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Association between fractional flow reserve, instantaneous wave-free ratio and dobutamine stress echocardiography in patients with stable coronary artery disease

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KEYWORDS

- fractional flow reserve
- non-invasive imaging
- other technique
- single-vessel disease

Abstract

Aims: The association between fractional flow reserve (FFR) and dobutamine stress echocardiography (DSE) in real-world stable angina patients is scant and controversial whereas no such comparison exists with instantaneous wave-free ratio (iFR). The current retrospective study aimed to investigate the associations among these modalities in patients with stable coronary artery disease (CAD) and intermediate coronary lesions.

Methods and results: We studied 62 consecutive stable angina patients who underwent DSE and subsequently coronary angiography with FFR (in all 62) and iFR (in 46/62 patients) assessment of intermediate single-vessel lesions between 2014 and 2015. Using receiver operating characteristic (ROC) curves we sought to identify the optimal FFR and iFR cut-off points with the highest discriminative power to predict the DSE result. The kappa coefficient was used to assess the agreement between FFR, iFR and DSE. The mean age of the study cohort was 63.5±12 years and 35 (56.5%) were males. Thirteen (21%) lesions were adjudicated as causing reversible ischaemia on DSE. Using ROC (FFR predicting DSE result), the area under the curve was 0.952 (95% CI: 0.902 to 1), whereas for iFR it was 0.743 (95% CI: 0.560 to 0.927), $p_{AUC\ comparison}$=0.03. The optimal FFR cut-off point predicting positive DSE was 0.80. There was strong agreement between DSE and FFR (kappa 0.682, p<0.001). There was only modest agreement between iFR and DSE (kappa 0.258, p=0.068) using a cut-off value of 0.9.

Conclusions: In patients referred for evaluation of stable CAD, there was good agreement between DSE and FFR (87%) but less so with iFR (71.7%).

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Abbreviations

DSE	dobutamine stress echocardiography
FFR	fractional flow reserve
iFR	instantaneous wave-free ratio
MI	myocardial infarction
ROC	receiver operating characteristic

Introduction

The safety and feasibility of dobutamine stress echocardiography (DSE) in patients following myocardial infarction (MI) was first demonstrated by Berthe et al[1] in the early 1980s. Pierard et al[2] validated this method against positron emission tomography in 17 patients while Picano et al revealed that DSE is safe and can be conclusive without any complications in 88% of cases[3]. The prognostic value of DSE was initially shown in a cohort of 778 post-MI patients[4] and established in a meta-analysis of 5,946 patients[5], demonstrating a negative predictive value (NPV) for MI and cardiac death of 98.4% over the 33 months of follow-up.

In the early 1990s Pijls et al[6] introduced the invasive coronary fractional flow reserve (FFR), adding a functional assessment to the anatomy-dominated world of coronary intervention. In a seminal paper[7], FFR was compared to a combination of several functional tests, among them DSE, and demonstrated satisfactory diagnostic accuracy in predicting a positive functional test using a cut-off of 0.75. The prognostic significance of FFR has been demonstrated in large randomised trials[8-10] using cut-offs of between 0.75 and 0.8 when defining a positive result. In 2012, the instantaneous wave-free ratio (iFR) non-hyperaemic index was introduced[11]. It was claimed to be able to predict a positive FFR result accurately ($r=0.9$, $p<0.001$) with a receiver operating characteristic (ROC) area under the curve (AUC) of 0.93, at FFR <0.8.

In a recent paper by Wu et al[12], 67 vessels with 50% to 80% diameter stenosis by quantitative coronary angiography (QCA) in 58 consecutive patients were examined with FFR and real-time myocardial contrast echocardiography (RTMCE). Even though 17/18 stenoses that were FFR positive had abnormal capillary blood flow (CBF) during RTMCE, 28/49 stenoses (57%) that were FFR negative also had abnormal CBF in the corresponding coronary artery territory during stress echocardiography. To our knowledge, to date no studies have compared both FFR and iFR to contrast-enhanced DSE.

In this study we aimed to identify the agreement between FFR, iFR and contrast-enhanced DSE using second-generation contrast agents in real-world stable angina patients with single intermediate coronary artery lesions. Furthermore, we aimed to identify the optimal FFR and iFR cut-off values that predict the presence of reversible ischaemia during DSE in such patients.

Methods

Two hundred and seventy-eight patients with stable angina underwent DSE and subsequently coronary angiography at Imperial NHS Trust Hospitals (Hammersmith, St. Mary's and Charing Cross) between 2014 and 2015. Patients with negative DSE underwent coronary angiography if their symptoms were typical. Eighty-three of them had lesions of intermediate severity and underwent invasive FFR. Interoperator variability for contrast DSE was excellent with a kappa of 0.92. Patients with inconclusive DSE imaging, previous CABG, multivessel disease, full thickness infarct of the culprit artery, sequential lesions, diffuse disease or significant valvular disease were excluded. In particular, after excluding five patients who had inconclusive DSE, 10 who had previous CABG, multivessel disease, tandem lesions in a single vessel or distal diffuse disease and six who had significant valvular disease, the final patient cohort consisted of 62 patients. In 16 of these patients iFR measurements were not performed due to operator preference. These patients had single-vessel, single lesion disease with no prior MI related to the target vessel. The hospital ethics committee approved this retrospective study and all participants signed informed consent for relevant procedures.

DOBUTAMINE STRESS ECHO

All patients underwent contrast DSE following the protocol suggested by the European Association of Echocardiography recommendations. Details are described in the **Supplementary Appendix 1**.

PRESSURE WIRE STUDIES

Coronary angiography and pressure-flow assessments of coronary stenoses were performed using conventional approaches within three months from DSE[13]. No changes in ischaemic symptoms or medical therapy occurred in any of the patients included in the study. Details of the procedures are described in the **Supplementary Appendix 2**.

QUANTITATIVE CORONARY ANGIOGRAPHY

QCA parameters (diameter stenosis [DS] %, minimal lumen diameter [MLD] mm, minimal lumen area [MLA] mm^2, area stenosis [AS] %, reference vessel diameter [RVD] mm, and reference vessel area [RVA] mm^2) were calculated using dedicated workstations (CAAS II; Pie Medical, Maastricht, the Netherlands).

STATISTICAL ANALYSIS

Results are presented as means±SD, medians (interquartile range) or percentages. In order to identify the optimal cut-off point for maximum diagnostic accuracy between FFR and DSE, ROC curves and the Youden's J statistic were used. We used sensitivity, specificity, positive and negative predictive values and the kappa coefficient to assess the agreement between FFR, iFR and DSE. Differences between areas under the curve (AUC) were compared using the Hanley and McNeil test[14].

Results

A total of 62 patients with single intermediate angiographic lesions (50-80% visually estimated maximum lumen narrowing) were assessed over the two-year period. Mean age was 63.5±12 years and 35 (56.5%) were males. Baseline demographics of the study

population are presented in **Table 1** and **Table 2**. The LAD was assessed in 53 cases (85.5%), the LCx in two (3.2%) and the RCA in seven (11.3%). The mean DS was 48.5±8.3% whereas the MLD was 1.44±0.32 mm **(Table 1)**.

Of the 46 patients who also underwent iFR, 40 (87%) had their LAD assessed, two (4.3%) their LCx and four (8.7%) the RCA. iFR evaluation always preceded FFR.

DOBUTAMINE STRESS ECHO AS THE GOLD STANDARD

Thirteen (21%) of these lesions were adjudicated as causing reversible ischaemia during DSE. The AUC for FFR predicting a DSE result was 0.952 (95% CI: 0.902 to 1.00), p<0.001 **(Figure 1A)**. The optimal FFR cut-off point (≥) to predict a negative DSE result was 0.8. Using this cut-off, 21 (33.9%) of these lesions were rendered "flow-limiting" **(Figure 1B)**. There was a strong agreement between the two modalities (kappa 0.682, p<0.001). Using DSE as the gold standard, FFR (with a cut-off point of 0.8) had a sensitivity of 100% and a specificity of 83.7%. The positive predictive value was 61.9%, whereas the negative predictive value was 100%. Diagnostic agreement was achieved in 87% of patients (54/62).

In the 46 patients who had both FFR and iFR measurements, the AUC for iFR predicting a positive DSE result was 0.743 (95% CI: 0.560 to 0.927), p=0.025 **(Figure 2A)**. The optimal iFR cut-off to predict a DSE result was 0.90. Using this cut-off value, 14 (30.4%) lesions were rendered haemodynamically significant **(Figure 2B)**. There was a modest agreement between iFR and DSE (kappa 0.258, p=0.068). Using DSE as the gold standard, iFR (with a cut-off value of 0.9) had a sensitivity of 55.6%, a specificity of 75.7%, a positive predictive value of 35.7% and a negative predictive value of 87.5%. Diagnostic agreement would have been achieved in 33/46 (71.7%).

Amongst the 46 patients who underwent both FFR and iFR measurements, the AUC, for pressure wire measurements using DSE as the gold standard, was significantly higher for FFR (0.935, 95% CI: 0.864 to 1.00) compared to iFR (0.743, 95% CI: 0.560 to 0.927); AUC difference 0.192 (SE difference 0.09, p=0.03) **(Figure 3)**.

A summary of sensitivity, specificity, NPV, PPV using DSE, FFR and iFR as gold standards is shown in **Table 3**.

Table 1. Demographics of the cohort.

General demographics		N=62
Age		63.5±12
Male gender, n (%)		35 (56.5)
Ethnicity, n (%)	White	32 (51.6)
	South Asian	14 (22.6)
	Afro-Caribbean black	2 (3.2)
	Other	14 (22.6)
Diabetes, n (%)		20 (32.3)
Hypercholesterolaemia, n (%)		40 (64.5)
Smoking status	Never smoked	38 (61.3)
	Ex-smoker	10 (16.1)
	Current smoker	14 (22.6)
Obesity, n (%)		6 (9.7)
Hypertension, n (%)		40 (64.5)
Family history of IHD, n (%)		17 (27.4)
Previous MI, n (%)		26 (41.9)
End-stage renal failure, n (%)		4 (6.5)
Left ventricular systolic function	Normal	47 (75.8)
	Mild impairment	9 (14.5)
	Moderate impairment	4 (6.5)
	Severe impairment	2 (3.2)
Quantitative coronary angiography		**N=62**
Vessel pressure wire performed, n (%)	LAD	53 (85.5)
	LCx	2 (3.2)
	RCA	7 (11.3)
Diameter stenosis (%)		48.5±8.3
Area stenosis (%)		72.8±8.4
Minimum lumen diameter (mm)		1.44±0.32
Minimum lumen area (mm^2)		1.7±0.76
Reference vessel diameter (mm)		2.78±0.41
Reference vessel area (mm^2)		6.21±1.87

IHD: ischaemic heart disease; MI: myocardial infarction

Table 2. FFR, iFR and DSE results in the study population.

Any vessel (N=62)	
FFR	0.83±0.07
iFR	0.91±0.05
FFR positive, n (%)	21 (33.9)
iFR positive, n (%)*	14 (30.4)
DSE positive, n (%)	13 (21)
LAD (N=53)	
FFR positive, n (%)	20 (37.7)
iFR positive, n (%)**	14 (35)
DSE positive, n (%)	12 (22.6)
LCx/RCA (N=9)	
FFR positive, n (%)	12 (22.6)
iFR positive, n (%)***	0 (0)
DSE positive, n (%)	1 (11.1)

*iFR measured in a total of 46 patients. **iFR measured in 40 LAD lesions. ***iFR measured in a total of 6 LCx/RCA lesions.
DSE: dobutamine stress echo; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio

Discussion

In this study we demonstrated a good correlation between contrast-enhanced DSE using second-generation contrast agents and invasive FFR measurements but a worse correlation with iFR in predicting reversible myocardial ischaemia in consecutive stable angina patients with intermediate coronary artery lesions. Using ROC curves, we identified that the optimal FFR cut-off value to

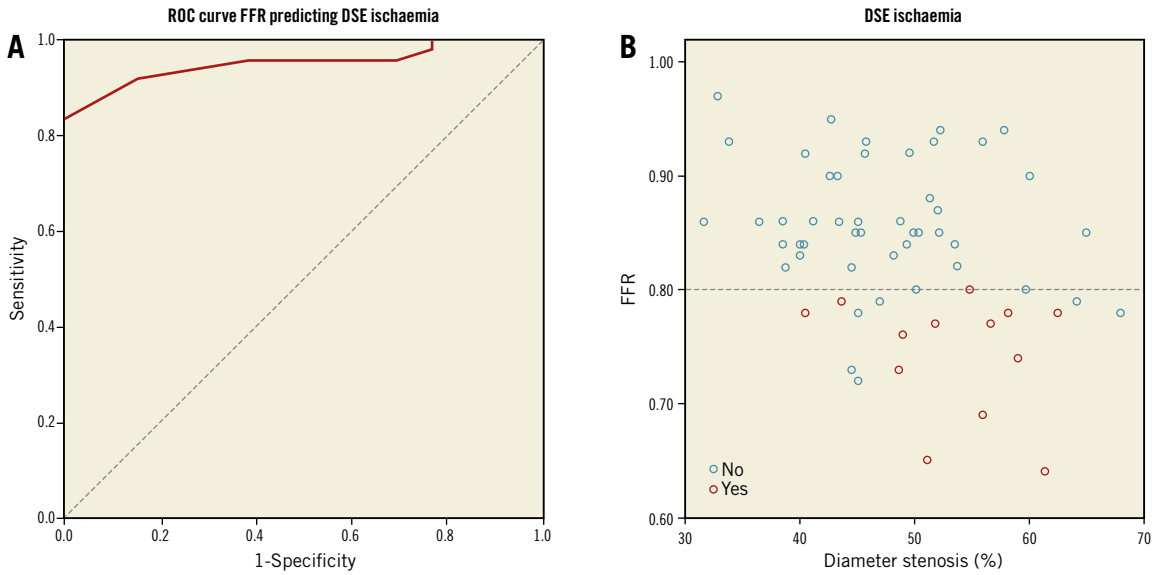

Figure 1. *Agreement between FFR and DSE. A) ROC curve demonstrating good correlation of FFR with DSE. B) Scatter plot demonstrating the agreement between FFR using the 0.8 cut-off and DSE across the range of anatomic lesions.*

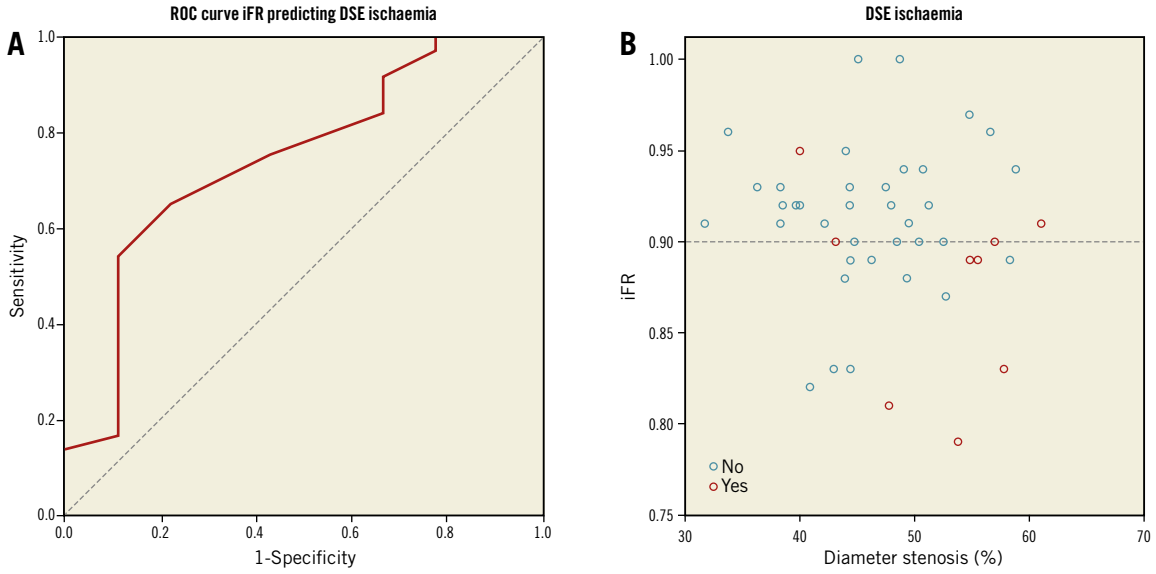

Figure 2. *Agreement between iFR and DSE. A) ROC curve demonstrating the modest correlation of iFR with DSE. B) Scatter plot demonstrating the agreement between iFR using the 0.90 cut-off and DSE across the range of anatomic lesions.*

predict the DSE result was 0.8, which coincides with the currently used cut-off in clinical practice.

In a seminal paper by Pijls et al[7], FFR was compared to exercise testing, thallium scintigraphy, DSE and quantitative arteriography in 45 consecutive patients with moderate coronary stenosis and chest pain, prospectively testing the earlier cut-off value of 0.75[15] to a true gold standard based upon the combination of the three non-invasive tests, all performed within 24 hours from the FFR measurement. Using a multi-testing sequential Bayesian approach, the sensitivity of FFR in the identification of reversible ischaemia was 88%, the specificity 100%, the positive predictive value 100%, and the negative predictive value 88%. In another early study of 75 stable angina patients[16], the degree of dobutamine-induced dyssynergy correlated well with FFR using a cut-off of 0.75 (r=0.77). Despite the excellent PPV of 98%, a very low NPV (61%) was observed using this cut-off. Based on this cut-off, the DEFER study[6] did not show any significant difference in patient outcomes with FFR ≥0.75 who underwent percutaneous coronary

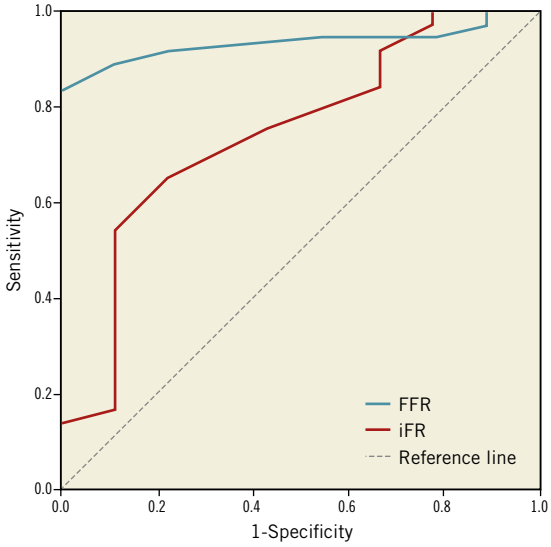

Figure 3. *ROC curves for FFR and iFR using DSE as the gold standard.*

Table 3. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) using DSE, FFR or iFR as gold standard in the group of 46 patients who underwent all three modalities.

DSE as gold standard					
	Sensitivity	Specificity	NPV	PPV	Accuracy
iFR	55.6	75.7	87.5	35.7	71.7
FFR	100	83.8	100	60	87
FFR as gold standard					
	Sensitivity	Specificity	NPV	PPV	Accuracy
DSE	60	100	83.8	100	87
iFR	73.3	90.3	87.5	78.6	84.8
iFR as gold standard					
	Sensitivity	Specificity	NPV	PPV	Accuracy
FFR	78.6	87.5	90.3	73.3	84.8
DSE	35.7	87.5	75.7	55.6	71.7

iFR cut-off of 0.9 and FFR cut-off of 0.8 used. DSE: dobutamine stress echo; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio

intervention compared to those treated medically. If a value of 0.80 had been used in the study by Piljs[7], the sensitivity would have been 100% and the specificity 92%, figures pretty similar to the ones reported in our study. In order to avoid not treating an ischaemic lesion rather than treating a non-ischaemic lesion, in the FAME[8] and FAME 2[17] trials a cut-off value of 0.80 was used, demonstrating the prognostic benefits of FFR-guided revascularisation. In a more recent retrospective study, in an attempt to justify the use of the 0.8 cut-off in clinical practice, Adjedj et al[18] investigated the outcomes of patients with single lesions in the so-called "grey zone" of FFR 0.76 to 0.80 who were either revascularised or treated with medical therapy alone. Of interest, even though there was no significant difference in overall major adverse cardiac events (MACE), there was a trend for higher mortality (p=0.059) and the combined outcome of MI/death (p=0.06) in the medical therapy group.

In the current study without presumptions, we have shown that the optimal FFR cut-off value to predict reversible myocardial ischaemia during DSE was 0.8. Using this cut-off, the negative predictive value was 100%, rendering it safe practice to treat patients with FFR values above 0.8 conservatively. In an early study by de Bruyne et al[19], a close correlation was found between relative flow reserve obtained by positron emission tomography (PET) and myocardial FFR (r=0.87), once again proving the validity of FFR against robust non-invasive modalities. In a recent meta-analysis by Danad et al[20], the sensitivity of DSE in predicting FFR was 75% (compared to 61.9% in the current study) and the specificity only 75% (compared to 100%). The discrepancies in the sensitivity and specificity figures can be attributed to differences in the population studied and the fact that we used contrast DSE rather than plain DSE. In the study by Jung et al[21], there was a significant improvement in sensitivity (for predicting FFR) from 48 to 83% when using contrast compared to plain imaging. In a small study of just 21 patients, Jimenez-Navarro et al[22] demonstrated only a moderate correlation of FFR with DSE with a kappa value of 0.51. The improvements of spatial resolution and image quality in modern cardiac ultrasound systems along with standardisation of the DSE examination[23] and the routine use of second-generation contrast agents may explain the better diagnostic accuracy observed in our study. In the COMPRESS trial[24], contrast echo DSE and single photon emission computed tomography (SPECT) were compared to FFR in 48 patients, 41 of whom had multivessel disease. The sensitivity of DSE in this patient substrate was similar to that in our study at 67% (61.9% in our study), whereas specificity was much lower at 77% (100%). The reduced specificity is partially explained by the different study population and design. Recently, Wu et al[12], putting a new spin on non-invasive test vs. pressure wire comparisons, showed that almost half of patients with negative pressure wire studies might suffer from microvascular disease, as evidenced by reductions in CBF. This suggests that the presence of severe microvascular disease can be missed by FFR, hence a separate methodology to assess the microvasculature is mandatory.

Recently, iFR has been validated against FFR[25-28] with ROC curves against FFR ranging from 0.81[26] to 0.9[27], but no comparison with DSE exists as yet. A comparison of iFR and PET perfusion imaging revealed a ROC of 0.86 for iFR, which was similar to the one for FFR at 0.85 (p=0.71). In our study, the ROC curve between iFR and FFR was also within the aforementioned range at 0.853[29]. Most operators in our institution would not perform FFR routinely in lesions with iFR or Pd/Pa over 0.95 or lower than 0.8, hence lesions with much higher agreement between

iFR and FFR have been excluded. This selection bias seen in our study is a reflection of the real-world experience and hence much more informative compared to studies which include cases at the extreme ranges of iFR and FFR. Recently, two large non-inferiority randomised trials compared the prognostic value of iFR versus FFR[30,31], establishing that coronary revascularisation guided by iFR is non-inferior to revascularisation guided by FFR with respect to risk of MACE at one year. Interestingly, despite similar one-year MACE, in both studies there were significantly more haemodynamically significant lesions in the FFR group[30,31], leading to more revascularisation procedures[30]. These two large iFR studies suggest that, by using the 0.8 FFR cut-off, physicians may be overtreating patients who could potentially do just as well with medical therapy. The modest agreement between iFR and DSE shown in the present study highlights the difficulties in achieving an optimal revascularisation cut-off consensus amongst different modalities and the need for larger outcome trials that incorporate non-invasive and pressure wire studies in their design.

Limitations

Limitations of the current study include its retrospective nature and the presence of a small time lag, albeit <3 months, between pressure wire studies and DSE. In the majority of cases the LAD was assessed, hence results should be viewed with caution when assessing non-LAD arteries. Another factor that should be taken into account is the potential for selection bias, as only patients with truly intermediate stenosis would have gone on to invasive pressure wire assessments. Nevertheless, it is the largest study yet comparing FFR with contrast-enhanced DSE using contemporary new-generation echocardiographic platforms with the routine use of second-generation contrast agents and pressure wire devices, and the first to use ROC curves to identify optimal FFR and iFR cut-offs to predict a DSE result. Furthermore, this is the first study to compare iFR with DSE directly. Future, multicentre studies are required to confirm our findings in large patient cohorts.

Conclusions

The current study shows that contrast-enhanced, state-of-the-art DSE correlates strongly with FFR but less so with iFR in real-world patients with single moderate coronary artery lesions. This highlights that contrast DSE can be used as a good gatekeeper, keeping patients with atypical symptoms and negative DSE studies away from invasive procedures. However, when positive, FFR is more likely to be in line with the DSE results compared to iFR.

Impact on daily practice

In real-world patients, contrast-enhanced, state-of-the-art DSE is a good gatekeeper for invasive procedures. When DSE is positive, FFR is more likely to agree with DSE compared to iFR.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Berthe C, Pierard LA, Hiernaux M, Trotteur G, Lempereur P, Carlier J, Kulbertus HE. Predicting the extent and location of coronary artery disease in acute myocardial infarction by echocardiography during dobutamine infusion. *Am J Cardiol.* 1986;58:1167-72.
2. Pierard LA, De Landsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol.* 1990;15:1021-31.
3. Picano E, Mathias W Jr, Pingitore A, Bigi R, Previtali M. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicentre study. Echo Dobutamine International Cooperative Study Group. *Lancet.* 1994;344:1190-2.
4. Sicari R, Picano E, Landi P, Pingitore A, Bigi R, Coletta C, Heyman J, Casazza F, Previtali M, Mathias W Jr, Dodi C, Minardi G, Lowenstein J, Garyfallidis X, Cortigiani L, Morales MA, Raciti M. Prognostic value of dobutamine-atropine stress echocardiography early after acute myocardial infarction. Echo Dobutamine International Cooperative (EDIC) Study. *J Am Coll Cardiol.* 1997;29:254-60.
5. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol.* 2007;49:227-37.
6. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. 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.
7. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703-8.
8. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med.* 2009;360:213-24.
9. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med.* 2014;371:1208-17.
10. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B; FAME Study Investigators. 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.

11. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE. 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.

12. Wu J, Barton D, Xie F, O'Leary E, Steuter J, Pavlides G, Porter TR. Comparison of Fractional Flow Reserve Assessment With Demand Stress Myocardial Contrast Echocardiography in Angiographically Intermediate Coronary Stenoses. *Circ Cardiovasc Imaging.* 2016 Aug;9(8).

13. Kern MJ, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, Higano ST, Lim MJ, Meuwissen M, Piek JJ, Pijls NH, Siebes M, Spaan JA; American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. 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.

14. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology.* 1982;143:29-36.

15. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation.* 1995;92:3183-93.

16. Bartunek J, Marwick TH, Rodrigues AC, Vincent M, Van Schuerbeeck E, Sys SU, de Bruyne B. Dobutamine-induced wall motion abnormalities: correlations with myocardial fractional flow reserve and quantitative coronary angiography. *J Am Coll Cardiol.* 1996;27:1429-36.

17. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991-1001.

18. Adjedj J, De Bruyne B, Floré V, Di Gioia G, Ferrara A, Pellicano M, Toth GG, Bartunek J, Vanderheyden M, Heyndrickx GR, Wijns W, Barbato E. Significance of Intermediate Values of Fractional Flow Reserve in Patients With Coronary Artery Disease. *Circulation.* 2016;133:502-8.

19. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, Paulus WJ, Heyndrickx GR, Wijns W. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation.* 1994;89:1013-22.

20. Danad I, Szymonifka J, Twisk JWR, Norgaard BL, Zarins CK, Knaapen P, Min JK. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J.* 2017;38:991-8.

21. Jung PH, Rieber J, Störk S, Hoyer C, Erhardt I, Nowotny A, Voelker W, Weidemann F, Ertl G, Klauss V, Angermann CE. Effect of contrast application on interpretability and diagnostic value of dobutamine stress echocardiography in patients with intermediate coronary lesions: comparison with myocardial fractional flow reserve. *Eur Heart J.* 2008;29:2536-43.

22. Jiménez-Navarro M, Alonso-Briales JH, Hernandez Garcia MJ, Rodriguez Bailon I, Gomez-Doblas JJ, de Teresa Galvan E. Measurement of fractional flow reserve to assess moderately severe coronary lesions: correlation with dobutamine stress echocardiography. *J Interv Cardiol.* 2001;14:499-504.

23. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL; European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr.* 2008;9:415-37.

24. Rieber J, Jung P, Erhard I, Koenig A, Hacker M, Schiele TM, Segmiller T, Stempfle HU, Theisen K, Siebert U, Klauss V. Comparison of pressure measurement, dobutamine contrast stress echocardiography and SPECT for the evaluation of intermediate coronary stenoses. The COMPRESS trial. *Int J Cardiovasc Intervent.* 2004;6:142-7.

25. Petraco R, Al-Lamee R, Gotberg M, Sharp A, Hellig F, Nijjer SS, Echavarria-Pinto M, van de Hoef TP, Sen S, Tanaka N, Van Belle E, Bojara W, Sakoda K, Mates M, Indolfi C, De Rosa S, Vrints CJ, Haine S, Yokoi H, Ribichini FL, Meuwissen M, Matsuo H, Janssens L, Katsumi U, Di Mario C, Escaned J, Piek J, Davies JE. Real-time use of instantaneous wave-free ratio: results of the ADVISE in-practice: an international, multicenter evaluation of instantaneous wave-free ratio in clinical practice. *Am Heart J.* 2014;168:739-48.

26. Jeremias A, Maehara A, Généreux P, Asrress KN, Berry C, De Bruyne B, Davies JE, Escaned J, Fearon WF, Gould KL, Johnson NP, Kirtane AJ, Koo BK, Marques KM, Nijjer S, Oldroyd KG, Petraco R, Piek JJ, Pijls NH, Redwood S, Siebes M, Spaan JA, van 't Veer M, Mintz GS, Stone GW. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol.* 2014;63:1253-61.

27. Escaned J, Echavarria-Pinto M, Garcia-Garcia HM, van de Hoef TP, de Vries T, Kaul P, Raveendran G, Altman JD, Kurz HI, Brechtken J, Tulli M, Von Birgelen C, Schneider JE, Khashaba AA, Jeremias A, Baucum J, Moreno R, Meuwissen M, Mishkel G, van Geuns RJ, Levite H, Lopez-Palop R, Mayhew M, Serruys PW, Samady H, Piek JJ, Lerman A; ADVISE II Study Group. Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance: Results of ADVISE II

International, Multicenter Study (ADenosine Vasodilator Independent Stenosis Evaluation II). *JACC Cardiovasc Interv.* 2015;8:824-33.

28. Härle T, Bojara W, Meyer S, Elsässer A. Comparison of instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR)--first real world experience. *Int J Cardiol.* 2015;199:1-7.

29. van de Hoef TP, Meuwissen M, Escaned J, Sen S, Petraco R, van Lavieren MA, Echavarria-Pinto M, Nolte F, Nijjer S, Chamuleau SA, Voskuil M, van Eck-Smit BL, Verberne HJ, Henriques JP, Koch KT, de Winter RJ, Spaan JA, Siebes M, Tijssen JG, Davies JE, Piek JJ. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: diagnostic accuracy for stenosis-specific myocardial ischaemia. *EuroIntervention.* 2015;11:914-25.

30. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Harle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med.* 2017; 376:1824-34.

31. Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Öhagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Tödt T, Venetsanos D, James SK, Karegren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Fröbert O; iFR-SWEDEHEART Investigators. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med.* 2017;376:1813-23.

Supplementary data

Supplementary Appendix 1. Dobutamine stress echo.

Supplementary Appendix 2. Pressure wire studies.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/131st_issue/319

Supplementary data

Supplementary Appendix 1. Dobutamine stress echo protocol

Beta-blockers as well as calcium channel blockers had been discontinued 48 hours prior to the test. A peripheral venous line was inserted and a baseline 12-lead ECG was obtained. A complete baseline transthoracic echocardiographic study was performed initially, followed by the DSE always with the use of a second-generation contrast agent (SonoVue®; Bracco Imaging SpA, Milan, Italy) to achieve the best possible image quality and diagnostic accuracy. Contrast was delivered by slow bolus injection (about 1 ml/30 seconds). Echocardiography was performed by experienced and accredited sonographers, who followed a standardised echocardiographic protocol, using commercially available ultrasound equipment (iE33; Philips Healthcare, Amsterdam, the Netherlands). During stress echocardiography, continuous intravenous infusion of dobutamine in three-minute increments started with 5 μg/kg/min and increased to 10, 20, 30 and 40 μg/kg/min. If the target heart rate was not achieved (85% of maximum age-predicted heart rate), handgrip was applied and/or atropine (0.25 mg up to a maximum of 2 mg) was given in the absence of the relative contraindications. The electrocardiogram was monitored continuously and blood pressure was measured and recorded in the last minute of each stage. Images were obtained using four views (apical four- and two-chamber views and parasternal long-axis and short-axis at papillary muscle level) and were continuously monitored and stored in quad screen format in all four stages: low dose – at the dose of 10 μg/kg/min, high dose – at 70% of the max HR predicted, and peak dose – at 85% of the max HR predicted just prior to discontinuing the test. Images during recovery were constantly monitored until total resolution of any abnormal regional wall motions that had been incurred. The endpoints for dobutamine infusion were:

achievement of 85% of the max predicted HR, development of left ventricular asynergy, severe chest pain, electrocardiographic changes suggestive of myocardial ischaemia or serious arrhythmias, blood pressure ≥220/110 mmHg, intolerable side effects (e.g., nausea, drop of blood pressure >20 mmHg from the baseline value), and patient's desire. DSE studies were stored electronically in four quad data set format using the ProSolv Cardiovascular, Inc. (Fujifilm Medical Systems, Indianapolis, IN, USA) and Medcon, Inc. electronic archiving software.

Data analysis was performed off-line at the Hammersmith Hospital core laboratory after collection of all DSE data, by one expert assessor (P. Nihoyannopoulos) blinded to any clinical/angiographic results, using the 16-segment LV model. DSE was considered positive if new or worsening wall motion abnormalities had occurred in segmental contractility.

Supplementary Appendix 2. Pressure wire studies

Intracoronary nitrates (200-300 mg) were administered in all cases. At the time of catheterisation, a 6 Fr coronary catheter was introduced into the right radial artery and advanced into the ostium of the coronary artery. A 0.36 mm (0.014 inch) pressure-monitoring guidewire (Verrata® wire; Volcano Corporation, San Diego, CA, USA) was used and the distal pressure sensor was equalised with the aortic guiding pressure at the coronary ostium before crossing the lesion. Measurements were made as distal to the stenosis as technically possible, maintaining the wire in the main epicardial vessel. Same sitting iFR measurements were performed in 46 (74%) patients prior to inducing steady-state hyperaemia (based on operator preference). iFR was calculated as the mean pressure distal to the stenosis during the diastolic wave-free period (Pd wave-free period) divided by the mean aortic pressure during the diastolic wave-free period (Pa wave-free period) as previously described [11] using a built-in wave-free algorithm (developed at Imperial College, London and licensed to Volcano Corp., San Diego, CA, USA). Adenosine was administered by intravenous infusion (140 μg/kg/min). When steady-state hyperaemia was achieved, FFR was calculated as the ratio of the mean distal intracoronary pressure measured by the wire to the mean arterial pressure measured by the coronary catheter, as described previously [14]. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. If drift was identified the measurements were repeated.