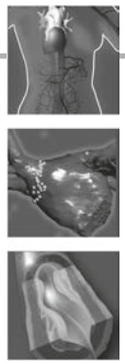

What has the RIPCORD trial told us about using fractional flow reserve for diagnostic angiography?

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"*We may be entering the era of ischemia-directed therapy for optimal treatment of patients with coronary disease and not just patient-level, but lesion-level assessment of that ischemia.*"

KEYWORDS: coronary angiography ■ coronary artery disease ■ fractional flow reserve ■ myocardial ischemia ■ pressure wire

We live in an era of clinical medicine in which we are blessed with an unparalleled armory of high-technology, noninvasive and invasive investigational tools. Yet in the field of cardiology, many practitioners continue to rely on a subjective angiographic assessment of coronary anatomy on which to base important management decisions. Indeed, UK guidelines issued by NICE for the assessment of patients with recent-onset stable chest pain suggest that, for a patient with an estimated likelihood of coronary artery disease (CAD) of 61–90%, coronary angiography (CA) should be offered as the first-line diagnostic investigation, even without any prior noninvasive assessment for ischemia [101]. It is widely accepted that an atheromatous lesion in a major epicardial coronary artery producing a visual narrowing of >70% (>50% in the left main coronary artery) is likely to be flow restrictive/able to produce angina and of prognostic importance when located in the proximal coronary tree. Accurate visual grading of CAD severity during CA may seem straightforward, but in many cases, the angiographic findings are not clear cut and fall into the intermediate severity range (50–70% stenosis), or a lesion appears hazy due to the presence of calcification or thrombus. In reality, it is well established that reliable and reproducible 'eyeball' quantification of stenosis severity during CA alone is inaccurate and prone to intra- and inter-observer variability [1–4]. Accuracy regarding disease severity can be improved with the use of intravascular ultrasound [3,4], but this is rarely performed during routine diagnostic CA, especially if the angiogram is performed by a noninterventional cardiologist and correlates poorly with vessel physiology. With the advent and validation of invasive physiological assessment of lesion-level ischemia, as offered by fractional flow reserve (FFR), the prognostic importance of targeting ischemia in the context of percutaneous coronary intervention (PCI) has become clear. However, data from the RIPCORD study now offer insight into the potential clinical value of routine FFR assessment at the stage of CA. RIPCORD has raised important questions about current practice. Can an operator be confident that each stenosis seen during CA is clinically important, and therefore can they make reliable decisions about revascularization on CA alone? Accurate physiological data may mean the difference between selecting optimal medical therapy (OMT) alone, PCI or multivessel coronary artery bypass grafting (CABG). More importantly, we know that revascularization of a nonischemic vessel, by PCI at least, offers no clinical benefit and, in fact, increases the risk of future events.

Coronary anatomy versus physiology: role in predicting prognosis

Whilst there are data to support the concept that risk of myocardial infarction correlates with lesion severity as determined by CA [5], reliably determining whether a coronary lesion of intermediate angiographic severity (i.e., 50–70%) is functionally and, therefore, prognostically important is imprecise based on CA alone. Thus, for example, only approximately half of patients with a coronary stenosis of ≥50% on multislice coronary computed tomography have associated inducible ischemia [6]. This is critically important given that it has been robustly demonstrated that inducible myocardial ischemia detected by noninvasive stress imaging reliably predicts risk of future

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cardiac events [7–9]. Conversely, and of equal importance, in patients with known CAD but no inducible ischemia on such tests, the likelihood of a myocardial infarction over the next few years is very low. Furthermore, the extent of total and left ventricular ischemia is associated with prognosis [7] and patients with a large ischemic burden have been shown to have an improved outlook following revascularization compared with OMT alone [10]. These data lay the foundation for the theory that it is the presence and extent of myocardial ischemia, rather than the angiographic severity of CAD, that most reliably predicts prognosis. Given the dominance of the presence and extent of ischemia in predicting outcome and the increased tendency to perform CA, the availability of a simple and reliable invasive test for ischemia represents a major step forward in the care of patients with angina.

Coronary pressure wire

The functional importance of any coronary stenosis can be assessed during CA using a coronary pressure wire. This technology enables the cardiologist to make real-time measurements of the intra-arterial pressure difference across a coronary stenosis, presented as an intuitive value known as the FFR. The FFR represents the degree of reduction in myocardial blood flow in a stenosed epicardial coronary artery compared with what would be expected if there was no restriction to flow in the same vessel. The pressure wire provides an accurate, reproducible and well-validated assessment as to whether a coronary stenosis is capable of inducing myocardial ischemia, and can be used to provide lesion-specific data [11,12]. It is not influenced by changes in hemodynamic parameters and, in experienced hands, has a low complication rate [12,13]. There is a clear and robust cutoff FFR value of 0.75, below which a lesion can be classified as able to cause ischemia (specificity: 100%; sensitivity: 88%; positive predictive value: 100%; and overall accuracy: 93%) [13]. On the other hand, a FFR of >0.80 is virtually never associated with ischemia. The DEFER study demonstrated that, in coronary stenoses with an FFR of ≥0.75, the risk of cardiac death or myocardial infarction is <1% per annum, and that PCI for such lesions can be safely deferred with the use of OMT [14]. More recently, the FAME study found that, in patients with stable angina and multivessel disease originally targeted for PCI, FFR-guided PCI is superior to angiogram-guided PCI when a cutoff FFR value of 0.80 is applied, despite fewer lesions treated and fewer stents deployed [15]. Subsequently, the FAME-2 study showed that PCI plus OMT is superior to OMT alone in patients with stable angina and a FFR of <0.80, with regard to rates of death or myocardial infarction at 2 years [16]. Revascularization of patients with angina and a FFR of <0.80 therefore allows us to achieve the optimal outcome for the patient: both a symptomatic and a prognostic benefit. This is reviewed fully in a recently published paper [17].

RIPCORD

The RIPCORD study was designed to investigate whether routine measurement of FFR in all major epicardial coronary branches would alter the management strategy from that based on CA alone. Why did the question arise as to whether FFR-based assessment of the coronary circulation may be valuable at the stage of diagnostic angiography? First, the evidence (as summarized above) suggests that ischemia is more predictive of adverse events than anatomy alone; second, because angiographic assessment is poorly reproducible and particularly inaccurate in moderate or very diffuse lesions; and finally, because in the field of PCI, FFR guidance has been shown to reduce the amount of revascularization delivered, but with improved clinical outcome. By contrast, there are pieces of our management challenge that are missing. First, there are very few data relating to the value of FFR-based assessment for determining optimal deployment of CABG or medical therapy alone; and second, the COURAGE trial has challenged cardiologists to understand who they should revascularize and why [18]. FFR guidance offers a potentially efficient solution to this challenge.

> *"...it is the presence and extent of myocardial ischemia, rather than the angiographic severity of coronary artery disease, that most reliably predicts prognosis."*

In the RIPCORD study, patients with cardiac-sounding chest pain were scheduled to undergo elective diagnostic CA as determined by their physician. The cardiologist who performed the CA selected a single management plan based on the clinical features and the angiographic appearance of any CAD according to their routine clinical practice. Treatment options were OMT, PCI, CABG or further information required (e.g., noninvasive ischemia test). Once CA was completed, a second interventional cardiologist then performed pressure wire

assessment of all coronary branches with a reference diameter of ≥2.25 mm and a ≥30% stenosis by visual assessment. A FFR result of <0.80 was taken to represent a physiologically significant stenosis. The FFR results were disclosed to the first cardiologist who was then invited to revise the management strategy based on the new FFR information gleaned. The primary aim of the trial was to determine to what extent the angiogram-derived management would be altered by the availability of FFR data. Second, the study sought to determine the degree of correlation of 'significant' lesions between standard angiographic assessment of stenosis severity and pressure wire assessment of the main coronary arteries.

Overall, 200 patients were studied across ten cardiac units in the UK [19]. The demographic characteristics of the cohort were typical for a UK-based population of patients with suspected angina – that is, the majority were male, had a mean age of 64 years and were overweight, with traditional risk factors of CAD. In total, 47% of patients had undergone an exercise treadmill ECG prior to CA, while 9% of the cohort had a noninvasive imaging ischemia test preangiography.

For 26% of the patients, the initial angiogram-based management strategy was modified after disclosure of the pressure wire results ($p < 0.001$). This change in management was explained by the discrepancy between the angiographically determined significance of coronary lesions and FFR-derived stratification, seen in 32% of the study population.

Discussion

In summary, the RIPCORD study demonstrated that there was a change in management strategy in just over a quarter of patients when FFR data were provided, compared with angiographic assessment alone. Patients committed to revascularization were found to have no physiologically significant disease, and patients in whom the angiogram detected no significant disease were found to have single, double and even triple vessel disease by FFR and were thus referred for PCI and even CABG.

The implications of this study, if the proof of concept is valid, are potentially profound. Rigorously conducted randomized trial data are now required. If they provide similar results, then relying on angiographic assessment of coronary disease alone, without FFR data, may be untenable. We may be entering the era of ischemia-directed therapy for optimal treatment of patients with coronary disease and not just patient-level, but lesion-level assessment of that ischemia.

Financial & competing interests disclosure

N Curzen received unrestricted research grants from Haemonetics, Medtronic and St Jude Medical. N Curzen also receives consultant/speaker fees from Haemonetics, Medtronic, St Jude Medical, Abbott, Boston Scientific and Daiichi-Sankyo. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Zir LM, Miller SW, Dinsmore RE, Gilbert J, Harthorne J. Interobserver variability in coronary angiography. *Circulation* 53(4), 627–632 (1976).

2 White CW, Wright CB, Doty DB *et al.* Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N. Engl. J. Med.* 310(13), 819–824 (1984).

3 Berry C, L'Allier PL, Grégoire J *et al.* Comparison of intravascular ultrasound and quantitative coronary angiography for the assessment of coronary artery disease progression. *Circulation* 115(14), 1851–1857 (2007).

4 Tu S, Xu L, Ligthart J *et al. In vivo* comparison of arterial lumen dimensions assessed by co- registered three-dimensional (3D) quantitative coronary angiography, intravascular ultrasound and optical coherence tomography. *Int. J. Cardiovasc. Imaging* 28(6), 1315–1327 (2012).

5 Zaman T, Agarwal S, Anabtawi AG *et al.* Angiographic lesion severity and subsequent myocardial infarction. *Am. J. Cardiol.* 110(2), 167–172 (2012).

6 van Werkhoven JM, Schuijf JD, Gaemperli O *et al.* Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. *J. Am. Coll. Cardiol.* 53(7), 623–632 (2009).

7 Bourque JM, Beller GA. Stress myocardial perfusion imaging for assessing prognosis: an update. *JACC Cardiovasc. Imaging* 4(12), 1305–1319 (2011).

8 Herzog BA, Husmann L, Valenta I *et al.* Long-term prognostic value of ^{13}N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. *J. Am. Coll. Cardiol.* 54(2), 150–156 (2009).

9 Jahnke C, Nagel E, Gebker R *et al.* Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 115(13), 1769–1776 (2007).

10 Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 107(23), 2900–2907 (2003).

11 Brigouri C, Anzuini A, Airoldi F *et al.* Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary arytery stenoses and comparison with FFR. *Am. J. Cardiol.* 87, 136–141 (2001).

12 Pijls NH, De Bruyne B, Bech GJ *et al.* Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation* 102, 2371–2377 (2000).

13 Muller O, De Bruyne B. Coronary physiology in clinical practice. In: *Oxford Textbook of Interventional Cardiology.* Redwood S, Curzen N, Thomas M (Eds). Oxford University Press, Oxford, UK, 130–146 (2010).

14 Pijls N, van Schaardenburgh P, Manoharan G *et al.* Percutaneous coronary intervention of functionally non-significant stenosis: 5-year follow up of the DEFER study. *J. Am. Coll. Cardiol.* 47, 2105–2111 (2007).

15 Tonino PA, De Bruyne B, Pijls NH *et al.* Fractional flow reserve versus angiography for guiding PCI. *N. Engl. J. Med.* 360, 213–224 (2009).

16 De Bruyne B, Pijls N, Kalesan B *et al.* Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N. Engl. J. Med.* 367, 991–1001 (2012).

17 Longman K, Curzen N. Should ischaemia be the main target in selecting a percutaneous coronary intervention strategy? *Expert Rev. Cardiovasc. Ther.* 11(8), 1051–1059 (2013).

18 Boden WE, O'Rourke RA, Teo KK *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N. Engl. J. Med.* 356(15), 1503–1516 (2007).

19 Curzen N. Oral hotline presentation. The RIPCORD study: does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain? Presented at: *EuroPCR 2013.* Paris, France, 21–24 May 2013.

■ Website

101 NICE. The management of stable angina. Clinical guideline 126 (2011). http://guidance.nice.org.uk/CG126