JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 10, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.12.026

Does the Routine Availability of CT–Derived FFR Influence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone?

The FFR_{CT} RIPCORD Study

Nicholas P. Curzen, BM, PhD,[a] James Nolan, MD,[b] Azfar G. Zaman, MD,[c] Bjarne L. Nørgaard, PhD,[d] Ronak Rajani, MD[e]

ABSTRACT

OBJECTIVES This study sought to determine the effect of adding computed tomography–derived fractional flow reserve (FFR_{CT}) data to computed tomography angiographic (CTA) data alone for assessment of lesion severity and patient management in 200 patients with chest pain.

BACKGROUND Invasive and noninvasive tests used in the assessment of patients with angina all have disadvantages. The ideal screening test for patients presenting for the first time with chest pain would describe both coronary anatomy and the presence of ischemia and would be readily accessible, low cost, and noninvasive.

METHODS Two hundred patients with stable chest pain underwent CTA for clinical reasons, and FFR_{CT} was calculated. Three experienced interventional cardiologists assessed the CTA result for each patient and by consensus developed a management plan (optimal medical therapy, percutaneous coronary intervention, coronary artery bypass graft surgery, or more information required). FFR_{CT} data for each vessel were then revealed, and the interventional cardiologists made a second plan by consensus, using the same 4 options. The primary endpoint for the study was the difference between the 2 strategies.

RESULTS Overall, after disclosure of FFR_{CT} data there was a change in the allocated management category on the basis of CTA alone in 72 cases (36%). This difference is explained by a discordance between the CTA- and FFR_{CT}-derived assessments of lesion severity. For example, FFR_{CT} was >0.80 in 13 of 44 vessels (29.5%) graded as having a stenosis $>90\%$. In contrast, FFR_{CT} was ≤ 0.80 in 17 of 366 vessels (4.6%) graded as having stenosis $\leq 50\%$.

CONCLUSIONS This study demonstrates proof of concept that the availability of FFR_{CT} results has a substantial effect on the labeling of significant coronary artery disease and therefore on the management of patients compared to CTA alone. Further studies are needed to determine whether FFR_{CT} has potential as a noninvasive diagnostic and management screening tool for patients with stable chest pain. (J Am Coll Cardiol Img 2016;9:1188–94) © 2016 by the American College of Cardiology Foundation.

From the [a]University Hospital Southampton & Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [b]University Hospitals of North Staffordshire, Stoke-on-Trent, United Kingdom; [c]Freeman Hospital, and Institute of Cellular Medicine Newcastle University, Newcastle upon Tyne, United Kingdom; [d]Aarhus University Hospital Skejby, Aarhus, Denmark; and the [e]Guy's & St. Thomas' Hospital, London, United Kingdom. This study was funded by an unrestricted research grant from HeartFlow. Dr. Curzen has received unrestricted research grants from Heart Flow, Boston Scientific, St. Jude Medical, Haemonetics, and Medtronic; honoraria/speaker fees from HeartFlow, St. Jude Medical, and Haemonetics; and travel sponsorships from Biosensors, Lilly/D-S, and Abbott Vascular. Dr. Zaman has received unrestricted research grants from St. Jude Medical. Dr. Norgaard has received unrestricted research grants from Edwards Lifesciences and Siemens. Dr. Rajani has received consultant fees from Edwards Lifesciences. Dr. Nolan has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received August 5, 2015; revised manuscript received December 2, 2015, accepted December 11, 2015.

The optimal pathway for the initial assessment of patients with stable chest pain of suspected cardiac origin is contentious. Some patients undergo noninvasive tests that seek objective evidence of reversible myocardial ischemia, whereas others are referred directly for invasive coronary angiography (ICA). The diagnostic yield of a dominant invasive strategy has been reported to be low and still carries a degree of clinical risk (1). In contrast, a strategy that is initially determined on the basis of noninvasive stress testing is potentially expensive, results in a delay for patients, particularly those for whom it ultimately leads to referral for diagnostic angiography, and has variable diagnostic accuracy (2). However, establishing the presence of coronary artery disease (CAD), even when it is not causing myocardial ischemia, can provide prognostic information and, in particular, indicate benefit from disease-modifying therapy such as a statin and aspirin (3).

SEE PAGE 1195

Increasing evidence suggests that it is predominantly the presence and extent of reversible myocardial ischemia that determine clinical event rates in patients with CAD, rather than the anatomy itself. Consequently, revascularization is most effective, in terms of symptoms and prognosis, in patients with the highest ischemia burden (4,5). The detection of ischemia and its extent can be achieved by some noninvasive tests and by invasive pressure wire assessment via fractional flow reserve (FFR). Invasive FFR has been shown to accurately predict clinical outcome in patients identified as being candidates for percutaneous coronary intervention (PCI), and as a result use of FFR-directed therapy in this population is dominant compared to angiogram-directed therapy (6,7).

Given this evidence, the ideal screening test for patients presenting for the first time with possible angina would be noninvasive and would define both the existence of CAD and myocardial ischemia. Currently, ICA with FFR is the only test that can achieve combined anatomic and physiological assessment. The simultaneous availability of FFR with coronary anatomy can refine interpretation of the significance of any coronary lesions identified and thus management of the patient. In the RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) study of 200 patients with stable chest pain undergoing clinically indicated diagnostic angiography, the routine measurement of FFR in all vessels of stentable diameter changed the management originally determined by angiography alone in 26% of cases (8). This change was the result of a mismatch in detection of vessel "significance" between the angiographic appearances and FFR ≤0.8 in 32%. Unfortunately, limitations to this invasive approach include procedural risk, cost, and universal access of all such patients to a cardiac catheterization laboratory.

The development and availability of coronary computed tomography angiography (CTA) have introduced this noninvasive assessment of the presence and extent of CAD as a useful additional option for the investigation of patients with suspected stable angina (9,10). For example, recent data from the SCOT-HEART (Scottish COmputed Tomography of the HEART) randomized trial highlight the diagnostic value of this technique in such a population (11). However, in the PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) trial, which randomized 10,003 patients with symptoms suggestive of CAD to stress testing or CTA, almost 50% more ICAs were performed in the CTA group without any difference in clinical outcome (12). Importantly, most revascularizations in the CTA group were performed in patients who had no objective evidence of myocardial ischemia. This finding highlights the potential limitation of anatomy-based screening in patients with symptoms thought to be due to myocardial ischemia.

Recently, using sophisticated image assessment, computational fluid dynamics, and computer modeling, it has become possible to model FFR from the data obtained from CTA, a technique known as computed tomography-derived fractional flow reserve (FFR_{CT}) (13). A series of validation studies have assessed the diagnostic accuracy of this technique (14,15), including most recently the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial, which demonstrated the superior accuracy of CTA plus FFR_{CT} versus CTA alone, using an invasive FFR ≤0.8 as the reference (16).

The primary aim of this study was to test the hypothesis that the routine availability of (noninvasive) FFR_{CT} data in 200 consecutive cases from the NXT trial would change the management strategy derived solely from assessment of the CTA data. Two hundred cases were chosen to reproduce the methodology of the invasive RIPCORD study. The secondary aim was to assess whether the findings from the original invasive RIPCORD study could be reproduced using noninvasive angiography and FFR_{CT}.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CTA = computed tomography angiography

FFR = fractional flow reserve

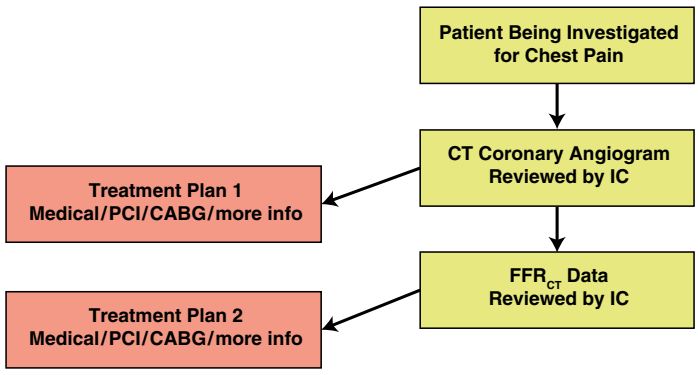
FFR_{CT} = computed tomography-derived fractional flow reserve

ICA = invasive coronary angiography

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

FIGURE 1 Schematic Diagram Demonstrating Study Methodology



The primary endpoint for the study was the difference between treatment plans 1 and 2. CABG = coronary artery bypass graft; CT = computed tomography; FFR_{CT} = computed tomography–derived fractional flow reserve; IC = interventional cardiologist; PCI = percutaneous coronary intervention.

METHODS

This study involved the assessment of CTA and FFR_{CT} data from 200 consecutive cases from the NXT trial. A total of 200 patients were selected to match the numbers in the original RIPCORD study. The NXT population consisted of elective patients with stable chest pain. All of these patients underwent invasive angiography for clinical reasons, and FFR was performed in at least 1 vessel with diameter ≥2 mm and diameter stenosis ≥30%. All patients also underwent CTA within 60 days before invasive angiography, and FFR_{CT} data were derived from the dataset using a methodology previously described (13-16).

In each case, 3 experienced interventional cardiologists (N.C., J.N., A.Z.) who had access to the expert report generated for clinical reasons, assessed the CT angiogram. They then recorded the location and severity of any coronary stenosis, specifically taking into account whether the lesion was anatomically "significant," by consensus on the basis of visual assessment and the standard expert report (Figure 1). Then, assuming that each patient was suitable for any 1 of 4 management options: 1) optimal medical therapy (OMT) alone; 2) PCI + OMT; 3) coronary artery bypass graft + OMT; or 4) more information about ischemia required—they committed to 1 option by consensus. Once this decision was made, the FFR_{CT} data were revealed for the case, and the 3 cardiologists were again asked to decide, by consensus, on a management plan, choosing from 1 of 4 options. The vessels that were considered to be "significant" according to whether they were ischemic by virtue of the FFR_{CT} result (cutoff value ≤0.80) also were recorded.

The primary endpoint for this study was the difference between management on the basis of interpretation of the CTA alone compared to management incorporating FFR_{CT} data. Secondary endpoints were: 1) correlation between vessels labeled as "significant" on the basis of interpretation of the CT angiogram alone versus interpretation with FFR_{CT} data available; and 2) comparison between individual coronary arteries labeled as targets for revascularization on the basis of the CTA alone versus those arteries labeled as targets with FFR_{CT} data available.

STATISTICAL CONSIDERATIONS. A sample size of 200 was calculated to be the minimum number of patients required to give a confidence level of 95% with a 0% margin of error and a response distribution of 50%. This was the same sample size evaluated in the RIPCORD study. All categorical data are presented as n (%). For comparison of categorical variables (change in management plan after FFR_{CT}), the percentage change and exact 95% confidence intervals are presented. All data were collected and analyzed on SPSS for MAC version 21 (IBM, Armonk, New York).

RESULTS

DISCREPANCY BETWEEN CTA AND ICA. In this study population, a stenosis was considered "significant" if it had diameter narrowing ≥50%. From the site-read cases, 8 (4%) reported as having no significant obstructive disease on CTA had obstructive disease on quantitative coronary angiography on the invasive catheterization. Of these 8 cases, 7 (87.5%) had a negative FFR_{CT}, and 1 (12.5%) had a positive FFR_{CT}. From the site-read cases, 94 (47%) reported as having significant obstructive coronary disease on coronary CTA were later found to have no obstructive disease on quantitative coronary angiography on the invasive catheterization. Of these 94 cases, 57 (60.6%) had a negative FFR_{CT}, and 37 (39.4%) had a positive FFR_{CT}.

EFFECT OF FFR_{CT} ON MANAGEMENT. After FFR_{CT} data became available, a change in the allocated management category on the basis of CTA alone was seen in 72 cases (36%) (Table 1). A detailed breakdown demonstrating the nature of the changes in management category is shown in Figure 2. Of the 38 patients originally allocated to the "more information required" category on the basis of CTA alone, 10 (26%) were reallocated to revascularization and the remaining 28 (74%) to OMT. Of the 67 cases originally

allocated to OMT on the basis of CTA alone, 8 (12%) were reallocated after FFR_{CT} to revascularization (PCI in 7). Of the 87 cases originally thought to require PCI on the basis of CTA alone, 26 (30%) were reallocated to OMT on the basis of no ischemic lesion detected by FFR_{CT}, and in 16 (18%) the target vessel(s) for PCI was changed on the basis of FFR_{CT}. Thus, the availability of FFR data resulted in an overall change in the decision for treatment (combining change in management category plus change in PCI target vessel) in 44% of the study population compared to CTA alone.

These changes resulted from a discordance between the CT angiographic and FFR_{CT} assessments of lesion severity, as illustrated in Figure 3. Specifically, of a total of 577 vessels, FFR_{CT} was ≤0.8 in 118 (20.5%). In 366 vessels (63.4% of the total) categorized as having CT angiographic severity ≤50% diameter stenosis, FFR_{CT} was ≤0.80 in 17 (4.6%). In contrast, FFR_{CT} was negative for ischemia (i.e., >0.80) in 13 of 44 cases (29.5%) graded as having diameter stenosis >90% and in 38 of 83 cases (45.8%) graded as having diameter stenosis of 71% to 90%.

TABLE 1 Summary of Overall Changes to Management in Patients According to Treatment Plan on the Basis of CT Angiography Alone and of FFR_{CT} Data in Addition to CT Angiography

	CT Angiography Alone	CT Angiography With FFR_{CT}	Strategy Change
More data required	38 (19.0)	0	–
Optimal medical therapy	67 (33.5)	113 (56.5)	23 (18 to 29)
Percutaneous coronary intervention	87 (43.5)	78 (39.0)	-5 (-2 to -8)
Coronary artery bypass graft surgery	8 (4.0)	9 (4.5)	0.5 (0.1 to 3)

Values are n (%) or % (95% confidence interval). n = 200 patients; $p < 0.001$ for between group change, angio alone versus FFR_{CT}.

CT = computed tomography; FFR_{CT} = computer tomography-derived fractional flow reserve.

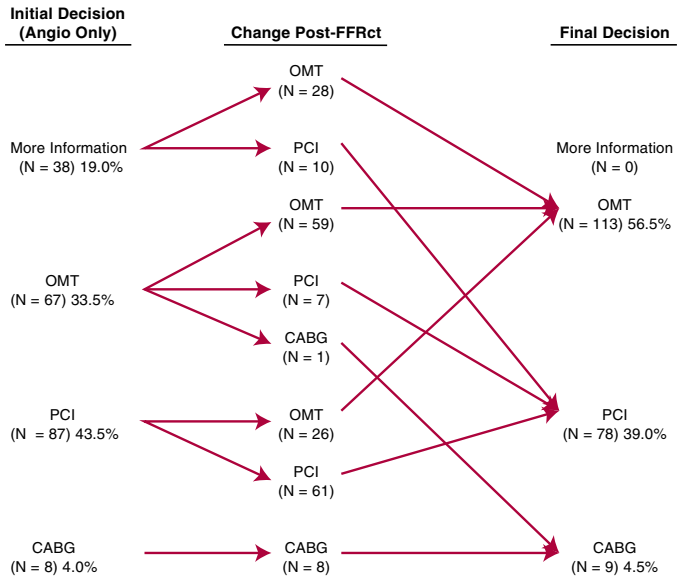
DISCUSSION

This study proved the hypothesis that the management of patients with stable chest pain on the basis of CTA results alone would be significantly different if FFR_{CT} data were available. This change in management is explained by a discordance between the assessment of lesion significance by CTA and FFR_{CT}. With respect to the secondary aim, it is interesting to note that these data mimic those seen in the original RIPCORD study of ICA and invasive FFR.

The data from this study should be considered as proof of concept. In invasive studies, the mismatch between angiographic assessment of lesion significance and FFR is well described and consistent across a large number of datasets, as illustrated by RIPCORD (8), FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) (17), FAMOUS (Fractional Flow Reserve vs. Angiography in Guiding Management to Optimize Outcomes in Non-ST-Segment Elevation Myocardial Infarction) (18), the French Registry (19), and a large series by Toth et al. (20). This mismatch inevitably leads to important changes in patient management, given the well-documented superiority of an FFR-directed strategy over an angiogram-directed strategy in predicting clinical outcome. The importance of RIPCORD is that it used FFR as a routine part of the initial invasive diagnostic assessment of patients by evaluating all vessels with a lesion diameter stenosis ≥30% at the time of ICA. Therefore, the physiological data were systematically available as part of the evaluation of all management options (OMT and revascularization), in contrast to the trials in which FFR was used in patients already committed to PCI of 1 or more vessels, such as FAME and FAME 2 (21,22).

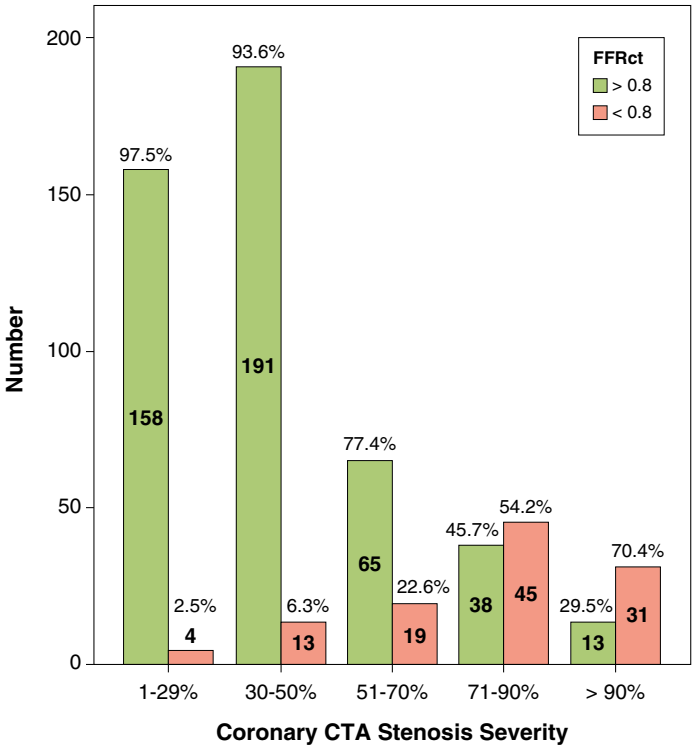
The value of the invasive strategy combining ICA and routine FFR of all vessels for comprehensive simultaneous assessment of anatomy and physiology as a diagnostic tool will be tested in the randomized RIPCORD 2 trial. However, the routine use of ICA alone to assess patients with stable chest pain has important limitations. First, the procedure carries a degree of clinical risk and requires catheter laboratory

FIGURE 2 Detailed Breakdown of Management Allocations by CT Angiography Data Alone (Angio Only) and After FFR_{CT} Available (Final Decision)



OMT = optimal medical therapy; other abbreviations as in Figure 1.

FIGURE 3 Distribution of Lesion Severity of Individual Coronary Vessels According to Visual Assessment of CT Angiogram Alone and Distribution of FFR_{CT} Graded as Positive or Negative According to Cutoff Value ≤0.8 or >0.8, Respectively



n = 577 vessels. CTA = computed tomography angiography; other abbreviations as in Figure 1.

access for all patients. Second, it is recognized that the diagnostic yield of a strategy on the basis of a low threshold for ICA is limited. For example, in 398,978 patients in 1 large U.S. registry undergoing diagnostic coronary angiography, only 37.6% had obstructive CAD (defined as ≥50% of the diameter of the left main coronary artery or ≥70% of the diameter of a major epicardial coronary artery) (1). Nevertheless, there is clinical value in diagnosing the presence of nonobstructive CAD in order to offer disease-modifying pharmacological treatment. Therefore, the ability to assess for the presence of CAD using noninvasive CTA is attractive, and its diagnostic utility is well established (9). Advances in the technology related to CTA have been associated with lower radiation exposure and higher resolution, although diagnostic quality remains compromised in certain patient groups, including those with arrhythmias, patients with high levels of coronary artery calcification, and the obese. The ability of CTA alone to aid in the diagnosis and management of patients with suspected angina is illustrated by the recent SCOT-HEART trial (11). In this trial, 4,146 patients with suspected angina were randomly assigned to standard assessment or standard assessment plus CTA. At 6 weeks, CTA reclassified the diagnosis of coronary heart disease in 27%, and after 1.7 years CTA was associated with a 38% reduction in fatal and nonfatal myocardial infarction, although the latter was nonsignificant.

In the assessment of patients with chest pain suspected to be caused by CAD, physicians have several possible diagnostic options, which search for anatomic evidence of coronary disease, evidence of myocardial ischemia, or both. Although defining the presence of CAD is valuable in terms of delivery of disease-modifying therapy, it is increasingly clear from both observational and randomized data that determining the presence and extent of myocardial ischemia is dominant as a tool to predicting adverse clinical events. Thus, in DEFER (A Multicenter Randomized Study to Compare Deferral Versus Performance of PCI of Non-Ischemia-Producing Stenoses), invasive FFR demonstrated that implanting stents in coronary lesions that are not ischemic has no benefit compared to OMT, regardless of lesion severity on ICA (23). Furthermore, in FAME, patients identified as having multivessel CAD were randomized to have FFR- or angiogram-guided PCI, and the former strategy was associated with fewer vessels treated, fewer stents inserted, lower cost, and better clinical outcomes. In addition, in FAME 2 there was prognostic benefit in a group randomized to PCI compared to medical therapy alone when the revascularization was guided by a positive FFR (21,22). Observational studies including RIPCORD and the French Registry have demonstrated the substantial additional effect on diagnosis and management of patients with chest pain when invasive FFR data are available at the diagnostic stage in addition to the ICA dataset alone.

These data strongly suggest that there is benefit to establishing the presence of both anatomic CAD and myocardial ischemia in patients who present with angina. The ideal screening test for such patients would be able to deliver both components noninvasively. FFR_{CT} is a novel diagnostic technique that allows derivation of FFR from CTA images without the need for additional radiation exposure or medication (13). Previous studies in patients with stable chest pain have demonstrated promising diagnostic accuracy for the technique, which is significantly superior to that of CTA alone, presumably because CTA cannot accurately predict whether a lesion is associated with ischemia.

Specifically, in the NXT trial the area under the receiver-operating characteristic curve was 0.9 for FFR_{CT} versus 0.81 for CTA alone ($p = 0.008$), using invasive FFR ≤0.8 as the reference (16). Given these promising diagnostic data, this study was designed to address the concept that FFR_{CT} would refine diagnosis, and therefore management, in a cohort of patients with stable chest pain in a manner similar to that we previously demonstrated invasively in RIPCORD.

The results from this study confirmed that FFR_{CT} is associated with a mismatch, compared to the anatomic dataset derived from CTA alone, in the assessment of lesion severity ("significance") similar to that seen in RIPCORD and other populations using invasive assessment. As a consequence of this mismatch, the availability of FFR_{CT} in this study translated into a substantial change in the management of these patients. It should be noted that the change in management includes both the predictable reduction in cases in which clinicians required more information about whether lesions were physiologically significant as well as the unpredictable changes arising from the discrepancy between the anatomic and physiological assessments of lesion significance. This study represents a proof of concept, and further larger-scale trials are required to fully assess the potential of using FFR_{CT} as a diagnostic and management screening tool in patients with stable chest pain. The technique has many of the requisite features for such a screening test: it is noninvasive; it provides anatomic and physiological data; the test can be performed quickly; and acquisition of the standard CTA data is straightforward.

STUDY LIMITATIONS. First, we used an existing dataset from another trial in order to test our current hypothesis. Second, not all patients with chest pain are suitable for CTA and therefore for FFR_{CT}. Third, derivation of FFR_{CT} results currently requires high degrees of computational capacity, which involves transfer of the CTA dataset for offsite analysis via a supercomputer; as a result, the turnover is 24 h. Such a delay may become impractical for a proportion of patients if this process were to be used in routine clinical practice. Finally, these specifications will inevitably have implications with regard to access and cost.

CONCLUSIONS

This study demonstrates a proof of concept that the availability of noninvasive FFR_{CT} has a substantial effect on the ability to identify significant CAD and therefore on the management of patients with stable chest pain compared to CTA alone. This finding mimics the observation seen using invasive ICA and FFR in the RIPCORD study. Further studies are required to assess whether FFR_{CT} may represent a candidate as a noninvasive diagnostic and management screening test for patients with stable chest pain.

REPRINT REQUESTS AND CORRESPONDENCE: Prof. Nicholas P. Curzen, Wessex Cardiothoracic Unit, Level North Wing, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, United Kingdom. E-mail: nick.curzen@uhs.nhs.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CTA is increasingly being established as a noninvasive method for assessment of patients with chest pain. The addition of FFR_{CT} (as a novel computer-derived estimate of vessel-specific physiology) to CTA data alone in a 200-patient dataset resulted in a significant change in decisions regarding lesion severity and patient management. This represents proof of principle and mimics the results of the invasive RIPCORD study.

TRANSLATIONAL OUTLOOK: This novel finding now demands further investigation of the potential for FFR_{CT} to be used as a frontline diagnostic and management tool for patients presenting with chest pain. Randomized trials are now being designed to test this hypothesis.

REFERENCES

1. Patel M, Peterson S, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.

2. Fihn S, Gardin J, Abrahms J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol 2012;60:e44–164.

3. Corbett S, Fox K, Curzen N. Optimal medical therapy in percutaneous coronary intervention patients: statins and ACE inhibitors as disease-modifying agents. In: Redwood S, Curzen N, Thomas M, editors. Oxford Textbook of Interventional Cardiology. New York, NY: Oxford University Press, 2010:457–78.

4. 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 2003;107:2900–7.

5. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous

coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.

6. Longman K, Curzen N. Should ischaemia be the main target in selecting a percutaneous coronary intervention strategy? Expert Rev Cardiovasc Ther 2013;11:1051–9.

7. Johnson N, Toth G, Lai D, et al. Prognostic value of fractional flow reserve: linking physiology to clinical outcomes. J Am Coll Cardiol 2014;64:1641–54.

8. Curzen N, Rana O, Nicholas Z, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain? The RIPCORD Study. Circ Cardiovasc Interv 2014;7:248–55.

9. Miller J, Rochitte C, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.

10. Neglia D, Rovai D, Chiara C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging 2015;8:e002179.

11. The SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open label, parallel group, multicentre trial. Lancet 2015;385:2283–91.

12. Douglas P, Hoffman U, Patel M, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.

13. Taylor C, Fonte T, Min J. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol 2013;61:2233–41.

14. Koo B, Erglis A, Doh J, et al. Diagnosis of ischaemia-causing coronary stenosis by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicentre DISCOVER-FLOW study. J Am Coll Cardiol 2011;58:1989–97.

15. Min J, Leipsic J, Pencina M, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;308:1237–45.

16. Norgaard N, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computer tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 2014;63:1145–55.

17. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177–84.

18. Layland J, Oldroyd K, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. Eur Heart J 2015;36:100–11.

19. Van Belle E, Rioufol G, Pouillot C, et al. Outcome impact of coronary revascularisation strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicentre FFR registry. Circulation 2014;129:173–85.

20. Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. Eur Heart J 2014;35:2831–5.

21. De Bruyne B, Pijls N, Kalesan B, et al., for the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) Trial investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

22. De Bruyne B, Fearon W, Pijls N, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014;371:1208–17.

23. Pijls NHJ, 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.

KEY WORDS chest pain, computed tomography angiography, computed tomography-derived fractional flow reserve