Leite et al. BMC Cardiovascular Disorders (2015) 15:127
DOI 10.1186/s12872-015-0122-1

BMC Cardiovascular Disorders

CASE REPORT Open Access

Fractional flow reserve of non-culprit vessel post-myocardial infarction: is it reliable?

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Abstract

Background: Multi-vessel disease is frequent in patients presenting with myocardial infarction and have an important prognostic impact. The decision to proceed to revascularization in non-culprit vessels can be postponed until ischemia is proven in non-invasive stress tests. On the other hand, there is an increasing evidence to support the role of fractional flow reserve (FFR) in acute coronary syndrome setting.

Case presentation: We report a case in which a FFR-guided strategy for non-culprit vessels, 3 weeks after an ST-segment elevation myocardial infarction, was followed by a short-term sub-occlusion of the evaluated vessel.

Conclusion: The timing of the coronary microcirculation recovery post-myocardial infarction, avoiding a possible false negative FFR, and the diagnostic gaps between ischemia and plaque vulnerability are under discussion. An FFR-guided strategy in this setting should be interpreted with caution.

Keywords: Multi-vessel disease, Myocardial infarction, Fractional flow reserve, Ischemia, Plaque vulnerability

Background

The prevalence of multi-vessel disease (MVD) in patients presenting with acute ST-segment elevation myocardial infarction (STEMI) approaches 40 % [1]. This subgroup of STEMI patients has a higher risk of major adverse cardiac events (MACE) in the first year after primary percutaneous coronary intervention (PCI) [2]. Therefore, the assessment of the actual severity of the non-culprit coronary artery stenosis and its optimal treatment is clinically important soon after primary PCI.

Case presentation

A 79-year-old female with a history of hypertension and dyslipidaemia, was admitted for an inferior STEMI and underwent primary angioplasty of the right coronary artery with implantation of a 3.0 × 33 mm Xience™ everolimus-eluting stent. The emergency coronary angiography also showed three intermediate stenosis in the mid-segment of the left anterior descending artery (LAD) – Fig. 1. Transthoracic echocardiogram demonstrated normal biventricular systolic function with a left ventricular ejection fraction of 60 %. The patient was clinically stable and was discharged 4 days later with optimized medical therapy (aspirin 100 mg qd, ticagrelor 90 mg bid, atorvastatin 40 mg qd, carvedilol 6.25 mg bid, ramipril 1.25 mg qd, pantoprazol 40 mg qd).

In order to assess the hemodynamic relevance of the LAD lesions, a 3 week scheduled coronary angiography with fractional flow reserve (FFR) measurements of LAD was performed (Fig. 2), using a 0.014″ pressure guide wire (PressureWire Aeris™, St Jude Medical, Uppsala, Sweden). Resting distal coronary pressure to aortic pressure ratio (Pd/Pa) was 0.94. FFR was 0.87, indicating physiologically non-significant stenosis. There was no damping of the proximal aortic pressure trace, ensuring an accurate FFR measurement.

Two months later, the patient was admitted for an anterior STEMI and the emergency coronary angiography revealed a sub-occlusion of the mid-LAD (Fig. 3). The lesion was treated with a 3.0 × 15 mm Xience™ everolimus-eluting stent. Right coronary angiography showed neither restenosis in the previously implanted stent nor other significant coronary lesions. The patient assured having good compliance with the therapeutic regimen since the first cardiovascular event.

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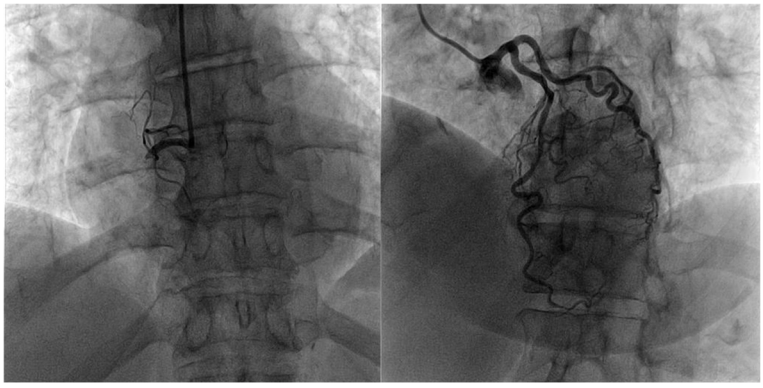

Fig. 1 Coronary angiography in the inferior STEMI. Total occlusion of the proximal-segment of the right coronary artery and three intermediate stenosis in the mid-segment of the LAD

Discussion

In patients with STEMI and MVD, the current recommendations state that primary PCI should be limited to the culprit vessel with the exception of cardiogenic shock in the presence of multiple, critical stenosis or highly unstable lesions, and if there is persistent ischemia after PCI on the supposed culprit lesion [3]. If staged PCI to non-culprit vessels is being considered, non-invasive stress testing (myocardial perfusion scintigraphy, stress echocardiography, positron emission tomography or magnetic resonance imaging) should be used for ischemia and viability testing prior to a decision to proceed with PCI [4].

Fractional flow reserve is a well-validated technique to guide coronary intervention by identification of lesion-level ischemia. In the DEFER study, the prognosis of intermediate lesions with an FFR of > 0.75 was excellent if treated medically, with a < 1 % risk of any AMI after 5 years of follow-up [5]. However, studies to date have mainly involved stable patients outside of acute myocardial infarction (AMI) [5–8]. The use of FFR to assess culprit and non-culprit lesions in the setting of acute ischemia represents a controversial area, although there is an increasing evidence base to support the role of FFR-guided strategy in acute coronary syndrome (ACS) [9].

The physiological principles underlying FFR are critically dependent on the ability to achieve maximal hyperaemia. In patients with AMI, pathophysiological disturbances in the microvasculature can have a potential impact on the ability to induce maximal hyperaemia, and thereby compromise the accuracy of FFR assessments in non-culprit vessels, theoretically leading to false negative results [10]. The 2011 ESC Guidelines for the management of ACS without ST-segment elevation [11] recommend that FFR should be ideally performed more than 5 days after the acute event in order to minimize the impact of any microvascular disturbance. The 2012 ESC Guidelines for the management

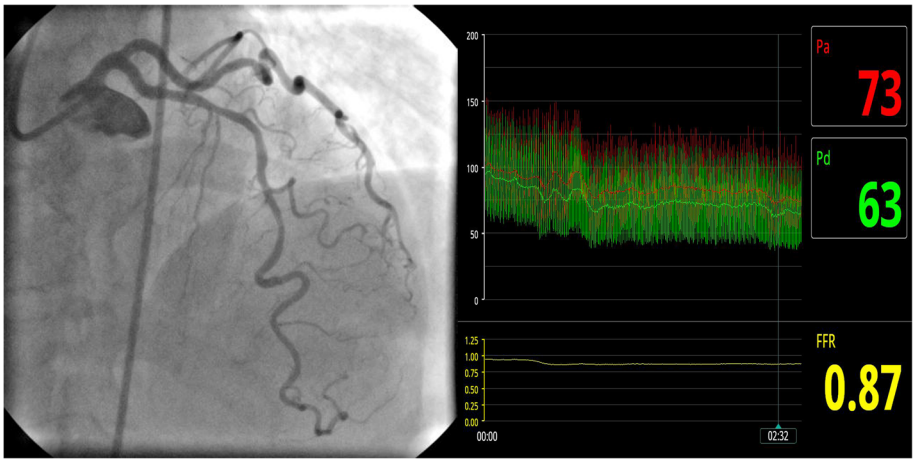

Fig. 2 Three-week follow-up with coronary angiography and FFR. Coronary angiography showing the intermediate LAD lesions and FFR evaluation with the result of 0.87

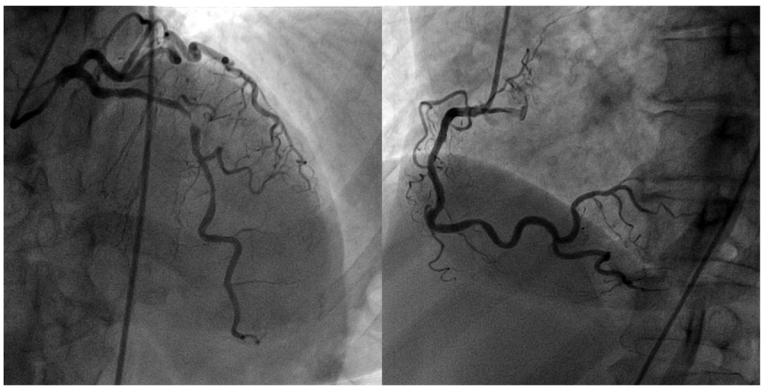

Fig. 3 Coronary angiography in the anterior STEMI. Sub-occlusion of the mid-LAD and right coronary artery without significant lesions

of STEMI [4] state the staged revascularization approach for STEMI with MVD can be guided by FFR if performed several days or weeks after primary PCI. In the case report presented, the functional assessment of the mid-LAD lesions was made 3 weeks later than the primary PCI, in concordance to the current guidelines.

One of the most important studies about the use of FFR in ACS was from Ntalianis et al. [12] who studied 75 acute STEMI patients and 26 NSTEMI patients (<72 h post onset) and measured FFR in the non-culprit stenosis immediately following PCI of the culprit vessel and then repeated the FFR at 35 ± 4 days post initial procedure. The FFR value remained unchanged between the acute and follow-up phases in patients with STEMI (0.78 ± 0.10 vs. 0.76 ± 0.10, p = NS) and NSTEMI (0.77 ± 0.10 vs. 0.77 ± 0.20, p = NS). In only 2 patients, the FFR value was higher than 0.80 at the acute phase and lower than 0.75 at follow-up. The authors stated the data support that FFR measurements are safe and reliable for evaluating the severity of non-culprit stenosis in the acute phase of ACS, even during primary PCI.

A more recent study from Cuculi et al. [13] performed an invasive assessment of coronary physiology in 82 STEMI patients, immediately following PCI of the culprit vessel and 6 months later, associated with a contrast-enhanced cardiac magnetic resonance imaging evaluation of microvascular obstruction. Baseline Pd/Pa remained stable over time, but FFR reduced significantly between primary PCI and 6 months (p = 0.008); this reduction was mainly observed in patients with microvascular obstruction. Therefore, the authors stated that coronary microcirculation recovery progresses further by 6 months, suggesting that using FFR soon after STEMI might underestimate the degree of non-culprit vessel stenosis in almost half of patients.

The index of microcirculatory resistance (IMR) is a validated invasive wire-based measure of microvasculature function [14] and could be useful to assess the status of the coronary microcirculation in the setting of AMI [15], which may be used to validate an FFR result. The other potential caveat in a FFR-guided strategy in ACS patients, as it was done in our case report, is the possible existence of vulnerable coronary plaques in absence of flow limitation [9]. In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study [16], patients presenting with ACS in whom PCI was successful, underwent 3-vessel radiofrequency intravascular ultra-sound (IVUS) imaging, and were followed for a median of 3.4 years for the incidence of MACE. In this study, the non-culprit lesions that led to MACE were frequently mild on angiographic assessment, but most were characterized by a large plaque burden, a small luminal area and were thin-cap fibroatheromas (TCFA); no MACE arose from untreated segments with a plaque burden resulting in less than 40 % loss of cross-sectional luminal area. Using data from PROSPECT study, some authors stated that clinical and angiographic characteristics had poor predictive accuracy in identifying patients with untreated high-risk plaques, at least not enough to obviate the need for intracoronary-imaging, although they assume that it is unrealistic to applicate 3-vessel invasive imaging in every clinical setting [17]. Others authors divided the same cohort into quartiles according to baseline angiographic diameter stenosis and concluded that the triad of predictors of future MACE increased in frequency with increasing angiographic diameter stenosis [18].

Some points of controversy involve the risk assessment of future MACE: do we have a cross-link between ischemia and plaque vulnerability? Can we expect that plaques with higher FFR values are stable and that lower FFR, with repetitive ischemia and high shear stress, induce vulnerability? Or do we have a diagnostic gap of vulnerable plaque between physiology and morphology? A study from Versteeg et al. [19] demonstrated that monocyte toll-like receptors 2 and 4 related to plaque vulnerability were significantly higher in patients with

FFR < 0.75 than in patients with an FFR measurement of > 0.80, suggesting that vulnerability may be preceded by ischemia. In the Fractional Flow Reserve and Intravascular Ultrasound Relationship Study (FIRST) [20], the aim was to evaluate the correlation between FFR, IVUS, and virtual histology (VH) in intermediate coronary lesions. Minimal lumen area obtained by IVUS showed a moderate correlation with FFR measurements and the optimal cut-off for a FFR of < 0.80 varied depending on the vessel size. Plaque composition assessed by VH-IVUS identified only plaque burden as having any correlation with FFR values. Lesions without TCFA had better correlation with FFR compared with lesions with TCFA. A study from Hüseyinova et al. [21] evaluated 48 non-ST-elevation ACS patients having paired hemodynamic and morphological data of the culprit vessel. It was demonstrated that for a given stenosis, FFR values decrease with an increase in necrotic core and dense calcium contents of the physiologically significant coronary plaques. However, plaque composition did not exert any influence on the hemodynamic effect generated by physiologically non-significant stenosis.

The COMPARE ACUTE trial is an ongoing study enrolling MVD patients undergoing primary PCI and randomly allocates patients to receive either FFR-guided PCI or culprit vessel-only PCI in the setting of STEMI [22]. This trial may help to define the role of FFR in STEMI patients with MVD.

Conclusions

The use of FFR to assess non-culprit lesions in AMI patients is useful to guide treatment if strongly indicative of ischemia. A negative FFR is this setting should be interpreted with caution and may be appropriate to access plaque vulnerability by intracoronary imaging, to consider subsequent non-invasive testing or alternatively repeat FFR at a later date. Further studies are required to stablish the ideal timing to perform FFR after AMI, in order to minimize the impact of any microvascular disturbance. The role of FFR in the assessment of vulnerable plaques *per se* also requires additional evaluation in clinical trials.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Abbreviations

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; FFR: Fractional flow reserve; IMR: Index of microcirculatory resistance; IVUS: Intravascular ultra-sound; LAD: Left anterior descending artery; MACE: Major adverse cardiac events; MVD: Multi-vessel disease; PCI: Percutaneous coronary intervention; Pd/Pa: Distal coronary pressure to aortic pressure ratio; STEMI: ST-segment elevation myocardial infarction; TCFA: Thin-cap fibroatheromas; VH: Virtual histology.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LL, conception and design, analysis and interpretation of data, manuscript writing. JSM, VM and JC, attending physician, acquisition and analysis of data, revising it critically for important intellectual content. JMF, EJ, JG and MP, interpretation of data, revising it critically for important intellectual content. All authors read and approved the final manuscript.

Authors' information

Not applicable.

Availability of data and materials

Supporting data is available to researchers in a repository (figshare.com/s/1e798de4404c11e59dda06ec4b8d1f61).

Acknowledgements

I do not have any specific acknowledge to make.

Received: 11 August 2015 Accepted: 1 October 2015
Published online: 14 October 2015

References

1. Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J. 2002;23:1190–201.
2. Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Eur Heart J. 2007;28:1709–16.
3. Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2014;35:2541–619.
4. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569–619.
5. Pijls NHJ, van Schaardenburgh P, Manoharan G, Boersma E, Bech J-W, van' t Veer M, 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.
6. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, Van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360:213–24.
7. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, 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.
8. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991–1001.
9. Hennigan B, Layland J, Fearon WF, Oldroyd KG. Fractional flow reserve and the index of microvascular resistance in patients with acute coronary syndromes. EuroIntervention. 2014;10 Suppl T:T55–63.
10. Claeys MJ, Bosmans JM, Hendrix J, Vrints CJ. Reliability of fractional flow reserve measurements in patients with associated microvascular dysfunction: importance of flow on translesional pressure gradient. Catheter Cardiovasc Interv. 2001;54:427–34.
11. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevatio. Eur Heart J. 2011;32:2999–3054.
12. Ntalianis A, Sels J-W, Davidavicius G, Tanaka N, Muller O, Trana C, et al. Fractional flow reserve for the assessment of nonculprit coronary artery

stenoses in patients with acute myocardial infarction. JACC Cardiovasc Interv. 2010;3:1274–81.
13. Cuculi F, De Maria GL, Meier P, Dall'Armellina E, de Caterina AR, Channon KM, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2014;64:1894–904.
14. Fearon WF, Balsam LB, Farouque HMO, Robbins RC, Fitzgerald PJ, Yock PG, et al. Novel index for invasively assessing the coronary microcirculation. Circulation. 2003;107:3129–32.
15. Fearon WF, Shah M, Ng M, Brinton T, Wilson A, Tremmel JA, et al. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2008;51:560–5.
16. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364:226–35.
17. Bourantas CV, Garcia-Garcia HM, Farooq V, Maehara A, Xu K, Généreux P, et al. Clinical and angiographic characteristics of patients likely to have vulnerable plaques: analysis from the PROSPECT study. JACC Cardiovasc Imaging. 2013;6:1263–72.
18. Yun KH, Mintz GS, Farhat N, Marso SP, Taglieri N, Verheye S, et al. Relation between angiographic lesion severity, vulnerable plaque morphology and future adverse cardiac events (from the Providing Regional Observations to Study Predictors of Events in the Coronary Tree study). Am J Cardiol. 2012;110:471–7.
19. Versteeg D, Hoefer IE, Schoneveld AH, de Kleijn DPV, Busser E, Strijder C, et al. Monocyte toll-like receptor 2 and 4 responses and expression following percutaneous coronary intervention: association with lesion stenosis and fractional flow reserve. Heart. 2008;94:770–6.
20. Waksman R, Legutko J, Singh J, Orlando Q, Marso S, Schloss T, et al. FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. J Am Coll Cardiol. 2013;61:917–23.
21. Hüseyinova G, Aslanger E, Çakır O, Atıcı A, Panç C, Demirkıran A, et al. Potential contribution of virtual histology plaque composition to hemodynamic-morphologic dissociation in patients with non-ST elevation acute coronary syndrome. Int J Cardiol. 2015;187:33–8.
22. Smits PC, Vlachojannis GJ, Lunde K, Omerovic E, Schotborgh CE, Richardt G, et al. TCT-328 FFR-guided complete revascularization during primary PCI: Preliminary data from the COMPARE ACUTE trial. J Am Coll Cardiol. 2014;64:11_S.

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