EDITORIAL

Assessing the Coronary Microcirculation in Patients After Primary Percutaneous Coronary Intervention

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The primary management goal in patients with ST-elevation myocardial infarction (STEMI) is to restore blood flow to the myocardium subtended by the occluded epicardial artery using pharmacologic and mechanical means. However, despite contemporary approaches with primary percutaneous coronary intervention (PCI) and subsequent medical therapy, the morbidity and mortality of patients with STEMI have not changed significantly over recent years.[1] Moreover, 10% to 20% of patients who survive to 5 years after STEMI will develop heart failure.[2] There is therefore a need to develop and validate methods that can identify patients early who are at risk of subsequent adverse events that might be reduced by targeted adjunctive therapies.

Microvascular impairment at the time of STEMI is an important determinant of subsequent prognosis. Cardiac magnetic resonance imaging (CMR) is considered to be the criterion standard for assessing the coronary microcirculation. Microvascular obstruction on CMR is a strong predictor of subsequent cardiovascular events even after controlling for infarct size, and may even be a more potent prognostic marker than patency status of the culprit epicardial artery.[3] However, it is currently not realistic to incorporate CMR into the routine care of patients with STEMI.

Angiographic methods for assessing microvascular dysfunction in the cardiac catheterization laboratory at the time of STEMI include Thrombolysis in Myocardial Infarction (TIMI) flow grade, TIMI frame count, and TIMI myocardial perfusion grade.[4] In a study of 456 patients with STEMI undergoing primary PCI, 50% of patients had evidence of impaired myocardial blush grade after reopening of the epicardial artery,[5] and patients with abnormal blush grade had a 3-fold increase in 1-year mortality. However, these methods are qualitative, not very reproducible outside of core laboratories, and difficult to apply to an individual patient.

More recently, coronary wire-based methods such as the index of microcirculatory resistance (IMR) have been developed to interrogate the coronary microcirculation. The IMR is measured using a 0.014-inch pressure–temperature sensor guidewire and represents the *minimal* coronary microcirculatory resistance of the myocardial territory being interrogated.[6] To measure IMR, 3 mL of room temperature saline is injected down the coronary artery during maximal hyperemia. A thermodilution curve is created after each injection by the temperature change, which allows quantification of the mean transit time, which is inversely proportional to coronary flow. The distal coronary pressure is measured simultaneously with the same wire and when divided by the inverse of the mean transit time, IMR is calculated.

IMR is more quantitative and reproducible than angiographic parameters and easier to obtain in the acute setting than CMR. IMR corresponds with the extent of coronary microvasculature disruption in humans,[6] and is stable and reproducible in the presence of varying hemodynamic conditions.[7] In earlier studies, IMR measured immediately after primary PCI correlated with myocardial infarct size as measured by peak creatine kinase, whereas other less quantitative or specific measures of the microcirculation (including TIMI myocardial perfusion grade, TIMI frame count, coronary flow reserve, and ST-segment resolution) did not.[8] An IMR >32 U has also been associated with worse wall motion score on echocardiogram 3 months post STEMI. IMR after primary PCI has a strong inverse relationship with myocardial viability, as assessed by fluorine-18 fluorodeoxyglucose positron emission tomography[9] and predicts infarct size, left ventricular ejection fraction, myocardial salvage, and the presence and extent of microvascular obstruction and myocardial hemorrhage as determined by CMR.[10] In a multicenter study involving 253 patients with STEMI treated with primary PCI and with a median follow-up of 2.8 years, it was found that an IMR >31

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was an independent predictor of death or rehospitalization, and an IMR >40 was an independent predictor of death.

In this issue of the *Journal of the American Heart Association*, Yew and colleagues undertook an elegant study by following 278 patients with STEMI and treated with primary PCI who underwent measures of microcirculatory function including IMR and TIMI blush grade, and compared these with the waveform of the thermodilution curves created when measuring IMR with respect to their ability to predict CMR-determined myocardial hemorrhage and microvascular obstruction, as well as subsequent death or heart failure.[11] The median follow-up was a little over 4 years.

The current study corroborated the findings of a previous smaller study involving 88 patients, which demonstrated that abnormal thermodilution wave morphology was associated with microvascular impairment, as assessed by IMR and CMR, and was predictive of subsequent adverse clinical outcome.[12] The current study is considerably larger and had a significantly longer follow-up period compared with its predecessor, and serves as an important validation of the previous results.

The comprehensive multivariable analysis using several different models demonstrated that infarct size, as assessed by CMR, was the best predictor of clinical outcome. However, when considering a method that can be used in the cardiac catheterization laboratory, either a bimodal waveform of the thermodilution curve or IMR could be used to predict poor prognosis. A bimodal thermodilution waveform was associated with very high IMR (median 54, interquartile range 32–101). It is therefore not surprising that the bimodal waveform was a stronger predictor when included in the model with IMR >40 to predict death or heart failure, as it is likely to reflect greater microcirculatory disruption. Only 13% of patients had a bimodal waveform, potentially limiting its use as a clinical target.

The strengths of this study include its large size, reasonably long follow-up, and clinical outcome data. In addition, it provides support for an adjunctive method in the catheterization laboratory beyond IMR alone for further discriminating patients at risk for adverse outcome after successful primary PCI.

There are a few limitations in the current study that are worth noting. First, the study originated from a single center and thermodilution wave morphology was analyzed by experienced analysts. It therefore remains uncertain whether accurate discrimination between the different waveforms can be achieved by other less experienced centers. In addition, it is not clear how to classify a patient if 1 of the 3 waveforms is bimodal, but the others are not. Second, the mechanism underlying waveform abnormalities such as the bimodal pattern remains unexplained. Last, the authors did not present data such as symptom to reperfusion or "door to balloon" time, and these factors could have interacted with the measures of microcirculatory disruption.

This article adds to the growing evidence that assessment of the coronary microcirculation after primary PCI can identify an at-risk population that could be the target of additional treatments. Several adjunctive therapies have been investigated in an attempt to improve STEMI outcomes but have had disappointing results. However, a small study by Sezer et al reported that patients randomized to receive low-dose intracoronary thrombolysis after primary PCI had improved microvascular reperfusion, as indicated by lower IMR values, than those randomized to placebo.[13] Moreover, the authors of the current study will soon report the results of a randomized clinical trial investigating the effect of intracoronary alteplase on CMR and invasive coronary physiology surrogate markers (T-TIME ClinicalTrials.gov identifier NCT02257294). In addition, a clinical trial randomizing patients with IMR >32 to a low-dose intracoronary thrombolytic or to placebo with clinical outcome end points is currently under way (RESTORE-MI anzctr.org.au identifier ACTRN12618000778280). Hopefully, with readily obtainable markers such as IMR and coronary thermodilution waveform analysis and validation of adjunctive methods to improve myocardial reperfusion beyond primary PCI, patients with STEMI can enjoy improved long-term outcomes.

Disclosures

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References

1. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics and Stroke Statistics. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6–e245.
3. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, Blumenthal RS, Lima JA. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation*. 1998;97:765–772.
4. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after

thrombolytic administration in acute myocardial infarction. *Circulation*. 2002;105:1909–1913.

5. Sorajja P, Gersh BJ, Costantini C, McLaughlin MG, Zimetbaum P, Cox DA, Garcia E, Tcheng JE, Mehran R, Lansky AJ, Kandzari DE, Grines CL, Stone GW. Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction. *Eur Heart J*. 2005;26:667–674.
6. Fearon WF, Balsam LB, Farouque HM, Caffarelli AD, Robbins RC, Fitzgerald PJ, Yock PG, Yeung AC. Novel index for invasively assessing the coronary microcirculation. *Circulation*. 2003;107:3129–3132.
7. Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. *Circulation*. 2006;113:2054–2061.
8. Fearon WF, Shah M, Ng M, Brinton T, Wilson A, Tremmel JA, Schnittger I, Lee DP, Vagelos RH, Fitzgerald PJ, Yock PG, Yeung AC. Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2008;51:560–565.
9. Lim HS, Yoon MH, Tahk SJ, Yang HM, Choi BJ, Choi SY, Sheen SS, Hwang GS, Kang SJ, Shin JH. Usefulness of the index of microcirculatory resistance for invasively assessing myocardial viability immediately after primary angioplasty for anterior myocardial infarction. *Eur Heart J*. 2009;30:2854–2860.
10. Payne AR, Berry C, Doolin O, McEntegart M, Petrie MC, Lindsay MM, Hood S, Carrick D, Tzemos N, Weale P, McComb C, Foster J, Ford I, Oldroyd KG. Microvascular resistance predicts myocardial salvage and infarct characteristics in ST-elevation myocardial infarction. *J Am Heart Assoc*. 2012;1:e002246. DOI: 10.1161/JAHA.112.002246.
11. Yew SN, Carrick D, Corcoran D, Ahmed N, Carberry J, Teng Yue May V, McEntegart M, Petrie MC, Eteiba H, Lindsay M, Hood S, Watkins S, Davie A, Mahrous A, Mordi I, Ford I, Oldroyd KG, Berry C. Coronary thermodilution waveforms after acute reperfused ST segment–elevation myocardial infarction: relation to microvascular obstruction and prognosis. *J Am Heart Assoc*. 2018;7:e008957. DOI: 10.1161/JAHA.118.008957.
12. Fukunaga M, Fujii K, Kawasaki D, Sawada H, Miki K, Tamaru H, Imanaka T, Iwasaku T, Nakata T, Shibuya M, Akahori H, Masutani M, Kobayashi K, Ohyanagi M, Masuyama T. Thermodilution-derived coronary blood flow pattern immediately after coronary intervention as a predictor of microcirculatory damage and midterm clinical outcomes in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv*. 2014;7:149–155.
13. Sezer M, Oflaz H, Goren T, Okcular I, Umman B, Nisanci Y, Bilge AK, Sanli Y, Meric M, Umman S. Intracoronary streptokinase after primary percutaneous coronary intervention. *N Engl J Med*. 2007;356:1823–1834.

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