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INTERVENTIONAL CARDIOLOGY

Fractional flow reserve and beyond

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In stable coronary artery disease, clinical decision making regarding percutaneous coronary intervention (PCI) of coronary artery stenoses is optimally based upon an evaluation of the functional severity of the coronary lesion.[1 2] As such, intracoronary (IC) physiology has emerged as a standard diagnostic modality in the contemporary armamentarium of the interventional cardiologist during cardiac catheterisation.[3] Direct assessment of IC haemodynamics distal to a coronary lesion, by means of sensor equipped guide wires, provides a unique opportunity to determine the physiological impact of a coronary stenosis before coronary intervention.[4] Physiological assessment of coronary lesion severity is notably more accurate to evaluate the functional severity of a lesion compared with visual assessment on angiographic images.[5 w1–w3] Consequently, physiologically guided PCI improves patient outcomes with respect to relief of anginal complaints and the necessity for (repeat) revascularisation.[2 6 7 w4–w6] Moreover, it is cost effective when compared with angiography guided PCI.[8]

Several parameters of functional coronary lesion severity have been introduced that provide an easily interpretable summary of information from the recorded IC pressure or Doppler flow velocity signal, facilitating the interpretation of IC physiology in the catheterisation laboratory.[3] These parameters have been validated against non-invasive stress testing for the presence of inducible myocardial ischaemia, and have yielded clinically useful cut-off values to guide revascularisation.[3 5 9] Although facilitating their practical ease, the use of strict cut-off values circumvents the necessity for understanding the underlying basic physiological concepts. As these concepts are important to bear in mind when interpreting the results derived from IC measurements, we present a comprehensive summary of IC physiological concepts, and the way they pertain to daily clinical practice.

THE DICHOTOMY OF PRESSURE AND FLOW IN CORONARY ARTERIES

At a constant myocardial oxygen demand level, coronary flow is relatively independent of perfusion pressure—a feature referred to as coronary autoregulation.[w7 w8] The larger epicardial arteries conduct the perfusion pressure without significant pressure loss, but perfusion pressure starts to decline rapidly within vessels <400 μm in diameter —the coronary resistance vessels.[4] Within a physiological range of pressures, dilation and constriction of the distal coronary resistance vessels can accommodate substantial changes in arterial pressure, resulting in a constant blood flow to the distal myocardial microvasculature. An increase in myocardial oxygen demand—for example, in exercise—results in compensatory vasodilation of the coronary resistance vessels, allowing an increase in coronary flow to the distal myocardium at a similar perfusion pressure (figure 1), a mechanism referred to as metabolic adaptation.

The coronary pressure–flow relationship is altered in the presence of a flow limiting coronary stenosis, as a perfusion pressure loss over the stenosis results in compensatory dilation of the resistance vessels to achieve a similar blood flow supply to the subtended myocardium (figure 2).[4] Although the corresponding curve during autoregulation reaches a similar blood flow level plateau, the vasodilator reserve of the coronary artery is partly exhausted during resting conditions. Progression of the epicardial disease results in progressive exhaustion of the vasodilator reserve, which may eventually result in reduced oxygen supply and angina pectoris.

In the assessment of functional coronary lesion severity, coronary autoregulation is counteracted by the use of a potent vasodilator, aiming at complete vasodilation of the coronary vascular bed, and inducing hyperaemia. During hyperaemia, the relationship between coronary pressure and flow tends more towards linearity, although it does not pass through the origin and has a slightly concave course (figure 1).[10] The functional coronary lesion severity is assessed during hyperaemia either by evaluating the reserve capacity of the coronary vascular bed (from resting conditions to hyperaemia), by evaluating the maximally achievable blood flow in relation to an estimated maximal flow that could have been achieved in the absence of the stenosis, or by directly calculating the resistance of the stenosis. These concepts will be discussed in more detail below.

THE PRESSURE GRADIENT–FLOW VELOCITY RELATIONSHIP

The haemodynamic influence of a coronary stenosis is best described by its coronary pressure gradient–flow velocity (ΔP-v) relationship (figure 3), which describes the incremental pressure gradient over the stenosis with increasing coronary flow, and is unique for each stenosis geometry.[4 11 w9 w10] As shown in figure 2, the ΔP-v curve is linear in the absence of a stenosis. In the presence of a stenosis, the ΔP-v curve is curvilinear. This originates from the fact that the pressure gradient across a stenosis results from the sum of linear viscous pressure losses due to friction (law of Poiseuille), and non-linear inertial pressure losses incurred at the exit of the stenosis (law of Bernoulli) that increase with the square of flow (figure 4A). The flow limiting

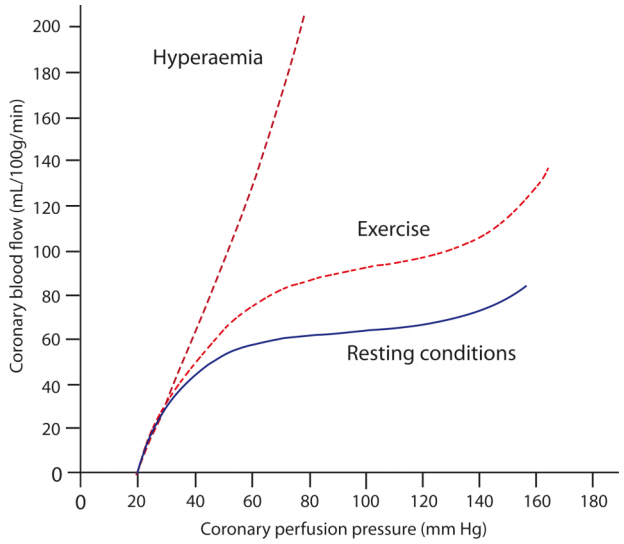

Figure 1 Coronary pressure–flow relationship. At a constant myocardial oxygen consumption level, coronary flow is autoregulated: coronary blood flow is constant within a physiological range of perfusion pressures (Resting conditions). An increase in myocardial oxygen demand results in an increase in the autoregulatory plateau, termed metabolic adaptation (Exercise). During hyperaemia, the relationship between coronary pressure and flow tends towards a linear relationship although it does not pass through the origin, and has a slightly concave course (Hyperaemia).

characteristics of a stenosis are mainly determined by the law of Bernoulli. Therefore, in the absence of a stenosis, the ΔP-v relationship is based on the linear viscous losses only, whereas a stenosis introduces the non-linear exit losses, resulting in a curvilinear relationship between the pressure gradient and flow velocity. Moreover, pressure loss over a normal epicardial segment is negligible, and therefore does not change significantly with increasing flow velocity (figure 3; reference vessel). With increasing stenosis severity (figure 3; increasing stenosis severity from stenosis A to C), the ΔP-v curve becomes steeper, reflecting a higher perfusion pressure loss over the stenosis. The ΔP-v curve therefore uniquely reflects the haemodynamic influence of a specific coronary stenosis geometry.[4]

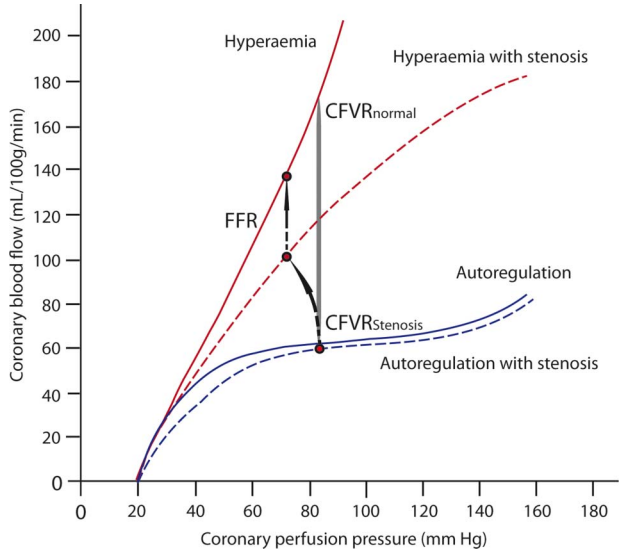

Figure 2 Coronary pressure–flow relationship in the presence of a stenosis. In the presence of a stenosis, the perfusion pressure loss over the stenosis results in compensatory vasodilation; although the corresponding curve during autoregulation reaches a similar plateau, the vasodilator reserve of the coronary artery is partly exhausted during resting conditions. This results in a limited coronary flow velocity reserve (CFVR) which is defined as the ratio of hyperaemic to basal distal flow velocity. Fractional flow reserve (FFR), defined as the ratio of mean distal coronary pressure to mean aortic pressure during maximal hyperaemia, can be used to estimate the amount of blood flow in relation to what would have been possible in the absence of the stenosis.

Coronary flow velocity reserve

Initially, technical limitations prohibited the direct construction of ΔP-v curves, as only pressure or flow velocity could be measured during cardiac catheterisation. To facilitate the interpretation of IC physiology in the cardiac catheterisation laboratory, several parameters have been proposed to estimate the haemodynamic significance of a stenosis from measurement of either coronary blood flow velocity or coronary perfusion pressure.[3]

The coronary flow velocity reserve (CFVR) is defined as the ratio of mean distal coronary peak flow velocity during maximal hyperaemia to mean peak flow velocity at rest at the same perfusion pressure (figure 4).[w10–w13] This parameter was the first to translate into daily clinical practice, and has been used to guide PCI for numerous years. However, CFVR is influenced to a large extent by variations in physiological conditions that alter baseline or hyperaemic flow velocity. Highly variable parameters such as heart rate and cardiac workload, in addition to gender and age, importantly influence CFVR.[12 w14] Furthermore, from a practical point of view, measurement of an accurate Doppler flow velocity signal is more difficult than measurement of an accurate IC pressure signal. The introduction of IC pressure derived parameters of physiological stenosis severity has therefore resulted in a wider adoption of this technique in clinical practice compared with Doppler flow velocity measurements.

FRACTIONAL FLOW RESERVE, OR BEYOND?

When coronary autoregulation is abolished, the relationship between coronary pressure and flow may be oversimplified to a linear relationship, and coronary pressure may then theoretically be assumed to be proportional to coronary flow. Based on this assumption, coronary pressure might then be measured as an estimate of coronary flow. From this approach, the concept of (myocardial) fractional flow reserve (FFR) was introduced,[13] defined as the ratio of mean distal coronary pressure to mean aortic pressure during maximal hyperaemia, and estimating the ratio of hyperaemic coronary flow in the presence of a stenosis to the coronary flow that could have been established in the absence of a stenosis (figures 3 and 4).[w15] Notwithstanding the clinical value of FFR,[2 6 w15 w16] it is important to acknowledge the assumptions that underlie its concept.[14]

First, within the theoretical framework of FFR, the relationship between coronary pressure and

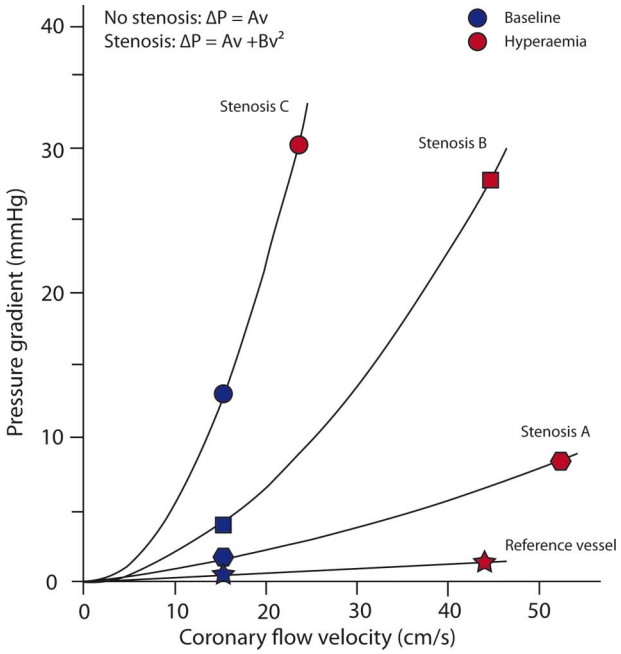

Figure 3 Pressure gradient–flow velocity relationship. Pressure loss over a normal epicardial segment is negligible, and therefore does not change significantly with increasing flow velocity (Reference vessel). With increasing stenosis severity (increasing stenosis severity from stenosis A to C), the pressure gradient–flow velocity (ΔP-v) curve becomes steeper, reflecting a higher perfusion pressure loss over the stenosis with increasing flow velocity.

flow is assumed to be proportionally linear when autoregulation is abolished; the hyperaemic pressure–flow relationship would then be straight and pass through the origin, which it does not as shown in figure 1; it has a slightly concave course and does not have a zero flow–zero pressure intercept.[4 10 14] The effects of cardiac contraction are not taken into consideration in the concept of FFR, which in fact is an important determinant of the relationship between coronary pressure and flow, as it has a direct influence on minimal microvascular resistance (MR).[14] This may pertain to daily clinical practice—for example, in the setting of left ventricular dysfunction, in which the properties of the contracting myocardium are altered, altering minimal MR, and resulting in an altered relationship between coronary pressure and flow to an unknown extent during measurement of IC haemodynamic variables. Even more pertinent is the effect of heart rate, because myocardial contraction is influenced by its frequency, and therefore is importantly interrelated with coronary pressure and flow.[14]

Second, the concept of FFR assumes a stable and minimal MR during maximal hyperaemia. However, in the absence of coronary narrowings, there is already a wide variation in MR between patients and even between adjacent perfusion territories.[15 w17–w20] On top of this biological variability, several other factors may add to variability in MR, and because alterations in MR have a direct impact on distal coronary pressure and vice versa, they have a direct impact on FFR values.[15 w17 w21] When MR is increased in the presence of diffuse coronary artery disease, distal coronary pressure will be higher, which leads to a higher FFR value,

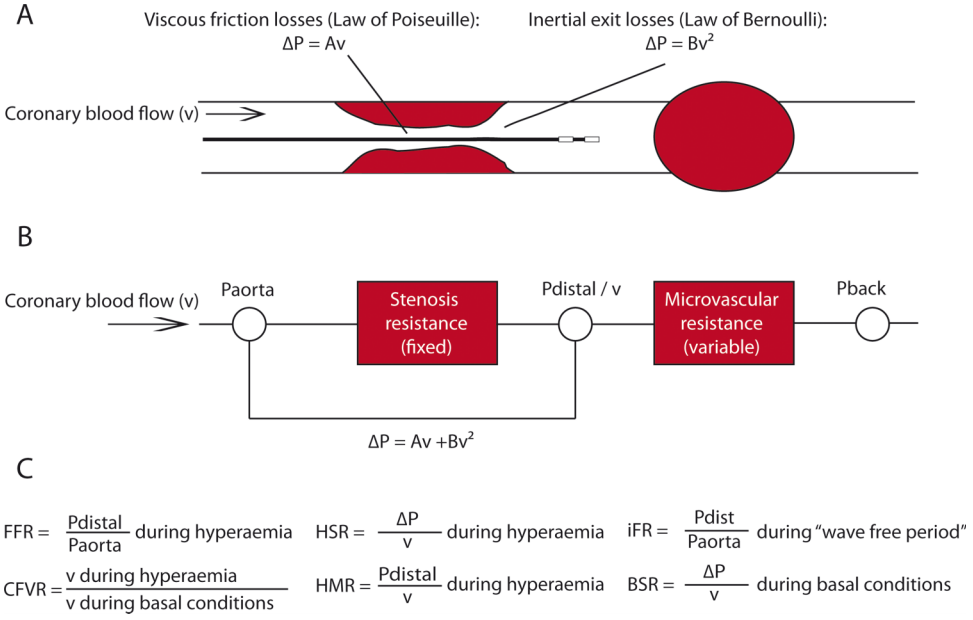

Figure 4 Resistance model of the coronary circulation and derived parameters. (A and B) Stenosis resistance model. The pressure gradient across a stenosis is determined by the sum of the stenosis' friction and exit losses. Friction losses are linearly related to the flow through the stenosis, whereas exit losses increase with the square of flow, resulting in a unique relation between pressure gradient and flow velocity for a given stenosis geometry. Measurement of intracoronary (IC) haemodynamics includes proximal perfusion pressure (Paorta), coronary pressure and flow velocity distal of the stenosis (Pdistal and v respectively), and the venous back pressure (Pback) that is usually assumed to be minimal. (C) Parameters derived from IC measurement of pressure and flow velocity. BSR, baseline stenosis resistance index; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; HMR; hyperaemic microvascular resistance; HSR, hyperaemic stenosis resistance; iFR, instantaneous wave-free ratio; Paorta, aortic pressure; Pdistal, distal coronary pressure; v, flow velocity; ΔP: pressure gradient.

independent of the stenosis severity. Notably, increasing doses of potent IC vasodilator, resulting in progressive vasodilation and lower MR, were shown to result in lower FFR values.[16] This finding uniquely illustrates the dependency of FFR on MR. Furthermore, coronary resistance vessels are not rigid tubes; an increase in distal perfusion pressure, for example, after PCI of an epicardial stenosis, results in a decrease in MR due to pressure distensibility of the coronary resistance vessels.[w17 w22] Therefore, MR also depends on perfusion pressure, which is not accounted for within the concept of FFR.[4 14 w22] Variability in MR, although obviously influencing FFR values to an unknown extent, are not identified when coronary pressure is the only IC haemodynamic parameter measured, but may influence clinical decision making by the use of a predefined cut-off value, as is current routine clinical practice (figure 5).[1 3]

Finally, FFR is considered to be independent of alterations in systemic haemodynamics—for example, variability in blood pressure and heart rate. This is in contradiction with the experimental physiological literature,[w23] and is another factor that must be taken into consideration when FFR is used to guide coronary intervention—especially if a potent vasodilator is administered intravenously, as its systemic vasodilator effects may alter the patient's haemodynamics.[17]

With all the assumptions that underlie its concept and the associated limitations taken into consideration, FFR has repeatedly shown to bear significant clinical benefit in daily practice;[2 6 18] evidence of this clinical benefit has accumulated in a wide variety of clinical settings, including multivessel coronary artery disease and left main coronary artery stenosis.[18] Although the use of FFR therefore unequivocally improves clinical outcome compared with angiography guided revascularisation, it may be appreciated that, considering the aforementioned limitations, optimalisation of physiologically guided revascularisation may well be possible by looking beyond FFR.

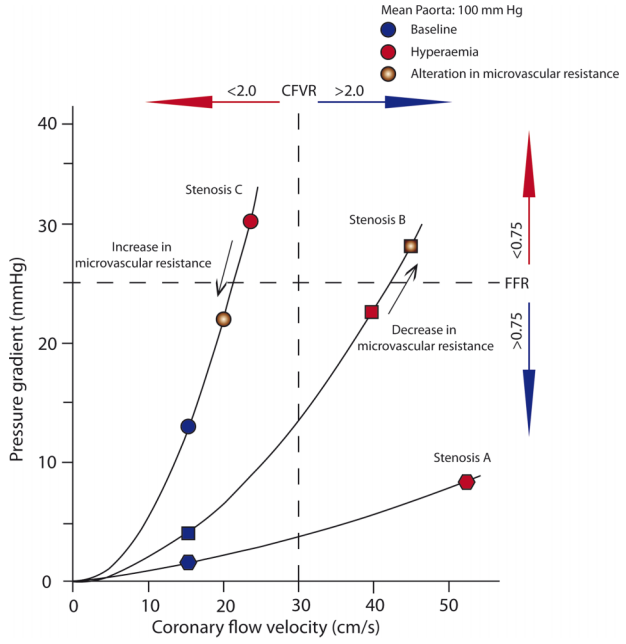

Figure 5 Pressure gradient flow velocity relationship and microvascular resistance (MR). Based on the clinically adopted cut-off values, the pressure gradient–flow velocity curve can be divided into four quadrants. Because the position along the ΔP-v curve where the measurement takes place is determined by the flow through the stenosis, which is in turn determined by MR, alterations in MR may influence the actual outcome of these measurements, and may thus influence treatment decisions. CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; Paorta, aortic pressure.

CFVR AND FFR: FRIENDS OR FOES?

Both FFR and CFVR have been extensively validated against non-invasive stress testing to evaluate their threshold for inducible myocardial ischaemia.[3] Cut-off values of <0.75 and <2.0 to indicate inducible myocardial ischaemia were established for FFR and CFVR, respectively, and diagnostic accuracy provided with these cut-off values is approximately 80% for both parameters.[5] As both parameters estimate the relative vasodilator reserve of the coronary artery of interest, and an equally high diagnostic accuracy was found for FFR and CFVR, agreement between these parameters would be expected when the same coronary stenosis is evaluated. However, in 30% of cases, FFR and CFVR were found to show discordant results that related to the previously discussed variability in distal MR (figure 6).[15 w6] Overall, this variability in MR determines the relative relationship between FFR and CFVR, and as such their accordance and discordance. This reflects important basic coronary pathophysiology that should be taken into consideration in daily clinical practice.[w24]

COMBINING IC PRESSURE AND FLOW VELOCITY

From a conceptual point of view it may be appreciated that the ΔP-v plot can be divided into quadrants based on the accepted clinical cut-off values as shown in figure 5. The ΔP-v curve, unique for each coronary stenosis, specifically indicates the physiological severity of the stenosis, but is difficult to translate into a clinical decision making tool. Clinical decisions are usually taken based on the FFR value only, allocating the lesion to PCI when the measurement falls into the top two quadrants. However, it may be appreciated that a single coronary lesion can fall into a different quadrant based upon how far along the ΔP-v curve the actual measurement takes place, directly influencing treatment allocation independent of stenosis severity.[9] This is importantly determined by the flow through the stenosis, which is in turn determined by the MR distal to the site of measurement, as depicted in figure 5.[4] An increase in MR due to microvascular disease or submaximal hyperaemia will be reflected in an increase in distal coronary pressure, and thus in an increase in FFR, while the hampered flow through the stenosis will result in a decrease in CFVR, and vice versa.

Combining simultaneous pressure and flow velocity information, by means of a dual sensor equipped guide wire,[w25] raises the possibility of

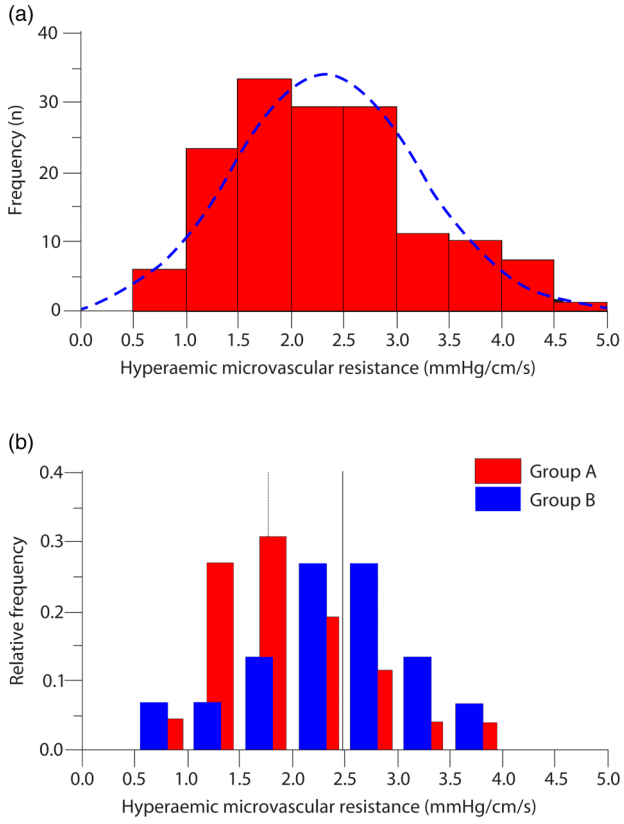

Figure 6 Frequency distribution of hyperaemic microvascular resistance (MR) in target vessels. (A) MR in target vessels (n=150) shows a Gaussian distribution. The same Gaussian distribution was found in myocardium subtended by normal coronary arteries[w18]. (B) The distribution of MR was found to differ between the two groups of discordant results between fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) (group A: CFVR ≥2.0, FFR <0.75; group B: CFVR <2.0, FFR ≥0.75). Data redrawn from Meuwissen *et* al.[15]

evaluating the relative contribution of stenosis and MRs as visualised in figure 4B.[9 15 w26] From the simultaneous measurement of IC pressure and flow velocity, the MR distal to the site of measurement is defined as the ratio between distal coronary pressure and flow velocity (figure 4B).[15] The hyperaemic stenosis resistance index (HSR), defined as the ratio between the pressure drop across the stenosis and distal peak flow velocity during maximal hyperaemia (figure 4),[9] was shown to result in a significantly higher diagnostic accuracy for myocardial ischaemia as compared to FFR or CFVR.[9 19] By definition, HSR is also determined during maximal hyperaemia. However, as the pressure gradient across a stenosis and distal flow velocity change in the same direction in the case of submaximal hyperaemia or an increase in MR, this has a limited effect on HSR. HSR may therefore be considered a more stenosis specific parameter. The major concern regarding HSR, and its adoption in daily clinical practice, remains that IC Doppler flow velocity measurements are more technically challenging than IC pressure measurements. Furthermore, despite its conceptual advantages and superior diagnostic performance,[9] no direct evidence for a clinical benefit of HSR guided revascularisation is available. In addition, no data are available on its validity in specific patient subsets, such as left main coronary stenosis.

MAXIMAL HYPERAEMIA

All three currently available parameters for functional lesion severity assessment per definition depend on the achievement of a maximal hyperaemic state, although HSR to a lesser extent. Hyperaemia is induced by the administration of a potent vasodilator,[5] most frequently adenosine, by either intravenous or IC administration. However, a continuous debate is ongoing with respect to which administration route is preferable, and which dose of adenosine is needed to achieve 'true' maximal hyperaemia. The Holy Grail of 'true' maximal hyperaemia is pursued because of its elementary importance within the concept of FFR,[13] as well as the direct influence of submaximal hyperaemia on CFVR values.[12] While adenosine was administered IC in dosages of 16–20 μg in the early days of physiologically guided PCI, recent reports show that increasing doses of IC adenosine of up to 720 μg result in significantly lower FFR values.[16] Intravenous administration of adenosine is considered more cumbersome, as it requires a continuous infusion, takes several minutes to obtain stable hyperaemia, is more frequently associated with side effects, and is associated with a decrease in blood pressure which may itself influence FFR.[w23] Nonetheless, intravenous administration is considered by some to be the only method to ensure 'true' maximal hyperaemia. However, extensive reports show equality between intravenous and IC adenosine[20 w27 w28] in terms of FFR values, and, moreover, an additional bolus of IC adenosine was shown to decrease FFR further, even during stable hyperaemia induced by intravenous adenosine.[w29] Therefore, it may be acknowledged that true maximal hyperaemia, indicating complete abolishment of coronary vascular tone, may not be achieved regardless of the adenosine dose or administration route used. This is likely, as it is well-known that adenosine is not the only mediator of coronary vascular tone. It is important to realise that early validation studies of FFR and CFVR have been performed using either low dose IC adenosine (40 μg maximum), or intravenous adenosine (140 μg/kg/min) to validate FFR against myocardial ischaemia assessed by non-invasive imaging modalities.[5] The cut-off value derived from these validation studies, 0.75, therefore has an established relationship with myocardial ischaemia, and both may be used to determine the presence of objective myocardial ischaemia that can be related to the coronary lesion of interest.

In summary, based on the FFR validation studies, we currently advise the use of either low dose (40 μg) IC adenosine bolus, or routine dose (140 μg/kg/min) intravenous adenosine to determine FFR. A cut-off value of 0.80 has been repeatedly shown to provide a significant clinical benefit, and, based upon our current knowledge, this cut-off value should be adopted in daily clinical practice.[1 2 6]

Fractional flow reserve and beyond: key points

Pressure and flow in coronary arteries

- Under normal conditions, coronary blood flow is constant within a physiological range of perfusion pressures: coronary autoregulation.
- The autoregulation plateau is determined by myocardial oxygen demand, a mechanism termed metabolic adaptation.
- Coronary autoregulation can be abolished by administration of a potent vasodilator, inducing hyperaemia.
- During hyperaemia, coronary blood flow depends on perfusion pressure, although the relationship is not strictly linear.

Pressure gradient–flow velocity relationship

- A coronary artery stenosis is uniquely described by its pressure gradient–flow velocity relationship.
- Pressure gradient is determined by the sum of linear friction losses and non-linear exit losses.
- The relationship between pressure gradient and flow velocity in reference vessels is determined by the linear friction losses, and therefore has a linear course. A stenosis introduces the non-linear exit losses and results in a curvilinear relationship, with increasing steepness of the curve with increasing stenosis severity.

Coronary flow velocity reserve and fractional flow reserve

- Several parameters have been introduced to guide percutaneous coronary intervention by estimation of the coronary lesion significance from intracoronary (IC) blood flow or pressure measurement.
- Coronary flow velocity reserve (CFVR) is defined as the ratio between hyperaemic to baseline flow velocity.
- Fractional flow reserve (FFR) is defined as the ratio of hyperaemic distal coronary pressure to hyperaemic aortic pressure.
- FFR and CFVR are complementary parameters, and may be discordant in evaluation of the same coronary lesion due to the relative contribution of focal and small vessel disease.

Intracoronary pressure and flow velocity

- Combining both pressure and flow velocity information allows construction of pressure gradient flow velocity curves (ΔP-v).
- The position on the ΔP-v curve where the measurement takes place is determined by microvascular resistance (MR).
- Depending on the MR at the time of measurement, the coronary lesion may be allocated to a different treatment strategy.
- The hyperaemic stenosis resistance index is defined is the ratio of the pressure gradient across the stenosis to distal flow velocity, and is a more stenosis specific parameter.

Maximal hyperaemia

- Maximal hyperaemia is crucial in the evaluation of IC parameters, because of its influence on MR.
- Maximal hyperaemia is difficult to achieve, as currently adopted potent vasodilators have been shown to be unable to achieve such a state.
- Recent reports have evaluated the use of parameters independent of hyperaemia that may overcome the issues with vasodilators.

VASODILATION-FREE FUNCTIONAL LESION SEVERITY ASSESSMENT

In response to the important ambiguities in the use of adenosine, which is considered an important limitation in the adoption of physiologically guided PCI in daily clinical practice,[w30 w31] recent interest has re-focused on the development of parameters that estimate the functional severity of a stenosis without the crucial need for potent vasodilators. This approach is of high interest, as it may circumvent the debate on adenosine if these parameters prove to be as diagnostically accurate, and as prognostically relevant, as hyperaemic parameters. Recently the instantaneous wave-free ratio (iFR) was introduced.[21] This parameter was determined as the distal coronary to aortic pressure ratio during a specific time window in mid diastole—the 'wave-free period'—where MR was found to equal MR during adenosine induced hyperaemia (figure 4). As this is the most important assumption underlying FFR, the concept of iFR is similar to that of FFR, and iFR by definition shares FFR's limitations. Furthermore, the assumption that MR during mid diastole in resting conditions equals hyperaemic microvascular resistance contradicts abundant experimental physiological literature. Nonetheless, initial clinical reports have provided favourable results,[21 w32] indicating a possible practical value of this novel parameter in daily clinical practice that should be investigated further.

Subsequently, the stenosis resistance index during baseline conditions—baseline stenosis resistance index (BSR)—was introduced,[19] a concept based on the limited influence of submaximal hyperaemia on HSR. Defined as the ratio of the pressure gradient across the stenosis to the distal flow velocity during baseline conditions (figure 4), this vasodilator-free parameter of functional stenosis severity was shown to provide a diagnostic accuracy for inducible myocardial ischaemia on non-invasive stress testing equal to FFR or CFVR. However, together with iFR, BSR is in need of further validation before its clinical adoption may be advocated.

Overall, the pursuance of these novel vasodilator-free approaches to functional lesion severity assessment must be considered an important progress in clinical IC physiology. As physiologically guided revascularisation results in an improvement of clinical outcome, and was shown to be cost effective, any increase in adoption of IC physiology in daily interventional practice facilitated by such a parameter must be considered important progress. However, these parameters must be evaluated rigorously to determine their true diagnostic accuracy, and prevent the possibility that an improvement in adoption goes hand in hand with a fall in accuracy. At this moment in time, evidence on diagnostic accuracy of these novel parameters is encouraging, but limited. Most importantly, a clinical benefit, as has been unequivocally shown during more than a decade of research on FFR, has not been evaluated for either iFR or BSR, which ultimately is the gold standard that should guide their adoption or abandonment.

CONCLUSIONS

The importance of physiologically guided revascularisation in contemporary interventional practice notwithstanding, simplification of coronary physiology to facilitate ease of interpretation comes at the cost of accuracy by discarding relevant haemodynamic information. Complete evaluation of the physiological importance of a stenosis involves a combination of pressure and flow (velocity)

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information. This combination of information forms the backbone of functional lesion severity evaluation: the pressure gradient–flow velocity relationship. This backbone may be summarised by a single parameter, but its origin, and the assumptions and limitations associated with its simplification, must be borne in mind. Assessment of coronary lesion severity goes beyond FFR.

Contributors TPH: drafting of the manuscript, final approval. MM: critical revision, final approval. JJP: critical revision, final approval.

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REFERENCES

1 Wijns W, Kolh P, Danchin N, *et al*. Guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardiothoracic Surgery (EACTS). *Eur Heart J* 2010;31:2501–55.
- Current guidelines on myocardial revascularisation.

2 De Bruyne B, Pijls NH, Kalesan B, *et al*. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991–1001.
- Study showing superiority of physiologically guided revascularisation for clinical outcome compared with medical treatment.

3 Kern MJ, Lerman A, Bech JW, *et al*. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation* 2006;114:1321–41.
- Review of physiological stenosis assessment in daily clinical practice.

4 van de Hoef TP, Nolte F, Rolandi MC, *et al*. Coronary pressure-flow relations as basis for the understanding of coronary physiology. *J Mol Cell Cardiol* 2012;52:786–93.
- Contemporary review on the physiological basis of clinically used parameters of functional lesion severity.

5 Meuwissen M, Siebes M, Chamuleau SAJ, *et al*. Role of fractional and coronary flow reserve in clinical decision making in intermediate coronary lesions. *Interv Cardiol* 2009;1:237–55.

6 Tonino PA, De Bruyne B, Pijls NH, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–24.

7 Pijls NH, van Schaardenburgh P, Manoharan G, *et al*. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol* 2007;49:2105–11.

8 Fearon WF, Bornschein B, Tonino PA, *et al*. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation* 2010;122:2545–50.

9 Meuwissen M, Siebes M, Chamuleau SA, *et al*. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. *Circulation* 2002;106:441–6.

10 Hoffman JI, Spaan JA. Pressure-flow relations in coronary circulation. *Physiol Rev* 1990;70:331–90.

11 Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res* 1978;43:242–53.

12 Hoffman JIE. Problems of coronary flow reserve. *Ann Biomed Eng* 2000;28:884–96.
- Review on pitfalls of coronary flow reserve.

13 Pijls NHJ, van Son JA, *et al*. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993;87:1354–67.
- Physiological basis and validation of FFR.

14 Spaan JA, Piek JJ, Hoffman JI, *et al*. Physiological basis of clinically used coronary hemodynamic indices. *Circulation* 2006;113:446–55.
- Basic science for clinicians on issues of microvascular resistance and collateral flow with regard to clinical indices of coronary stenosis severity.

15 Meuwissen M, Chamuleau SA, Siebes M, *et al*. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. *Circulation* 2001;103:184–7.
- Rationale for the use of combined intracoronary pressure and flow velocity.

16 De Luca G, Venegoni L, Iorio S, *et al*. Effects of increasing doses of intracoronary adenosine on the assessment of fractional flow reserve. *JACC Cardiovasc Interv* 2011;4:1079–84.

17 Pijls NHJ, Kern MJ, Yock PG, *et al*. Practice and potential pitfalls of coronary pressure measurement. *Catheter Cardiovasc Interv* 2000;49:1–16.
- Review on the practical aspects and potential pitfalls of FFR.

18 Echavarria-Pinto M, Escaned J. Use of fractional flow reserve in contemporary scenarios of coronary revascularization. *Minerva Med* 2011;102:399–415.

19 van de Hoef TP, Nolte F, Damman P, *et al*. Diagnostic accuracy of combined intracoronary pressure and flow velocity information during baseline conditions: adenosine-free assessment of functional coronary lesion severity. *Circ Cardiovasc Interv* 2012;5:508–14.

20 De Bruyne B, Pijls NHJ, Barbato E, *et al*. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation* 2003;107:1877–83.
- Study showing equality of intracoronary and intravenous adenosine for determining accurate FFR.

21 Sen S, Escaned J, Malik IS, *et al*. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol* 2012;59:1392–402.

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