International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

# Usefulness of hybrid assessment for coronary functional abnormalities by non-invasive and invasive techniques

Approximately 70% in women and 50% in men who undergo coronary angiography due to chest pain and the evidence of myocardial ischemia do not have a significant epicardial organic coronary stenosis (luminal narrowing ≤50% angiographically) [1]. Epicardial spasm and coronary microvascular dysfunction (CMD), which represent typical manifestations of coronary functional abnormalities, account for such condition termed ischemia with non-obstructive coronary arteries (INOCA) or angina and non-obstructive coronary arteries (ANOCA) [2,3]. Etiologies of impaired coronary vasomotion, which are apparently complex and heterogeneous, always encompass coronary vasodilator and vasoconstrictive properties in various combinations, where endothelial dysfunction and hypercontraction of vascular smooth muscle cells are substantially involved [2,3]. Although various techniques have been developed to evaluate impaired coronary vasomotion during the last decades, invasive coronary reactivity testing, such as acetylcholine (ACh) provocation testing, remains the gold standard of diagnostic approach for coronary spasm at present because of concerns for security in non-invasive spasm provocation testing. Additionally, invasive provocation testing involving coronary angiography enables us to precisely identify the corresponding spastic coronary artery, as to whether epicardial coronary artery and/or coronary microvessels. Especially, since visualization of coronary microvascular spasm (MVS) is still difficult due to the limited spatial resolution of state-of-the-art imaging modalities, the development of MVS is generally identified by the reproduction of chest discomfort suggestive of angina with ischemic ECG changes, in the absence of ≥90% epicardial spasm during intracoronary ACh administration [3].

On the other hand, coronary microvascular vasodilator function could be assessed non-invasively by various methods, including transthoracic Doppler echocardiography of the left anterior descending coronary, positron-emission-tomography (PET), and cardiac magnetic resonance (CMR), which provide estimates of coronary blood flow at rest and during maximal hyperemia in response to a vasodilatory stimulus [3]. Among them, PET and CMR are the most reliable modalities for non-invasive assessment of coronary vasodilator function as evidenced by the fact that both techniques have been validated in animal models by blood flow experiments with microspheres to detect coronary perfusion abnormalities. Also, in a cohort with ANOCA, there is a significant correlation between CMR and PET for identification of CMD. However, compared with PET, advantages of CMR include high spatial resolution that allows transmural characterization of myocardial blood flow, no radiation exposure, and the ability to perform a comprehensive assessment of both structure and function of the heart. CMR has been used to semi-quantify myocardial perfusion by using first-pass gadolinium images with acceptable reproducibility with a low inter- and intra-observer variability [4]. CMR-derived myocardial perfusion reserve index (MPRI), an indexed ratio of perfusion-time intensity curve upslopes in response to vasodilator stress, is a robust semi-quantitative imaging surrogate that reflects vasodilator capacity of coronary microvessels [5]. Recent studies demonstrated that MPRI threshold of ≤1.84 has a diagnostic predictive value for CMD and that of ≤1.47 is associated with the occurrence of major adverse cardiac events [6,7]. Meanwhile, there are several important limitations with a reference to MPRI, which is influenced by resting perfusion and tissue contrast concentration. Indeed, it is difficult to identify the causative factor for the lower MPRI, because a reduction in MPRI could be caused by a reduction in hyperemic perfusion or by increased resting perfusion. Moreover, at high contrast doses, there is a non-linear relationship of tissue contrast concentration and MR signal intensity. Despite these difficulties, CMR has emerged as a one-stop-shop tool for the comprehensive assessment of cardiac anatomy, morphology, functionality, and myocardial perfusion. Thus, it is reasonable for physicians to use this versatile modality as a gate-keeper before performing coronary angiography in ANOCA patients. However, no study has ever evaluated coronary functional abnormalities in ANOCA patients by combining non-invasive stress perfusion CMR and invasive ACh provocation testing. In this regard, the study by Pirozzolo et al. is a welcome addition to the literature on ANOCA [8].

In this issue of the Journal, Pirozzolo et al. [8] investigated not only the association between coronary spasm endotypes and impaired coronary vasodilator function but also predictors for coronary functional abnormalities among 129 patients with ANOCA by using a combination of invasive ACh provocation testing and non-invasive adenosine stress CMR. Intracoronary ACh evoked epicardial and microvascular spam in 22% and 53% among the patients, respectively. Meanwhile, abnormal perfusion defects on qualitative visual assessment during stress perfusion CMR were noted in 37% of the cohort. Importantly, patients with epicardial spasm had significantly lower MPRI than those without the spasm or microvascular spasm, whereas MPRI was similar between no spasm group and microvascular spasm group (no spasm group, 1.41 ± 0.25; microvascular spasm group, 1.37 ± 0.23, and epicardial spasm group,1.14 ± 0.24, $p < 0.001$). Also, multivariable regression analysis demonstrated that advanced age, previous myocardial infarction, and LVEF in addition to epicardial spasm were significantly associated with lower MPRI, whereas previous PCI was identified as an independent predictor for epicardial spasm and also female sex for microvascular spasm.

Pirozzolo et al. should be congratulated on demonstrating that

https://doi.org/10.1016/j.ijcard.2021.10.023
Received 12 October 2021; Accepted 15 October 2021
Available online 20 October 2021

enhanced epicardial vasomotor reactivity and impaired microvascular vasodilator capacity could coexist in a patient with ANOCA and they may have a lot of influence on each other by fully utilizing stress perfusion CMR. Their findings are also in line with our recent works [9,10]. Their diagnostic approach with non-invasive stress CMR in ANOCA patients could provide important information concerning the presence or absence of myocardial injury as well as the distribution pattern of impaired microvascular vasodilator response, as such information cannot be obtained by interventional diagnostic procedure with a pressure/temperature sensor-tipped guidewire.

The hybrid approach with non-invasive and invasive testing for detecting coronary vasomotor dysfunction should promote clinical studies on patients with ANOCA and further improve clinical practice of the disorder.

## Disclosures

The authors declare that there is no conflict of interest concerning this paper.

## Declaration of Competing Interest

None.

## List of abbreviations

| | |
|---|---|
| ACh | acetylcholine |
| ANOCA | angina and non-obstructive coronary arteries |
| CMD | coronary microvascular dysfunction |
| CMR | cardiac magnetic resonance |
| ECG | electrocardiogram |
| INOCA | ischemia with non-obstructive coronary arteries |
| MPRI | myocardial perfusion reserve index |
| MVS | microvascular spasm |
| PET | positron emission tomography |

## References

[1] L. Jespersen, A. Hvelplund, S.Z. Abildstrom, et al., Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events, Eur. Heart J. 33 (6) (2012) 734–744.

[2] H. Shimokawa, 2014 Williams Harvey lecture: importance of coronary vasomotion abnormalities-from bench to bedside, Eur. Heart J. 35 (45) (2014) 3180–3193.

[3] J. Takahashi, A. Suda, K. Nishimiya, et al., Pathophysiology and diagnosis of coronary functional abnormalities, Eur. Cardiol. Rev. 16 (2021) e30, https://doi.org/10.15420/ecr.2021.23.

[4] A.M. Larghat, N. Maredia, J. Biglands, et al., Reproducibility of first-pass cardiovascular magnetic resonance myocardial perfusion, J. Magn. Reson. Imaging 37 (4) (2013) 865–874.

[5] J. Wohrle, T. Nusser, N. Merkle, et al., Myocardial perfusion reserve in cardiovascular magnetic resonance: correlation to coronary microvascular dysfunction, J. Cardiovasc. Magn. Reson. 8 (6) (2006) 781–787.

[6] L.E. Thomson, J. Wei, M. Agarwal, et al., Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation, Circ. Cardiovasc. Imag. 8 (4) (2015), e002481, https://doi.org/10.1161/CIRCIMAGING.114.002481.

[7] W. Zhou, J.C.Y. Lee, S.T. Leung, et al., Long-term prognosis of patients with coronary microvascular disease using stress perfusion cardiac magnetic resonance, JACC Cardiovasc. Imaging 14 (3) (2021) 602–611.

[8] G. Pirozzolo, V.M. Pereyra, A. Hubert, et al., Coronary artery spasm and impaired myocardial perfusion in patients with ANOCA, Int. J. Cardiol. (2021 Sep 6), https://doi.org/10.1016/j.ijcard.2021.09.003. S0167-5273(21)01327-9.

[9] A. Suda, J. Takahashi, K. Hao, et al., Coronary cunctional abnormalities in patients with angina and nonobstructive coronary artery disease, J. Am. Coll. Cardiol. 74 (19) (2019) 2350–2360.

[10] J. Sugisawa, Y. Matsumoto, M. Takeuchi, et al., Beneficial effects of exercise training on physical performance in patients with vasospastic angina, Int. J. Cardiol. 328 (2021) 14–21.

Jun Takahashi*, Hiroaki Shimokawa, Satoshi Yasuda
*Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan*

* Corresponding author at: Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
*E-mail address:* jtakahashi@cardio.med.tohoku.ac.jp (J. Takahashi).