Robustness of Fractional Flow Reserve for Lesion Assessment in Non–Infarct-Related Arteries of Patients With Myocardial Infarction

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Two recent randomized trials (PRAMI [Preventive Angioplasty in Acute Myocardial Infarction] trial and CvLPRIT [Complete versus Lesion-only Primary PCI trial]) have demonstrated reduced rates of major cardiovascular events with a strategy of complete revascularization compared with infarct-related artery (IRA) only revascularization in patients with ST-segment–elevation myocardial infarction (STEMI) and multivessel coronary artery disease (MV-CAD).[1,2] On the basis of these studies, the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline changed the recommendation for non–IRA revascularization in patients with STEMI from class III to class IIb,[3] and the European Society of Cardiology guidelines now recommend nonculprit vessel PCI of patients with STEMI and MV-CAD as class IIA.[4] The question of whether fractional flow reserve (FFR) could help guide revascularization of the nonculprit vessels in patients with STEMI and MV-CAD, as it has been shown to effectively do in patients with stable CAD,[5,6] required evidence that FFR on the nonculprit bed is relatively accurate early after MI. This was initially investigated in the nonculprit vessels of patients with STEMI and non-STEMI, demonstrating that both FFR and the index of microcirculatory resistance did not change significantly between the index procedure and 6-week follow-up.[7] Subsequently, the COMPARE-ACUTE (Complete Revascularization in the Acute Setting of Primary PCI) and DANAMI-3-PRIMULTI (The Third Danish Study of Optimal Acute Treatment of Patients With STEMI: Primary PCI in Multivessel Disease) trials demonstrated that an FFR-based revascularization approach of the nonculprit vessel, performed either during the index STEMI procedure or in a staged manner, was also superior to performing IRA-only PCI in patients with STEMI and MV-CAD.[8,9] However, given the pathophysiologic rationale for variability in the microvascular resistance in both the culprit and the nonculprit beds early after STEMI, the higher incidence of adverse events in nonculprit beds on patients in whom revascularization is deferred, on the basis of FFR or instantaneous wave-free ratio (iFR), compared with patients with stable angina,[10] and the relative paucity of data supporting the use of FFR at non-IRA of patients with STEMI and MV-CAD, further investigation of the reliability of the nonculprit vessel FFR in this clinical setting is warranted.

In this issue of the *Journal of the American Heart Association* (*JAHA*), an interesting study is published comparing the coronary epicardial and microcirculatory status in the non-IRA of patients with acute coronary syndromes in the subacute phase of MI (5.9±2.4 days after STEMI or non-STEMI) with propensity-matched vessels in patients with stable angina.[11] Comprehensive physiologic assessment was performed using pressure-derived FFR, index of microcirculatory resistance, and coronary flow reserve (CFR) in 108 vessels of patients with STEMI and stable angina, who were propensity matched 1:1 for age, sex, previous MI, and target vessel. The authors found the following: (1) Angiographic parameters, such as minimal lumen diameter, diameter stenosis, and lesion length, were similar between groups. (2) FFR, index of microcirculatory resistance, and hyperemic flow were also not different between groups. (3) CFR, assessed by thermodilution, was lower in non-IRA of patients with STEMI/non-STEMI than in patients with stable angina; and this was driven by higher baseline flow and not differences in hyperemic flow. The authors provide additional evidence that support the utility of FFR measurements in the nonculprit bed of patients with MI, which is in keeping with the favorable FFR-based outcome trials in this setting (namely, COMPARE-ACUTE and DANAMI-3-PRIMULTI). Interestingly,

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although CFR was blunted in the nonculprit bed of patients with MI compared with that of patients without infarction, the *hyperemic flow*, which is precisely the determinant for the FFR value, did not appear to be different between patients with and without an infarct.

However, nonculprit infarct beds investigated in this study were in patients with both STEMI and non-STEMI, and although the ejection fractions were significantly lower in patients with MI compared with patients with stable angina (55% versus 59%; P=0.02), differences in ejection fraction were not marked, suggesting a lower-risk population with MI. Furthermore, the acute MI group had a similar distribution of STEMI (N=37) and non-STEMI (N=33) vessels, and the authors do not present data on biomarkers of myocardial necrosis to establish the size of the infarcts in the 2 groups. However, somewhat surprisingly, they do find similar FFR, index of microcirculatory resistance, and CFR values in the noninfarct beds of patients with STEMI and non-STEMI. The disturbed autoregulation that results in variation of physiologic indices in the non-IRA beds[12] is more likely to occur in patients with STEMI than in patients without STEMI. Therefore, comparing a larger cohort enriched with STEMIs with patients with stable angina would have tested the hypothesis of the impact of infarction on the pathophysiological characteristics of the noninfarct bed more rigorously than a combined cohort of patients with STEMI and non-STEMI and with preserved ejection fraction, as performed in this study.

Another interesting finding of this study is the reduced CFR in the noninfarct bed of the patients with MI compared with the patients with stable angina. Although this observation is not in itself novel, the observation that the reduced flow reserve is driven by higher baseline rather than blunted hyperemic flow is interesting and may potentially have clinical implications with respect to whether resting or hyperemic indexes (eg, iFR or FFR) are more accurate for assessing these nonculprit lesions after MI. These observations are in keeping with the finding that iFR, measured in the nonculprit bed early after MI, is likely to overestimate lesion severity compared with a later date, suggesting that iFR can safely defer lesions but may lead to overtreatment of vessels in this scenario compared with FFR.[13] However, outcome-based trials of iFR versus FFR in patients with stable angina and acute coronary syndromes have demonstrated similar efficacy of these indexes for guiding revascularization. Specific trials designed to the performance of resting and hyperemic indexes in the nonculprit vessels of patients with STEMI and MV-CAD are warranted.

Why should resting flow be higher in the noninfarct beds of infarcted patients compared with patients with stable angina? One possibility is that the increase in resting flow is in response to adjacent edema, hemorrhage, and necrosis that can increase myocardial resistance in the remote bed. However, findings from an elegant investigational study,[14] the present study,[11] and a previous clinical study[7] suggest that myocardial resistance, in fact, does not increase in the remote noninfarct bed early after MI. Another postulated mechanism of the increased resting flow in noninfarct beds relates to neurohumoral mechanisms initiated by the adjacent myocardial necrosis. Regardless of the mechanism, the extent and longevity of these early hemodynamic perturbations in the noninfarct beds are likely closely related to the size of the adjacent infarction and ultimate residual ejection fraction.

The study by Lee et al[14] has extended our understanding of the pathophysiological characteristics of nonculprit vessel beds in patients with MI. Furthermore, outcomes data have demonstrated that an FFR-based strategy of guiding revascularization in patients with STEMI and MV-CAD is superior to IRA revascularization only. Given that the risk of subsequent events is higher in patients with MI (than stable CAD) in whom the nonculprit vessel is deferred on the basis of physiological characteristics, what is warranted are outcome-based studies in patients with STEMI and MV-CAD comparing physiological strategies with angiographic-, intravascular ultrasound–, or optical coherence tomography–based strategies for guiding revascularization. Until then, the present study provides further evidence of the robustness of FFR for lesion assessment in this high-risk subset of patients.

Disclosures

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References

1. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115–1123.
2. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McCann GP. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol*. 2015;65:963–972.
3. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Ting HH, O'Gara PT, Kushner FG, Ascheim DD, Brindis RG, Casey DE Jr, Chung MK, de Lemos JA, Diercks DB, Fang JC, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2016;67:1235–1250.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention*. 2019;14:1435–1534.

5. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm 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;360:213–224.
6. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-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.
7. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv*. 2010;3:1274–1281.
8. Smits PC, Abdel-Wahab M, Neumann F-J, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med*. 2017;376:1234–1244.
9. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L; DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet*. 2015;386:665–671.
10. Escaned J, Ryan N, Mejía-Rentería H, Cook CM, Dehbi H-M, Alegria-Barrero E, Alghamdi A, Al-Lamee R, Altman J, Ambrosia A, Baptista SB, Bertilsson M, Bhindi R, Birgander M, Bojara W, Brugaletta S, Buller C, Calais F, Silva PC, Carlsson J, Christiansen EH, Danielewicz M, Di Mario C, Doh J-H, Erglis A, Erlinge D, Gerber RT, Going O, Gudmundsdottir I, Härle T, Hauer D, Hellig F, Indolfi C, Jakobsen L, Janssens L, Jensen J, Jeremias A, Kåregren A, Karlsson A-C, Kharbanda RK, Khashaba A, Kikuta Y, Krackhardt F, Koo B-K, Koul S, Laine M, Lehman SJ, Lindroos P, Malik IS, Maeng M, Matsuo H, Meuwissen M, Nam C-W, Niccoli G, Nijjer SS, Olsson H, Olsson S-E, Omerovic E, Panayi G, Petraco R, Piek JJ, Ribichini F, Samady H, Samuels B, Sandhall L, Sapontis J, Sen S, Seto AH, Sezer M, Sharp ASP, Shin E-S, Singh J, Takashima H, Talwar S, Tanaka N, Tang K, Van Belle E, van Royen N, Varenhorst C, Vinhas H, Vrints CJ, Walters D, Yokoi H, Fröbert O, Patel MR, Serruys P, Davies JE, Götberg M. Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes. *JACC Cardiovasc Interv*. 2018;11:1437–1449.
11. Mejía-Rentería H, Myung Lee J, Nvan der Hoeven N, Gonzalo N, Jiménez-Quevedo P, Nombela-Franco L, Nuñez-Gil I, Salinas P, Del Trigo M, Cerrato E, van Royen N, Knaapen P, Koo BK, Macaya C, Fernández-Ortiz A, Escaned J. The coronary microcirculation downstream non-infarct-related arteries in the subacute phase of myocardial infarction: implications for physiological-guided revascularization. *J Am Heart Assoc*. 2019;8:e011534. DOI: 10.1161/JAHA.118.011534.
12. Bax M, de Winter RJ, Koch KT, Schotborgh CE, Tijssen JGP, Piek JJ. Time course of microvascular resistance of the infarct and noninfarct coronary artery following an anterior wall acute myocardial infarction. *Am J Cardiol*. 2006;97:1131–1136.
13. Thim T, Götberg M, Fröbert O, Nijveldt R, van Royen N, Baptista SB, Koul S, Kellerth T, Bøtker HE, Terkelsen CJ, Christiansen EH, Jakobsen L, Kristensen SD, Maeng M. Nonculprit stenosis evaluation using instantaneous wave-free ratio in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2017;10:2528–2535.
14. Lee JM, Kim HK, Lim KS, Park JK, Choi KH, Park J, Hwang D, Rhee TM, Yang JH, Shin ES, Nam CW, Doh JH, Hahn JY, Koo BK, Jeong MH. Influence of Local Myocardial Damage on Index of Microcirculatory Resistance and Fractional Flow Reserve in Target and Nontarget Vascular Territories in a Porcine Microvascular Injury Model. *JACC Cardiovasc Interv*. 2018;11:717–724. DOI: 10.1016/j.jcin.2017.11.028. Epub 2018 Mar 28.

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