The Anatomic–Functional Duality of So-called ‘Significant’ Atherosclerotic Stenosis – Update on Invasive Diagnostic Strategies in Coronaropathy

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Abstract

So-called ‘significant’ atherosclerotic coronary stenosis is defined by a simple binary morphological index of tightness – percent diameter stenosis (%DS >50 %). Invasive diagnosis of atherosclerotic coronary lesions classically comprises two consecutive stages, which can be fairly accurately described as angiographic visual perception and functional deduction. This anatomic–functional duality should be seen as not so much antithetic as causal and finally quite complex. The present update seeks to: define the ambiguous relationship between functional impact and morphology in atherosclerotic coronary stenosis; to specify the means of invasive diagnosis complementing coronary angiography to compensate the anatomic and functional limitations intrinsic to the latter (cross-sectional intravascular ultrasound [IVUS] and optical coherence tomography [OCT] imaging and fractional flow reserve [FFR] determined by pressure guide); and to bring these preliminary considerations to bear on the design of algorithms to guide the use of complementary invasive diagnostic exploration and draw up a novel diagnostic strategy in interventional cardiology (first-line coronary angiography).

Keywords

Fractional flow reserve, coronary angiography, intravascular ultrasound, percutaneous coronary intervention, clinical decision-making

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“Nothing comes to us except falsified and altered by our senses.”
Michel de Montaigne (1533–1592)

Coronary angiography (CA) has been performed in cardiology centres for more than 50 years. The diagnosis it provides soon became the gold standard in coronaropathy. It is a purely anatomic diagnosis, and this approach has made a deep mark on cardiology, although the need for a prior non-invasive functional approach was quickly admitted and developed.^{1,2} Nevertheless, our view of the functional impact of coronary stenosis was quickly reduced to a hypothetico-deductive inference drawn from a simple morphological index. So-called ‘significant’ atherosclerotic coronary stenosis is defined by a simple binary morphological index of tightness – percent diameter stenosis (%DS >50 %) – to which the most recent guidelines on myocardial revascularisation still refer for clinical decision-making.³ A ‘stenosis’ is visualised as a pathological focal anatomic entity on imaging, and its functional impact on myocardial perfusion (i.e. its significance) is then, still to the present day, inferred by a process of hypothetico-deductive reasoning.

Interventional cardiologists presently dispose of at least three complementary techniques supplementing CA: intravascular ultrasound (IVUS) and optical coherence tomography (OCT), and pressure guide to determine fractional flow reserve (FFR). The present update seeks to:

- define the ambiguous relationship between functional impact and morphology in atherosclerotic coronary stenosis;

- specify the means of invasive diagnosis, both anatomical and functional, complementing CA in order to compensate for the anatomic and functional limitations intrinsic to the latter; and
- bring these preliminary considerations to bear on the design of different diagnostic exploration strategies in interventional cardiology.

The Ambiguous Relationship Between Anatomy and Functional Impact in Atherosclerotic Coronary Stenosis

Haemodynamic impact is determined by many purely morphologic factors such as minimum lumen area, upstream arterial reference area, lesion length, wall lesion irregularity, lesion entry and exit angles, and vascular remodelling, but also by haemodynamic (flow and pressure) and rheological factors (haematocrit and blood viscosity).⁴ However, the overall ischaemic impact of coronary stenosis on underlying myocardial perfusion is the outcome of even more complex interactions, involving the effect of any spread of atherosclerosis to the epicardial arterial segment as a whole, and of changes in arteriolar resistive microcirculation, collateral circulation and myocardial tissue itself.⁵

Given the underlying physiopathological complexity, it seems highly reductive to see the haemodynamic impact of obstructive coronary artery stenosis as a simple change in relative diameter between an upstream segment considered to be normal and the minimum stenosis diameter (% DS).²

The 1974 Gould et al. study of a dog model of progressive quantified circumflex artery obstruction, statistically determined the degrees of stenosis associated with significant flow change at rest or under hyperaemia.⁶ Experimental hyperaemia is induced by 10 seconds total coronary artery obstruction. This was later replaced by a pharmacological effect, at first using papaverine, quickly changed to a continuous intravenous perfusion, or as is still used today, an intracoronary bolus injection of adenosine.⁷ At rest, an 85 % reduction in lumen diameter reduces coronary flow, while the hyperaemic response is affected as of 45 % stenosis and becomes significant as of 60 %. Gould therefore suggested that obstructive coronary stenosis becomes haemodynamically significant under effort or, more generally, under hyperaemia when diameter is reduced by 60 % or more. Cut-off quickly came to be set at a 50 % binary threshold, which became the functional index for significant coronary stenosis. This index has held sway for more than 40 years, although already criticised in the 1980s.⁸

Percent stenosis does seem to predict haemodynamic impact in a dog model in which the arterial network as a whole is strictly normal except for the mechanical obstruction. However, even in his princeps animal model, Gould reported variability in measurements, presaging greater uncertainty in patient-to-patient and artery-to-artery values.⁹ A clear discrepancy soon emerged between degree of stenosis (%DS) and maximal hyperaemia or coronary flow reserve (CFR) in several human studies using invasive or computed tomography (CT) coronary arteriograms.^{10,11}

Indices such as CFR or myocardial microvascular resistance index fail to answer the question as to whether an epicardial coronary stenosis in itself accounts for observed myocardial ischaemia.² CFR assesses the ratio of myocardial blood flow to hyperaemic flow; it cannot be compared to a patient's normal value, so that normal CFR is poorly defined and highly variable from patient to patient.¹² Moreover, the technique involves several limitations and above all is not specific to epicardial coronary stenosis exploration. The index of myocardial resistance (IMR) expresses only the resistance of intramyocardial microvasculature.^{13,14} Myocardial resistance pathologically elevated by microangiopathy or myocardial fibrosis cannot be improved by any epicardial coronary revascularisation.⁹

Thus only a physiopathological index specific to epicardial stenosis, and more precisely to the epicardial compartment itself, can be of use in indicating revascularisation. Such an index of epicardial circulation physiology should take account of normal and pathological (stenotic) epicardial flow rates. It also needs to:

- be independent of haemodynamic loading and rheological conditions;
- take possible collateral function into account; and
- take account of any myocardial pathology.

This is what FFR succeeds in assessing precisely, lesion by lesion and more generally coronary artery by coronary artery.^{15,16}

The Intrinsic Limitations of Coronary Angiography

X-ray CA has been in use for more than 50 years; it gives planar projection images, leading to a confusion of planes. It provides only a densitometric luminogram by iodine contrast injection. Its spatial resolution has not improved over the 50 years, and the development

of digital flat panels enhanced the images only by increasing the contrast resolution and eliminating geometric distortions. Visual and even computer-assisted quantitative analysis has never been very precise.¹⁷ The most widely used quantitative parameter is variation in %DS according to differential diameter between a reference segment and the minimum lesional diameter. In one study, only 60 out of 884 angiographically normal reference segments (6.8 %) were normal on intravascular ultrasound;¹⁸ moreover, the detection and quantification of minimum lumen diameter is imprecise.¹⁹ Detection and quantification of left coronary artery lesions on CA alone are also inaccurate.²⁰ Finally, CA does not provide precise anatomic information on the different types of atherosclerotic lesion and their complications; it is thus impossible to detect plaques, quantify plaque burden, specify plaque composition, or detect intraparietal or adventitial haematoma or certain dissections. Even in analysing the lumen itself, intraluminal densitometric variations are ambiguous – endoluminal thrombus, calcified protrusion, highly excentric stenosis, flap and plaque rupture. Equivalent limitations in CT coronary angiography have also been described.²¹

The Need to Overcome the Morphologic Limitations of Coronary Angiography

All of these morphologic limitations intrinsic to CA inspired the development of realtime high-resolution invasive complementary imaging techniques. These cross-sectional images provide full information from the lumen to the complete arterial wall. They enable precise quantification, with the possibility of three-dimensional (3D) reconstruction. Thus in the early 1990s, intravascular ultrasound (IVUS) began to complement the morphologic failings of CA by supplying cross-sectional imagery. Progressive advances have notably concerned improved spatial resolution by increasing the ultrasound frequency (90 micrometer [μm] at 40 megahertz [MHz]). Quantitative analysis thus gained in precision, overall assessment of the arterial wall and its impact on the lumen became clearly defined, and pathological mechanisms at work in the wall can now be rapidly detected and correctly described.²² Analysis of plaque composition is more limited, being based on simple acoustic reflectivity, providing only approximate assessment of the ternary aspect of the usual plaque components (anechogenic or hypoechogenic structures), which merely indicate the absence of a reflective ingredient such as calcium, collagen or elastin.²³ IVUS resolves certain endo- or extra-luminal ambiguities with a more or less complex additional image; and precisely detects plaque rupture following acute coronary syndrome, parietal thrombus, intra-plaque or intra-adventitia haematoma and certain ambiguities in the distribution or protrusion of calcification. Alongside the development of complex coronary angioplasty, IVUS has become a tool for selecting, guiding and assessing percutaneous coronary intervention (PCI) with stent implantation.²⁴ Long-term clinical outcome after IVUS-guided stent implantation and long-term mortality in stenting for unprotected left main coronary artery stenosis have improved significantly.²⁵ Taken together, these advantages, completing classical CA diagnosis with precision, have been drawn up into a level IIa/IIb set of recommendations.²⁶

Endocoronary imaging has recently seen the advent of OCT, based on a different physical principle from IVUS and providing much-improved spatial resolution of around 13 μm.²⁷ Unfortunately, the physics underlying this technique means that the wavelengths used cannot penetrate deep in a plaque (not more than 0.5–1.0 millimetres [mm]), depending on the type of tissue) thus the

Figure 1: Algorithm of Invasive Anatomic and Functional Diagnosis in Coronary Artery Disease Without Prior Stress Testing

ATS = atherosclerotic; CA = coronary angiography; CAD = coronary artery disease; FFR = fractional flow reserve; IVUS = intravascular ultrasound; NIFT = non-invasive functional testing; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; %DS = percent diameter stenosis.

Figure 2: Algorithm of Invasive Anatomic and Functional Diagnosis in Coronary Artery Disease with Prior Stress Testing Positive for Myocardial Ischaemia

ATS = atherosclerotic; CA = coronary angiography; CAD = coronary artery disease; FFR = fractional flow reserve; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; %DS = percent diameter stenosis.

advantage of greatly enhanced resolution applies only to the juxtaluminal wall and endoluminal evolutive processes. Analysing the surface of a stented lumen, for example, corresponds exactly to the field of application of OCT. However, its drastic limitation in deep exploration means that it is not an alternative in those applications for which IVUS is especially useful and recommended, such as guiding complex or left coronary angioplasty.²⁸

The Need to Overcome the Functional Limitations of Coronary Angiography

Determining FFR by pressure guide was a critical advance, fully confirmed first experimentally and then clinically over the last 15 years by the work of Pijls and de Bruyne.^{15,16,29,30} After numerous precise cumulative validations, it has been shown to be an exact technique, specific to all obstructive epicardial lesions. FFR is independent of heart rate, arterial pressure and myocardial contractility. FFR has an unequivocal value of 1.0 in any patient with a normal coronary artery. An FFR equal to or less than 0.8 precisely determines the functional impact of a significant as compared to a non-significant stenosis with a high degree of accuracy. FFR also takes into account the contribution of any collateral flow to myocardial perfusion, and can be applied in single or multivessel disease, as it does not require having a normal coronary artery to serve as control. It is moreover easy to perform, highly reproducible and can be implemented without difficulty in both diagnostic and therapeutic procedures. The key point in applying this technique is that it is specific to the functional impact of an epicardial stenosis on coronary circulation, independently of the patient's individual microvascular resistance patterns. In this respect, it is completely different from CFR, which characterises the functional association of the epicardial network with the microvascular resistive network, so that it is not specific to epicardial stenosis. Several studies demonstrated that coronary stenoses of 30–70 % DS are functionally ambiguous, as they may or may not be associated with any myocardial ischaemia.³¹ The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study of 1,414 lesions assessed by FFR clearly showed that 65 % of tight (50–70 % DS) stenoses and 20 % of 71–90 % DS stenoses were not inducing any myocardial ischaemia (FFR >0.80).³² Only 235 out of 509 patients with multivessel disease as shown on CA (46 %) had functional multivessel disease (≥2 coronary arteries with FFR >0.80). In other words, when an intermediate coronary stenosis (between 30 and 90 %) is detected, its functional implications remain entirely ambiguous. Pressure guide determination of FFR precisely assesses impact on the epicardial network, independently of haemodynamics and particularly of the resistive effect of myocardial microcirculation. Thus FFR is a major stage in determining indications for revascularisation where stenosis shows a functional impact.

In 1999 Takagi et al. again attempted to correlate stenosis anatomy (IVUS minimum lumen area [MLA], square millimetre [mm²]) and functional impact (FFR), and reported a 3 mm² IVUS MLA cut-off as detecting stenosis with FFR <0.75 with 83 % sensitivity and 92 % specificity.³³ This 3 mm² IVUS MLA value became a functional surrogate index. However, in a recent rigorous study of 267 lesions, Koo et al.³⁴ found no lumen area cut-off reliably associated with FFR <0.80, in agreement with Kang et al.³⁵ In fact, each coronary artery bifurcation displays a fractal geometry, with diameters progressively narrowing in line with the law of conservation of mass³⁶ – thus, no one functional coronary lumen area criterion is conceivable, and

Figure 3: Algorithm of Invasive Anatomic and Functional Diagnosis in Acute Coronary Syndrome

ACS = acute coronary syndrome; CA = coronary angiography; FFR = fractional flow reserve; IVUS = intravascular ultrasound; NSTEMI = non-ST segment elevation myocardial infarction; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction; %DS = percent diameter stenosis.

no quantitative CA stenosis index can be precisely correlated with and predictive of myocardial functional impact. Another functional scenario to be detected is when an epicardial artery is diffusely infiltrated by atherosclerosis, with diameters that are reduced overall, not letting focal stenoses appear – should any exist, they will be poorly quantified as the reference segment will be seriously underestimated. FFR determined with long pressure-guide pullback provides perfect analysis of this anatomic–functional situation.³⁷

Accumulated evidence shows that the functional significance of the coronary stenosis determines the potential benefit of revascularisation in patients with stable coronary artery disease (CAD).³⁸ When an artery in stable CAD is revascularised by FFR-guided CA, the rate of coronary events diminishes.^{38,39} Moreover, there is serious evidence that medical treatment can be preferable to PCI in patients with stable coronary artery disease.⁴⁰ The results of the Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Versus Optimal Medical Treatment Alone in Patients With Stable Coronary Artery Disease (FAME II) study refine this body of evidence, showing that in stable angina with functionally significant coronary stenosis, FFR-guided PCI associated to optimal medical treatment (evidence-based medicine) reduces the rate of emergency revascularisation compared with optimal medical treatment alone.⁴¹

Practical Strategic Synthesis for the Use of Different Invasive Diagnostic Exploration Techniques

Coronary angiography is the foundation of any invasive exploration, rapidly and reliably detecting whether any coronary lesion is present or not.

Figure 4: Proposed First-line Coronary Angiography Strategy (Without Prior Stress Testing) After Risk Stratification by Precise Clinical Assessment

CA = coronary angiography; CAD = coronary artery disease; FFR = fractional flow reserve; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.

However, anatomic descriptive (or qualitative) analysis of the angiogram may be difficult or ambiguous – realtime invasive cross-sectional imaging with high spatial resolution, depth exploration going beyond the adventitia and a single complete acquisition of the entire epicardial arterial axis is then indispensable. IVUS meets these requirements, usefully complementing angiography.⁴²

Functional analysis of coronary stenosis needs to be definitively freed from lesion anatomy, and requires a specifically dedicated technique for each patient, artery and lesion. Pressure guide determination of FFR fully meets these requirements, and should be implemented in all intermediate (30–90 %DS) lesions.³

Twenty years ago, many interventional cardiologists, already aware of the limitations of CA, were imagining the advent of new complementary anatomic and functional techniques.⁸ Now in 2013, such techniques are actually available. Two major complementary techniques have been developed and received wide scientific validation, with precise recommendations – IVUS and FFR.

Algorithms for the Implementation of Complementary Invasive Diagnostic Techniques

In everyday interventional cardiology, several algorithms may guide the implementation of these two complementary techniques: functional (using FFR) and anatomical (using IVUS or OCT).

Most patients undergoing CA have not had prior non-invasive functional testing.^{43,44} The functional ambiguity of any coronary lesions found on CA will then be unattenuated (see Figure 1).

Even if non-invasive functional testing is performed ahead of CA, functional ambiguities may still appear in cases of multiple lesions on one or more coronary arteries (single or multivessel disease). Another problem recently emerged, the value of non-invasive testing

for location purposes. While effort tests do not help with location, myocardial scintigraphy and stress echo are claimed to do so. However, using FFR and its ability to analyse stenosis-by-stenosis and, more generally, artery-by-artery, several reports have demonstrated the locational imprecision of these tests in multivessel disease.^{45,46} These findings have a real impact on strategy, if myocardial revascularisation is indicated only on positive results on these non-invasive tests and on their topographic analysis, only partial revascularisation of myocardial ischaemia will be achieved (see Figure 2).

In acute coronary syndrome, the need for early treatment means that other lesions over and above the culprit lesion may be discovered, and frequently dilated without objective proof of ischaemia (see Figure 3).⁴⁷

First-line Coronary Angiography – A Provocative Diagnostic Strategy?

There is a new strategy that should be mentioned and can now be argued for; implementing CA in first-line without preliminary non-invasive testing (see Figure 4). This attitude may seem at first glance to be provocative, but now in 2013 that is not really the case.

In reality, non-invasive tests are rarely performed ahead of angioplasty. The accuracy of non-invasive functional tests is often poor.^{48–51} The various stress imaging techniques (stress echocardiography, perfusion scintigraphy and cardiac magnetic resonance imaging [MRI] stress testing), while known to show better diagnostic performance than conventional exercise electrocardiography (ECG),⁵² seem to be less effective for locating myocardial ischaemia than artery-by-artery FFR measurement.^{45,46,53–55}

Even so, CA performed without non-invasive testing in patients at intermediate or high-risk of clinically significant coronary disease will involve intrinsic anatomic and especially functional limitations. A decade ago, this attitude would have been difficult to defend; in the

present day however, it is coherent – the twofold limitations of CA can and should be corrected by FFR and IVUS.⁵⁶

First-line coronary angiography after risk stratification by precise clinical assessment can be an effective strategy,⁵⁷ with:

- detection and anatomic analysis of focal or diffuse atherosclerotic coronary lesions;
- precise functional assessment by artery-to-artery and lesion-to-lesion measurement of FFR;⁵
- provocative tests in case of vasospastic or variant angina;⁵⁸
- documented topographic decision-making for any revascularisation (by PCI or CABG);⁵⁹ and finally
- early comprehensive treatment with greater diagnostic certainty than achieved with non-invasive testing (whether single or successive) on a classic Bayesian approach to the diagnosis of coronary artery disease.

Algorithms may be drawn up for a revascularisation strategy functionally determined by FFR and anatomically guided by IVUS.⁶⁰

Conclusion

The interventional cardiologist is above all a clinician, whose diagnosis of coronary artery disease is greatly refined by the systematic anatomic and functional confirmation provided by the various forms of invasive exploration now available. Indeed, the interventional cardiologist has probably become a better pathologist of coronary disease, and certainly a physiopathologist. The non-redundant complementarity of pressure guides and IVUS (or OCT) in correcting the functional and anatomic uncertainties inherent to coronary angiography has, over the years, acquired major IA recommendation in the case of FFR and Ila/b-B/C recommendation as useful and effective in the case of IVUS. These important recent developments now guarantee unambiguous management adapted to each CAD patient's individual case. ■

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