Screening high-risk patients and selecting treatment options in stable coronary artery disease using myocardial perfusion imaging

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In stable coronary artery disease (CAD), one of the key questions in clinical practice is whether and when a patient needs invasive study and revascularization such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG). Currently, there are two major therapeutic strategies for stable CAD; the invasive strategy including early coronary angiography (CAG) and subsequent revascularization if indicated, and the non-invasive strategy including optimal medical therapy (OMT). In both the strategies, there have been major advances in the last few decades including the use of drug-eluting stent for PCI and addition of statins in OMT. However, the basic principle of selecting treatment option in stable CAD has not been changed; to reduce futile invasive CAG and revascularization using non-invasive studies for selecting high-risk patients.

Myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) has been used in stable CAD for selecting high-risk patients who require revascularization. In a milestone study by Hachamovitch et al., it was reported that revascularization is more beneficial than OMT in patients who showed moderate to large amounts of inducible ischemia on SPECT.[1] However, there have been some conflicting results. For example, in the nuclear substudy of the COURAGE trial, it was reported that the extent of ischemia on MPI was not predictive of adverse events and did not affect treatment effectiveness.[2] Despite these conflicting results, there have been hundreds of reports on the prognostic role of MPI in CAD, which were summarized in several review articles.[3,4] Additionally, there have been other studies that demonstrated effectiveness of MPI in selecting treatment options. In an observation study that followed up 13,969 patients for more than 7 years, early revascularization was beneficial in patients who exhibited significant ischemia without extensive scar on SPECT, whereas OMT was superior to revascularization in patients with minimal ischemia.[5] In another study that used MPI PET, coronary flow reserve (CFR) measured on PET was an independent factor from CAG in modifying the effectiveness of early CABG or PCI.[6]

In the current issue of *Journal of Nuclear Cardiology*, Boiten et al. reported treatment effectiveness according to MPI SPECT findings.[7] They followed up 702 patients who exhibited ischemia on SPECT for a median of 12 years, and observed that early revascularization was more beneficial than OMT in this group. Additionally, prognosis was associated with the extent of ischemia on SPECT. Although the study has some limitations of retrospective design, enrollment of only patients with ischemia, and treatment based on relatively old methods like bare metal stent or old drug regimens, it demonstrated again the effectiveness of MPI in selecting high-risk patients who require revascularization. MPI-based decision of invasive treatment is still a valid strategy.

Another option of non-invasive imaging method in CAD is coronary computed tomography angiography (CCTA). Because CCTA targets for anatomical stenosis that is also the diagnostic target in CAG, it has high diagnostic performance for CAG-confirmed CAD.[8,9] Thus, CCTA can be effectively used for determining the need for CAG; in the SCOT-HEART trial in which 4146 patients were randomly assigned to standard care group or standard care plus CCTA group, CCTA led to more

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appropriate use of CAG and alterations in subsequent medication.[10] In terms of prognosis, a meta-analysis reported that annual event rates for obstructive and normal CCTA were 8.8% and 0.17%, respectively.[11] However, it is still not clear whether CCTA can be used for selecting treatment option. In the PROMISE trial that compared CCTA and functional studies as initial testing strategy, a strategy of initial CCTA did not improve clinical outcome, although it reduced futile CAG compared with a strategy of initial functional study (3.4% and 4.3%, respectively).[12] Currently, it appears that the most effective role of CCTA is gatekeeping to invasive CAG.

In recent years, intervention cardiologists consider functional significance of a stenotic lesion as an important factor for decision making of revascularization. When a patient undergoes CAG, functional significance of a stenotic lesion can be evaluated using a pressure wire. Fractional flow reserve (FFR) is calculated as the pressure ratio of proximal and distal parts of a lesion. In the famous FAME study, FFR-guided PCI was performed in 509 patients and CAG-guided PCI, in 496 patients.[13] In this study, FFR-guide group exhibited lower rates of cardiac events and lower cost than CAG-guide group. In the subsequent report of the FAME study that included 1220 patients, patients who had functionally insignificant (FFR $>$ 0.80) lesions were treated with OMT.[14] Their cardiac event rate was not different from that of patients who had significant lesions (FFR $\leq$ 0.80) and treated with PCI. In contrast, those who had significant lesions and treated with OMT exhibited higher rate of cardiac event like urgent revascularization. In the DEFER trial, FFR-guided deferral of PCI exhibited excellent outcome compared with early performance of PCI, even in a 15-year follow-up study.[15] Based on the successful results of FFR-guided treatment decision, FFR is deemed to be a standard index to determine revascularization by intervention cardiologists.

Thus, non-invasive imaging has been pursuing diagnosis of significant ischemic lesions of low FFR in recent studies. If FFR can be correctly predicted on a non-invasive imaging method, it could be used to determine the need of CAG and revascularization. In CCTA, a method has been developed to calculate FFR based on hydraulic assumptions.[16] The PLATFORM study enrolled patients who had intermediate likelihood of CAD and randomly assigned them into usual non-invasive test, standard CAG, and CCTA-based FFR measurement group as the initial testing.[17] When combined criteria of CAG and invasive FFR were used as the gold standard, futile CAG was reduced in CCTA-based FFR measurement group (12%), compared with standard CAG group (73%). In the EVINCI trial, hybrid imaging of CCTA/MPI was used to diagnose significant CAD that was defined by combined criteria of CAG and invasive FFR. The hybrid imaging exhibited negative and positive predictive values of 88% and 87%, respectively.[18]

However, CFR can be measured directly using dynamic MPI. It was reported that relative CFR (RFR) on PET exhibits excellent correlations with invasive FFR.[19,20] In a recent study, Lee et al. also reported that RFR on ammonia PET has a significant correlation with FFR, and the diagnostic performance of RFR for diagnosing significant stenosis (FFR $\leq$ 0.80) was 0.897 of area under curve.[21] Currently, heart-dedicated SPECT scanners that have cadmium-zinc-telluride detector and fixed-angle geometry are available, and it has been attempted to perform dynamic scans and to measure flow reserve using these scanners.[22,23] The efficacy of MPI SPECT-based flow reserve measurement needs to be evaluated in further studies. Additionally, it should be proved in further researches whether MPI-based flow reserve measurement is a prognostic factor and whether it can be used for selecting treatment options.

Currently, one of the biggest requests for non-invasive imaging study in stable CAD is to select patients who needs invasive CAG (Fig. 1). Once a patient is referred to CAG, functional significance as well as presence of stenotic lesions can be determined on CAG using FFR measurement. Both CCTA and MPI can be used effectively for this purpose because they can detect anatomically or functionally significant stenotic lesions. Another request for non-invasive imaging is a prognostic role that can predict or complement FFR. It has

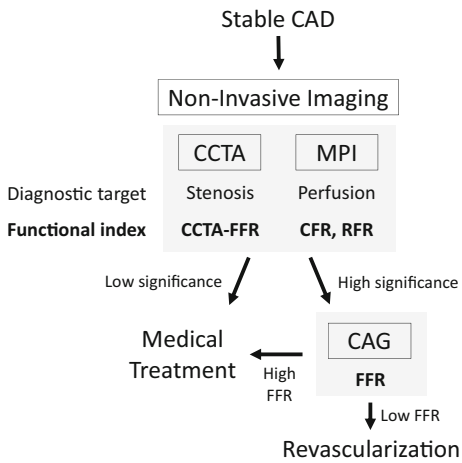

Fig. 1. A flow chart for risk assessment and treatment selection in stable coronary artery disease. Non-invasive imaging can be used for screening low-significant CAD that can be medically treated and selecting highly significant CAD that needs to be referred for CAG. Currently, functional significance of a lesion can also be determined on CAG by using FFR. *CAD* coronary artery disease, *CAG* coronary angiography, *CCTA* coronary computed tomography angiography, *CFR* coronary flow reserve, *FFR* fractional flow reserve, *MPI* myocardial perfusion imaging, *RFR* relative flow reserve.

been shown that revascularization is superior to OMT alone when MPI is extensively abnormal, as reported by Boiten et al. in the current issue.[1,5,7] Additionally, RFR measured on MPI has a significant correlation with FFR measurement. Thus, it should be investigated in further researches whether and how MPI can predict FFR effectively, and whether MPI has an independent diagnostic power for selecting patients who need invasive CAG. Based on the results of these future studies, the effectiveness of MPI for stable CAD in the era of FFR would be determined.

Disclosure

None.

References

1. 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.
2. Shaw LJ, Weintraub WS, Maron DJ, Hartigan PM, Hachamovitch R, Min JK, et al. Baseline stress myocardial perfusion imaging results and outcomes in patients with stable ischemic heart disease randomized to optimal medical therapy with or without percutaneous coronary intervention. Am Heart J 2012;164:243–50.
3. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004;11:171–85.
4. Shaw LJ, Hage FG, Berman DS, Hachamovitch R, Iskandrian A. Prognosis in the era of comparative effectiveness research: Where is nuclear cardiology now and where should it be? J Nucl Cardiol 2012;19:1026–43.
5. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. Eur Heart J 2011;32:1012–24.
6. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. Circulation 2015;131:19–27.
7. Boiten HJ, van den Berge JC, Valkema R, van Domburg RT, Zijlstra F, Schinkel AFL. Ischemia burden on stress SPECT MPI predicts long-term outcomes after revascularization in stable coronary artery disease. J Nucl Cardiol 2016. doi:10.1007/s12350-016-0735-5.
8. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 2008;52:1724–32.
9. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.
10. Williams MC, Hunter A, Shah AS, Assi V, Lewis S, Smith J, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. J Am Coll Cardiol 2016;67:1759–68.
11. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: A systematic review and meta-analysis. J Am Coll Cardiol 2011;57:1237–47.
12. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.
13. Pijls NH, Fearon WF, Tonino PA, 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.
14. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.
15. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J 2015;36:3182–8.
16. Taylor CA, Fonte TA, Min JK. 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.
17. Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: The prospective longitudinal trial of FFR(CT): Outcome and resource impacts study. Eur Heart J 2015;36:3359–67.
18. Liga R, Vontobel J, Rovai D, Marinelli M, Caselli C, Pietila M, et al. Multicentre multi-device hybrid imaging study of coronary artery disease: Results from the Evaluation of INtegrated Cardiac Imaging for the Detection and Characterization of Ischaemic Heart Disease (EVINCI) hybrid imaging population. Eur Heart J Cardiovasc Imaging 2016;17:951–60.
19. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation 1994;89:1013–22.
20. Marques KM, Knaapen P, Boellaard R, Lammertsma AA, Westerhof N, Visser FC. Microvascular function in viable myocardium after chronic infarction does not influence fractional flow reserve measurements. J Nucl Med 2007;48:1987–92.
21. Lee JM, Kim CH, Koo BK, Hwang D, Park J, Zhang J, et al. Integrated myocardial perfusion imaging diagnostics improve detection of functionally significant coronary artery stenosis by 13N-ammonia positron emission tomography. Circ Cardiovasc Imaging 2016;9:e004768.
22. Ben-Haim S, Murthy VL, Breault C, Allie R, Sitek A, Roth N, et al. Quantification of myocardial perfusion reserve using dynamic SPECT imaging in humans: A feasibility study. J Nucl Med 2013;54:873–9.
23. Shiraishi S, Sakamoto F, Tsuda N, Yoshida M, Tomiguchi S, Utsunomiya D, et al. Prediction of left main or 3-vessel disease using myocardial perfusion reserve on dynamic thallium-201 single-photon emission computed tomography with a semiconductor gamma camera. Circ J 2015;79:623–31.