:

$$\Delta P = AQ + BQ^2, \quad (1)$$

where Q is flow, A and B are constants related, respectively, to Poiseuille (frictional) resistance and stenosis geometry (flow separation).

It is immediately apparent the pressure drop across the stenosis is directly related to flow through it and that the pressure loss related to stenosis geometry is geometrically greater than that related to Poiseuille resistance. Hence, any factor which impacts flow in the vascular bed distal to the stenosis (e.g., diffuse disease or microvascular dysfunction or both) must be reflected in the pressure drop across it. Accordingly, for any given anatomical stenosis severity, even if precisely known, less flow means less pressure loss and vice versa.[18] This principle is crucial to understanding all pressure-based metrics of stenosis hemodynamic severity (see below and Figure 1A, B).

Another important point to recall is that pressure-based measurements of stenosis hemodynamic severity, beginning with FFR, represent efforts to estimate maximal flow which can be attained in the coronary vessel of interest.[19] Indeed, it was demonstrated in the



◀**Figure 1. A** Stenosis Flow (Q), Pressure Gradient (ΔP) Relationship: The above figure demonstrates the quadratic relationship between coronary flow (Q) and pressure drop (ΔP) as defined by Eq. 1 (see text) across a hypothetical 62% diameter reduction, 7 mm long stenosis. Note, with perfusion territory of ~ 50 g, transmural flows would range from 1 to 4 mL/min/g. The change in ΔP for a given change in flow is ~1.3× greater and so may have an important impact on FFR especially when dichotomized, normal vs abnormal, at a particular set point (e.g., 0.80). **B** FFR Dependence on Mean Aortic Pressure (MAP; Pa). The above figure demonstrates the dependence of FFR on the level of mean aortic pressure (MAP, Pa) at a given (i.e., constant) level of coronary blood flow. The curve was generated by solving Eq. 1 for constant level of adenosine-stimulated flow, 125 mL/min (2.5 mL/min/g to 50 g segment) and hypothetical stenosis of intermediate anatomical severity (62% Dia, length 7 mm) with resulting ΔP = 32 mmHg. Depending on mean aortic pressure (MAP, Pa), FFR ranges from 0.64 to 0.75. Thus, if Pa = 90, then Pd = 90 − 32 = 58 and FFR = 58/90 = 0.64 and so on. Accordingly, depending on aortic mean pressure (MAP, Pa on abscissa), FFR, illustrated above, for the given hypothetical flow and anatomical stenosis severity, spans the meta-analysis based on cut point of 0.67 (Pa ~100) at which coronary revascularization potentially may reduce death or myocardial infarction.[26,61] Thus, if Pa is less than ~ 100 mmHg, FFR is less than 0.67 and revascularization is suggested. However, if Pa is greater than ~100 mmHg then FFR is greater than 0.67 and depending on other relevant clinical factors medical management may be preferred. Further, if rest flow was 60 mL/min (1.2 mL/min/g to 50 g segment), then CFR = 2.1 (''normal'') and associated with favorable prognosis though discordant with all values of FFR (all associated with unfavorable prognosis). However, if rest flow was 72 mL/min (1.4 mL/min/g to 50 g segment; + 20% vs 1.2 mL/min/g), then CFR = 1.7, a level associated with ''definite ischemia'' with PET ^{82}Rb dipyridamole stress[64] in which case both CFR and FFR concordant and unfavorable. However, regardless of CFR, the hypothetical level of stress flow (2.5 mL/min/g) likely is adequate to meet myocardial oxygen demand required to perform 10-12 METs of exercise (e.g., hiking with 20 kg pack, up 5% grade at 7.2 km/h).[44,73,74] Accordingly, reference to the absolute level of stress MBF provides an unambiguous indicator not only of the patient's potential exercise capacity but also prognosis (≥ 10METS, very low risk, death myocardial infarction)[75].

original description of the metric, under conditions of maximal coronary vasodilation (papaverine, 8 mg IC) that as stenosis severity was increased the ratio Pd/Pa correlated linearly ($R^2 \geq 0.94$) with the decline in the ratio of observed to maximal flow in the absence of a stenosis.[19] Hence, the designation fractional flow reserve (FFR). It has been pointed out that the ratio represents relative as opposed to absolute flow reserve, since the observed ratio implicitly is compared to a ratio of unity in the absence of the stenosis.[19,20] Accordingly, the FFR ratio, as discussed in the original paper, was developed as a surrogate for maximal coronary blood flow. The authors noted that this metric was superior to flow reserve (maximal/rest flow) since (1) it was not subject to variation associated with resting flow and (2) it directly addresses the clinical question of interest which is, the extent, if any, to which the stenosis compromised the ability of the artery to supply blood to the heart under conditions of stress.[19] The myocardium lives on blood flow (mL/min/g) and not unit less ratios. The authors noted at the time, however, PET, which was (and still is) the optimal way to quantitatively measure maximal myocardial blood flow in humans, was not widely available and of course was not feasible for immediate clinical decision making re: PCI in the cardiac catheterization laboratory.[19] Hence the advantage of a pressure wire-based metric, FFR, which provided a measure, in the presence of the stenosis, of the fraction of maximal MBF attainable in the absence of the stenosis assuming normal coronary circulation.

One other general principle worth considering is the unfortunate though perhaps necessary expedient of dichotomizing both pressure- and flow-related metrics for purposes both of clinical decision making and data analysis. An empirical cut point is chosen, and so continuous variables are transformed to ''normal'' and ''abnormal'' categories. While in individual clinical decision making, values on or just either side of the line may be weighed accordingly with other relevant factors, in research work the data must be grouped as defined and are counted just as those very far from the line.

Moreover, much attention has been drawn to the problem of metrics, once dichotomized, pointing in opposite directions. Thus, ''normal'' FFR (> 0.80)

coupled with an ''abnormal'' CFR (< 2.0) has been addressed in at least one clinical study[21] and a comprehensive review.[22] The frequency of the issue has been reported as high as 30%.[21] CFR can be measured invasively at the same time as FFR with a pressure wire which incorporates either a Doppler flow velocity sensor or thermistor for thermodilution (cold saline bolus) measurement of mean transit time (MTT $\sim$ k/Q). Recalling Eq. 1 and Figure 1, it is apparent if flow across the stenosis is insufficient to generate a mean pressure drop such that mean distal pressure (Pd) declines to a level which is still greater than 80% of mean aortic pressure (Pa), then Pd/Pa will be > 0.80 (FFR ''normal''). At the same time CFR may be ''abnormal'' (< 2.0) due to some combination of diffuse distal small vessel and microvascular disease, which prevents a vigorous flow response to a primary coronary vasodilator such as adenosine or dipyridamole.[22]

The opposite condition also may arise if the flow response for example to adenosine is sufficient to lower mean distal pressure (Pd) to a level less 80% of mean aortic pressure, hence FFR < 0.8 (''abnormal'') while CFR remains ''normal'' (> 2.0) as for example with rest flow 1.0 mL/min/g and adenosine response 2.5 mL/min/g.

Considering the above, a strong argument can be made for obtaining the primary data; i.e., rest and stress absolute MBF whenever possible. Measurements of absolute volume flow in humans have been made in the catheterization lab[23] but currently are hindered by the inability to rapidly and accurately determine the size of the perfusion territory being measured. Contrast, 3D echo may provide a solution to the problem in the future.

Invasive metrics

(1) Fractional flow reserve (FFR)

As discussed above FFR currently is the ''gold standard'' for assessment of coronary stenosis severity. It is important to recognize it is sensitive to hemodynamic conditions, such as the level of mean aortic pressure (Figure 1A, B).[24,25] Further, since the ratio reflects flow across the stenosis, it is sensitive both to small vessel and true microvascular disease in the distal coronary bed and so is not necessarily a measure of stenosis severity alone. Moreover, a submaximal flow response, for any reason, to coronary vasodilator stimulus has the potential to mask the potential hemodynamic severity of the lesion, particularly once the parameter has been dichotomized into normal and abnormal categories. Finally, it has been suggested that redrawing the line at 0.67 will have greater likelihood in selecting more hemodynamically severe lesions,[26] revascularization of which will not only relieve symptoms but also improve clinical outcomes such as reduced frequency of death or myocardial infarction[26]; a hypothesis which remains to be tested.

(2) Instantaneous wave-free ratio and rest full cycle mean distal coronary pressure (Pd)/mean aortic pressure (Pa) (Figure 2)

The instantaneous wave-free ratio (iFR) was developed to facilitate objective assessment of coronary stenosis severity in the interventional setting. It relies on the assumption that coronary microvascular resistance during the pressure wave-free interval of diastole (Figure 2) will be at a minimum at rest and equal to that averaged over the entire cardiac cycle under conditions of maximal coronary dilation.[27] Accordingly, the measurement can be made under resting conditions with a pressure wire and dedicated measurement system which reports out mean pressure distal to the stenosis during the diastolic wave-free interval (Pd) along with mean aortic pressure during the same period (Pa) and the ratio Pd/Pa, known as iFR (Figure 2). A critical value, < 0.89 was determined based on reference to FFR $\leq$ 0.80.[7,27,28] However, some clinical trials and theoretical considerations indicated the 2 parameters are not interchangeable[29-31] and that values of iFR may be ± 0.17 those of FFR with greatest scatter in the 0.60 to 0.90 range.[29,31,32] Accordingly, use of the metric for clinical decision making has been discouraged by some.[29,31] However, its proponents provided further empirical data indicating iFR performed as well or better than FFR when compared to a gold standard metric, hyperemic stenosis resistance.[28,33] Subsequently, 2 large clinical trials indicated, theoretical objections notwithstanding, that iFR when employed as a guide to coronary revascularization was non-inferior to FFR with respect to clinical outcomes.[7,8] The results of the 2 trials though not universally accepted in the interventional community, nonetheless very likely will encourage more widespread adoption iFR as well as full cycle Pd/Pa.[10]

Measurement of rest full cycle Pd/Pa is very easily accomplished with modern pressure wires and has been shown to have diagnostic accuracy for stenosis severity (FFR gold standard) assessment (cut point $\leq$ 0.91) comparable to that of iFR (cut point $\leq$ 0.90).[9] There are data indicating that prediction of MACE is very similar for the 2 indices though iFR may be the more stable of the 2 and therefore marginally superior to the rest full cycle Pd/Pa.[9,10]

(3) Basal Stenosis Resistance (BSR), Hyperemic Stenosis Resistance(HSR)[33] and Index Microvascular Resistance (IMR)[34]

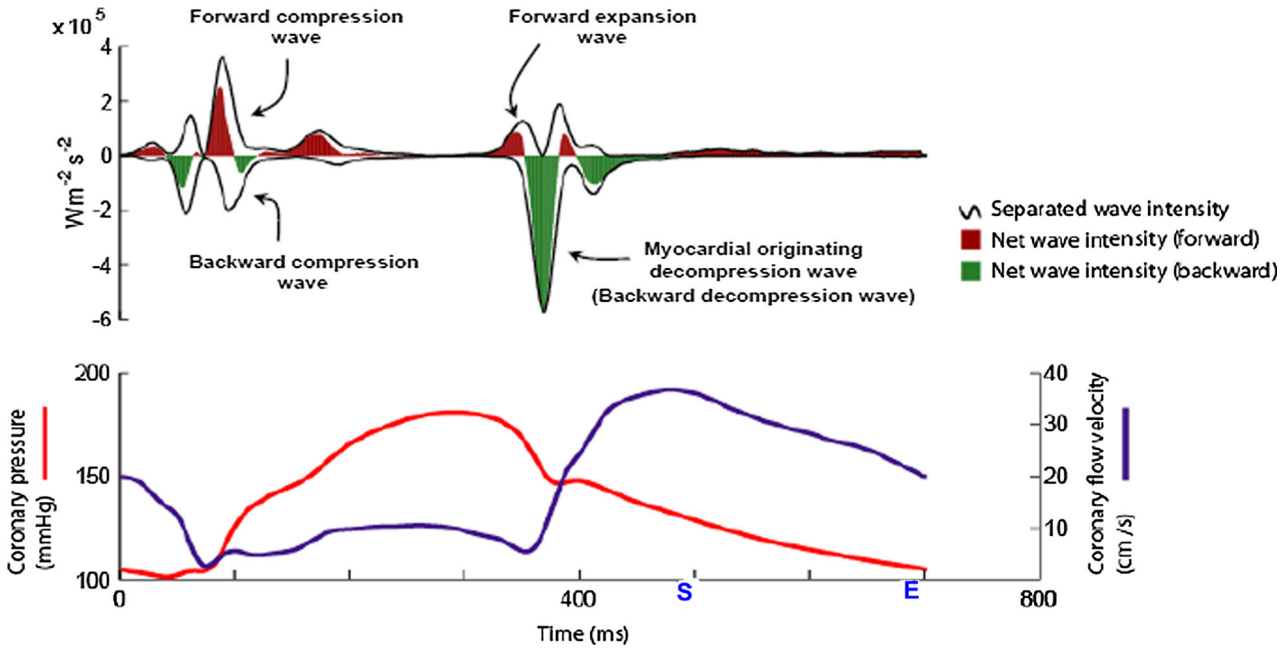


Figure 2. Instantaneous Wave-Free Ratio (iFR) Defined: The period beginning ~25% following distal coronary pressure dicrotic notch (lower panel; ''S'' on abscissa) and ending ~ 5 msec before the end of diastole (''E'' on abscissa) is defined as the wave-free interval[27]. Forward and backward wave intensity are nil during this interval (upper trace). Note coronary flow velocity (blue line) is at a maximum at the start of the interval and declines in direct proportion to decline in distal coronary pressure during the same interval (red line). Accordingly, distal coronary resistance (distal pressure/flow) is constant and at its minimum during the period. Figure 1.02 (''S'' and ''E'' added for clarity) reproduced courtesy of Sen, Sayan MBBS, PhD (from Sen, S. PhD thesis[76]).

Each of these metrics assumes a simple Ohm's Law model of resistance in the coronary circulation. Thus:

$$I = V/R,$$

where I is the current, V is the voltage, R is the resistance.

Blood flow (Q) is substituted for current, mean arterial pressure (MAP) for voltage. The equation typically is rearranged such that

$$R = \mathrm{MAP}/\mathrm{Flow}(Q).$$

Accordingly, basal stenosis resistance (BSR) is given as

$$\mathrm{BSR} = (\mathrm{Pa} - \mathrm{Pd})/Q,$$

where Q is determined by a thermistor tip pressure wire which allows simultaneous measurement of distal coronary pressure and the mean transit time (MTT) of a cold saline bolus injected proximal to the lesion. Alternatively, a Doppler flow velocity (cm/s) sensor has been employed in which case the equation is modified accordingly (see below).

MTT = k/Q, so ignoring the constant (blood volume assumed unchanged)

$$\mathrm{BSR} = (\mathrm{Pa} - \mathrm{Pd}) * \mathrm{MTT\ rest}$$
$$\mathrm{BSR} = (\mathrm{Pa} - \mathrm{Pd})/(\mathrm{cm/s})\mathrm{rest}$$

Hyperemic stenosis resistance[33] employs the same model and simply uses MTT (or flow velocity) and Pd measured under conditions of maximal coronary dilation (dil), typically with adenosine or dipyridamole.

$$\mathrm{HSR} = (\mathrm{Pa} - \mathrm{Pd}) * \mathrm{MTT\ dil}$$
$$\mathrm{HSR} = (\mathrm{Pa} - \mathrm{Pd})/(\mathrm{cm/s})\ \mathrm{dil}$$

The index of microvascular resistance (IMR) also may be computed in the same way and at the same time as BSR and HSR (i.e., at rest and under conditions of maximal coronary vasodilation).

Thus:

$$\mathrm{IMR\ rest} = \mathrm{Pd} * \mathrm{MTT\ rest}$$
$$\mathrm{IMR\ rest} = \mathrm{Pd}/(\mathrm{cm/s})\mathrm{rest}$$
$$\mathrm{IMR\ dil} = \mathrm{Pd} * \mathrm{MTT\ dil}$$
$$\mathrm{IMR\ dil} = \mathrm{Pd}/(\mathrm{cm/s})\mathrm{dil}$$

While there is a considerable body of basic research indicating that the model is an oversimplification,[35-37]

since it assumes that backpressure is zero despite abundant evidence to the contrary both at rest and under conditions of maximal coronary dilation.[35-37] Collateral input distal to a stenosis also may render the coronary occlusive pressure considerably greater than zero.[13] An empirical formula has been published to correct Pd under such conditions.[38]

The utility of any of these indices either alone or in combination for use in clinical decision making regarding coronary revascularization remains a topic of debate among interventional cardiologists, especially since large clinical trials with outcomes as endpoints are lacking. However, one small trial with end point of myocardial ischemia on SPECT imaging, demonstrated equivalence of BSR, iFR, FFR as well as Pd/Pa.[39] HSR was superior to all though the focus of the study was on investigating the value of a vasodilator-free index of stenosis severity against the clinical gold standard FFR.[39]

(4) Coronary flow reserve

While there is an abundance of data available demonstrating the prognostic utility of this parameter,[40-42] its potential limitations, especially sensitivity to the rest measurement of myocardial blood flow, has been noted by several authors.[10,43-46] Invasive measurement also requires special dual sensor pressure wire capable of recording either Doppler flow velocity or a thermistor to measure mean transit time of a cold saline bolus. The dual sensor methodology has not gained wide clinical acceptance. However, the DEFINE-FLOW clinical trial[20] (NCT02328820, clinicaltrials.gov) will employ the Doppler-equipped pressure wire to determine if coronary revascularization may safely be deferred for patients with coronary stenosis having CFR > 2 in face of FFR < 0.80.[20] Since the data would potentially be available, it would be of interest to determine the predictive value of a measurement of absolute hyperemic CBF either alone or in combination with HSR and IMR as predictors of clinical outcomes, especially death and myocardial infarction.

Non-invasive metrics

(1) PET: quantitative myocardial blood flow (MBF; rest, stress, coronary flow reserve)

PET methodology for quantitative assessment of absolute MBF remains the gold standard for non-invasive evaluation of patients with known or suspected coronary artery disease and has been reviewed extensively.[20,40,43,44,47-49] Data from several centers indicate stress (typically adenosine) MBF has superior predictive accuracy (ROC/AUC analysis) for detection of anatomically (70% Día) or functionally (FFR < 0.80) significant coronary stenosis in comparison with that either of relative retention or CFR.[45,50-52] Indeed, in 7 studies in which AUC analysis was employed to test predictive accuracy of stress MBF vs CFR for detection of hemodynamically significant CAD (FFR ≤ 0.80) stress MBF was superior in each (AUC $0.87 \pm$ vs 0.82 ± 0.07, respectively, $P < .001$).[20,45,50,53-57] Further, it is known absolute CFR, which is the metric almost exclusively employed with PET measurements of MBF, is sensitive both to heart rate and systemic arterial pressure.[58] These hemodynamic variables have greater impact on rest in comparison with stress MBF (Figure 3) and so cause greater variation CFR than that of stress MBF alone which obviously is independent of changes in rest MBF. Efforts to standardize rest MBF by normalizing it to rate pressure product either measured directly or some arbitrary common level (e.g., 9 K; assumes HR = 75 and systolic arterial pressure = 120) are conceptually fraught since (1) they fail to account for differences in myocardial contractility, (2) assume a close linear relationship between RPP as an index of myocardial oxygen demand and rest MBF when in fact considerable scatter is generally seen and 3) the notion of normalizing primary coronary vasodilator stress MBF to an index of myocardial oxygen demand (to make the numerical values comparable) makes very little physiological sense (Figure 3).

Moreover, given the relatively recent appreciation that anatomically more severe lesions are in fact more likely to be associated with cardiac death or MI than milder ones,[59,60] the superior predictive accuracy of stress MBF vs CFR for detection of such lesions indicates that the parameter may be a very useful one for identifying high-risk CAD populations which would benefit most from coronary revascularization.[26,61] It should be noted cut points for stress MBF employed for hemodynamically (typically FFR < 0.80) or anatomically ($\geq$ 70% lumen diameter reduction) significant coronary stenosis have ranged from 1.83 to 2.20 mL/min/g.[45,50-52] Computing CFR, however, does facilitate identification of coronary steal (stress MBF less than rest MBF). Steal is often associated with clinical evidence of myocardial ischemia with dipyridamole stress and thus indicates high-risk disease which likely would benefit from revascularization.[62] The ratio when computed for global MBF also appears to have prognostic information.[40-42]

A recent study introduced a new parameter, FFR_{PET} and tested it against standard PET parameters including stress MBF alone for detection of a hemodynamically significant coronary stenosis (FFR < 0.80).[20,45] FFR_{PET} is defined as the ratio of absolute stress MBF in the

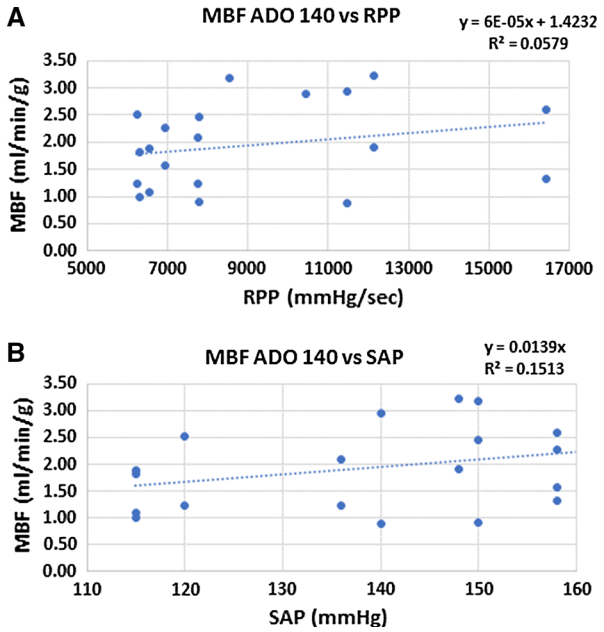


Figure 3. **A** Stress MBF (Ado 140) vs Rate Pressure Product (RPP). **B** Stress MBF (Ado 140) vs Systolic Arterial Pressure (SAP). **A** and **B** demonstrate relationship between PET (^{13}N-ammonia) measured stress MBF (IV adenosine 140 μg/kg/min × 5 min) and rate pressure product (RPP; **A**) and systolic arterial pressure (SAP; **B**) over ~ 3× range of flow. Data reflect functionally defined normal (≥ 1.82 mL/min/g with adenosine 140 dose) and abnormal (< 1.82 mL/min/g) myocardial segments ($n = 20$; 12 normal) of 11 patients with stable, chronic ischemic heart disease.[72] It is evident over the range observed (0.91-3.22 mL/min/g) that stress MBF failed to correlate either with RPP or SAP.

stenosis zone to that of a normal one. Accordingly, it is meant to mirror invasive FFR, which employs the ratio Pd/Pa of the stenotic artery to that of the same vessel in the absence of the stenosis, in which the ratio would be 1, assuming normal coronary circulation. Thus, conceptually FFR_{PET} is analogous to relative MFR since a comparison is made of flow in the target vessel to that in a normal one. Absolute MFR or stress MBF is simply the value in the target artery alone. Since FFR_{PET} requires a normal vessel for reference it cannot be computed in the presence of triple vessel disease, a limitation of the parameter. Moreover, in comparison with stress MBF alone it failed to improve upon predictive accuracy for detection of a hemodynamically significant coronary stenosis.[45] The extent to which the parameter correlates with invasive FFR also is quite variable with various studies reporting values of R^2 ranging from 0.19[45] to 0.76,[63] with the largest sample ($n = 130$ subject with 307 lesions) being 0.61[56](data per Figure 1[20]).

Finally, an effort to combine both PET CFR and absolute stress MBF into a single construct termed coronary flow capacity (CFC) has been proposed to assess the physiological status of the coronary circulation in the setting of coronary artery disease.[48,64] Briefly, an *x*, *y* plot of pixel values of CFR (*y*) vs stress MBF (*x*) is produced and projected on a fixed background of color-coded, adjacent, rectilinear zones of varying size and shape, each of which is categorized along a spectrum from ''normal flow'' to ''predominately transmural scar'' with various shapes and sizes of impaired CFC in between (e.g., ''no ischemia, minimally reduced'' to ''definite ischemia'' and ''myocardial steal''; see Figure 1 of Ref #64). While the construct may be helpful for straightforward data points, basically concordant stress MBF (cut point 0.91 mL/min/g) and CFR (cut point 1.74×),[62] simple inspection of the zones indicates it is possible to have, for instance, stress MBF < 0.91 (''definite ischemia'') paired with CFR ≥2.0X (''no ischemia'' with anywhere from ''mildly reduced CFC'' to ''normal'' CFR). It is unclear how stress MBF < 0.91, almost invariably associated with ischemia (AUC 0.98),[62] is compatible with a favorable prognosis and ''no ischemia'' simply because it's corresponding rest MBF = 0.45 mL/min/g (CFR 2.0×). A similar dilemma exists for stress MBF ~ 2.5 mL/min/g (''normal flow'') associated with rest MBF 1.5 mL/min/g (CFR 1.67X; ''definite ischemia'', AUC 0.91).[62] A standard linear x, y plot reflects an ''AND'' condition and so logically is unable to accommodate, against a fixed, background, categorical map, data pairs (stress MBF, CFR) which contradict one another vis-à-vis the category of the map upon which they fall. Accordingly, caution is indicated in using the CFC maps without reference to the ''raw'' CFR vs stress MBF plots.

(2) Computed Coronary Tomographic Angiography (CCTA) and Cardiac Magnetic Resonance (CMR)

A detailed analysis of the technology and mathematical modeling employed both by CCTA and CMR to measure absolute MBF (CCTA and CMR) and FFR (CCTA and FFR_{CT}) is beyond the scope of this review. Both imaging modalities have been employed to obtain quantitative measurements of absolute MBF.[65-67] At least 2 have been validated against microsphere measurements of MBF in animal lab studies.[66,67] However, further refinements of methodology, data acquisition, and analysis will be required before widespread clinical application can occur.

Nevertheless, the excellent spatial resolution of CMR has been taken advantage of to obtain endocardial and epicardial quantitative measurements of MBF[66] and

thereby apply a very important physiological parameter, the endocardial:epicardial MBF ratio, to the non-invasive assessment of the human coronary circulation. In a small study it was shown under conditions of dipyridamole stress that decline in the ratio to < 0.50 (primarily because of decline vs rest in endocardial flow) had excellent predictive accuracy for detection of anatomical coronary stenosis $\geq$ 70% (AUC 0.92).[66] The same study demonstrated that transmural stress MBF cut point 1.58 mL/min/g also performed well (AUC 0.77). Further, in true positive segments, stress MBF was 1.73 ± 0.71 mL/min/g vs 2.99 ± 0.59 in normal segments ($P < .001$).[66] The transmural mean for abnormal segments matches very closely that of previously reported PET measurements[50,51] though the optimal cut point is somewhat lower and very likely reflects methodological differences. Nevertheless, the ability to make endocardial:epicardial measurements of absolute MBF adds an important dimension to the methodology.

In contrast to CMR, FFRCT has advanced more rapidly with respect to widespread clinical application. The measurement is obtained from routine CCTA and does not require vasodilator stress since flows are computed based on individual coronary anatomy and advanced mathematical modeling.[68] Correlation with invasive FFR over many studies has been very good[3,68,69] and the approach was sufficiently cost effective[69] to persuade National Health Service (UK) to adopt CCTA with FFRCT as the preferred initial study in patients with stable typical or atypical angina who are being evaluated for suspected CAD (NICE chest pain algorithm; http://pathways.nice.org.uk/pathways/chest-pain). A disadvantage of the metric, in addition to those of invasive FFR noted above, is the fact, presently, that data must be uploaded to a private company (HeartFlow™, Redwood City, CA) for analysis with turnaround time of 48 hours. The methodology also has not been approved for use in patients with ACS and given 48 hours turnaround time, in any case would not be useful in this setting.

SUMMARY/CONCLUSIONS

Since its introduction into clinical practice in mid '90s,[63] FFR has become the gold standard invasive measurement for physiological assessment of the hemodynamic severity of coronary stenosis. Accordingly, it is important to reiterate what the measurement reflects and what purpose it attempts to achieve. In a word, it is to provide an estimate of the maximal flow in a coronary vessel as a fraction of which could be obtained if the vessel was normal. Under conditions of maximal coronary vasodilation in a canine model with normal coronary circulation, the ratio Pd/Pa was shown to reflect very closely the ratio of flow in the presence of a given stenosis severity to flow in the same vessel in the absence of the stenosis.[19]

The pressure ratio was (is) attractive since it can be used in real time in the catheterization laboratory to guide revascularization decision making and presently is supported by many studies demonstrating improved clinical outcomes when revascularization decisions are guided by it.[4-6,70] It functions as a practical, real-time method to measure the parameter of clinical and physiological interest, namely maximal myocardial blood flow (mL/min/g). Moreover, the advantage of the method (FFR) over CFR, namely the susceptibility of the latter to changes in the level of rest flow was recognized at the time of its initial laboratory report.[19] FFR, considered relative flow reserve, expresses coronary flow as a fraction of maximal flow in a normal vessel. In contrast, CFR of a given vessel reflects absolute flow reserve since it expresses coronary flow as a multiple of resting flow measured in that vessel.

While it is true that methods currently are available for measuring both coronary flow velocity and volumetric flow, they are limited by the fact that they cannot provide absolute MBF in mL/min/g. The volumetric method provides mL/min but the size of the perfusion bed, critical to interpreting the measurement at the myocardial level, is left undetermined absent an independent measurement technique (e.g., echo, CCTA, CMR).

The introduction of iFR as an alternative to FFR is based on the notion that coronary resistance in the CAD setting is minimal at rest during the wave-free interval of diastole and so will provide physiological information equivalent to that of FFR without the inconvenience and potential adverse effects of adenosine or dipyridamole. Notwithstanding the fact that the assumption is demonstrably untrue,[31] iFR has been shown to be non-inferior to FFR re: clinical outcomes, in guiding coronary revascularization.[7,8] Like FFR, it too represents an effort to do what is practical in real time in the catheterization laboratory, namely, to estimate maximal myocardial blood flow. The rest, whole-cycle Pd/Pa ratio, largely equivalent to iFR, attempts the same and with greatly improved technology reprises original work (1986) by Gruentzig and co-workers.[71]

PET presently is the gold standard for measurement of absolute MBF, rest, and stress. Accordingly, it can obtain the key parameter of clinical and physiological interest for assessment of the status of hemodynamic severity of coronary stenosis, namely maximal myocardial blood flow. The measurement, like any other, however, is not without its limitations. At maximal coronary dilatation, arterial pressure and heart rate potentially may influence stress MBF principally due to

hydraulic considerations. However, over a range encountered in a clinical study there was no correlation between stress MBF (IV adenosine 140 μg/kg/min × 5 minutes) and either RPP or SAP (Figure 3A, B; respectively).[72] Diffuse small vessel or microvascular disease or both may render maximal MBF relatively reduced either with no or only mild/moderate anatomical stenosis.[22] Accordingly, there will be occasions when invasive coronary arteriography or CCTA correlations will be required. In such cases FFR may be ''normal'' (i.e., > 0.80) which would then suggest that relatively reduced maximal MBF reflects more diffuse small vessel/microvascular disease.[22] CFR if measured would be expected to be abnormal ($< 2.0\times$),[22] especially in face of relatively reduced or normal rest MBF ($\sim$ 0.5 to 1.0 mL/min/g). Finally, in progress DEFINE-FLOW trial (NCT02328820, clinicaltrials.gov) seeks to determine if revascularization may safely be deferred in the face of FFR < 0.80 but CFR > 2.0 (combined Doppler flow velocity, pressure wire),[20] which may be thought of as an effort to employ CFR (that which can be easily measured in the invasive setting) for maximal MBF (that which cannot, mL/min/g) and may be better understood with reference to Eq. 1 and Figure 1A, B.

Disclosure

H. Gewirtz has nothing to disclose.

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