Myocardial ischemia without obstructive CAD: there is more than meets the eye!

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The prevalence of obstructive coronary artery disease (CAD) in contemporary populations of patients with stable angina is decreasing. This may express a true change in the prevalence of severe CAD as a result of the more effective treatment of major cardiovascular risk factors^{1,2} and may be the effect of the frequent inappropriate referral of these patients directly to invasive coronary angiography (ICA) without the recommended non-invasive work-up.^{3,4} Indeed, in a huge subset of patients (up to 40% in recent appraisals) with anginal chest pain, a symptom classically believed to indicate the presence of significant CAD, ICA does not evidence any obstructive coronary lesion.³

Consistent evidence has shown that coronary endothelial/microvascular dysfunction may cause typical angina and even significant myocardial ischemia in patients without obstructive CAD or with apparently normal epicardial coronary arteries.⁵ Despite the significant relationship between increasing CAD severity and downstream myocardial perfusion abnormalities,⁶ the degree of underlying coronary endothelial/microvascular dysfunction is an additional determinant of myocardial ischemic threshold,⁷ having a relevant impact on both patients' clinical status and overall prognosis.^{8,9}

Different non-invasive imaging techniques that assess myocardial perfusion and may also measure

coronary blood flow (CBF) under various stress conditions are used in the clinical setting to describe overall coronary function.¹⁰ In this setting, nuclear perfusion imaging, either with position emission tomography (PET) or single-photon emission computed tomography (SPECT), is considered one of the most versatile tools for the non-invasive assessment of the functional effects of coronary abnormalities.¹¹ Possible integration with coronary computed tomography angiography (CCTA) allows to couple regional myocardial perfusion with underlying individual coronary anatomy.¹²

Alteration of myocardial perfusion due to isolated coronary microvascular dysfunction can be documented non-invasively, after exclusion of coronary atherosclerosis, but is a relatively rare condition, limited almost entirely to pathologies characterized by the primitive adverse remodeling and fibrosis of intramural coronary arterioles, such as in the case of primary and secondary cardiomyopathies (i.e., hypertrophic cardiomyopathy, arterial hypertension, aortic stenosis).⁵ More frequently, abnormal myocardial perfusion may express a regional or global impairment of coronary vasodilating capability, involving both epicardial and microvascular coronary vessels, associated with cardiovascular risk factors^{5,13} or dilated cardiomyopathy.¹⁴ In addition, diffuse non-significant coronary atherosclerosis may impact profoundly coronary perfusion parameters by adding a further resistance to coronary blood flow, and associating with altered coronary vasomotion under stress conditions.^{15,16} Thus, it is well known that, besides its inverse relationship with the degree of coronary stenosis, CBF regulation is intimately complex in pathological conditions leading to considerable inter-individual variability.¹⁷ Still, the presence of myocardial perfusion abnormalities at non-invasive testing, in the absence of obstructive coronary lesions at ICA, is mostly considered a false-positive finding which does not usually require any further investigation even in

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patients with typical anginal chest pain. Since CBF abnormalities caused by coronary microvascular dysfunction, endothelial dysfunction, and/or non-obstructive coronary atherosclerosis held adverse prognostic impact,^{16,18} it would be relevant to know in the single patient whether one or more of these mechanisms subtend “true” inducible perfusion defects and anginal symptoms. Unfortunately, non-invasive technologies allow a comprehensive estimation of coronary perfusion parameters, but they are generally unable to segregate the specific contributions of the individual coronary functional compartments (i.e., conductive arteries, pre-arterioles, and arterioles) to the genesis of perfusion abnormalities.

The results published by Verna et al in this number of the *Journal* shed some light on the possible mechanisms of coronary vasomotor dysfunction and inducible myocardial ischemia in patients with stable anginal chest pain and non-obstructed coronary arteries.¹⁹ The population of this study consisted of 101 highly selected patients with suspected stable ischemic heart disease, who had been submitted to both exercise-stress myocardial perfusion SPECT and ICA with the evidence of normal coronary arteries or non-significant CAD (<50% stenosis or FFR <0.8). All the patients underwent a comprehensive invasive evaluation of coronary vasomotor function, by monitoring intracoronary Doppler flow velocity and coronary perfusion pressure and performing serial coronary angiographies in response to intracoronary vasoactive drugs. In every patient, epicardial coronary vasomotricity was evaluated in terms of coronary luminal diameter change in response to acetylcholine and nitroglycerine, while global vasodilating capability was assessed in terms of coronary flow velocity reserve in response to adenosine (after nitroglycerine). Absolute CBF was also computed from Doppler flow velocity and quantitative angiography in all the study conditions.

The study showed that coronary vasomotor function was abnormal in the great majority of the patients ($\approx 77\%$) with a divergent response to acetylcholine and adenosine in almost half of them. Specifically, while an isolated abnormal vasodilation to intracoronary adenosine, interpreted by the authors as a marker of endothelium-independent microvascular dysfunction, was revealed in a minority of patients ($\approx 20\%$), the majority of the subjects showed signs of coronary endothelial dysfunction ($\approx 57\%$), as identified by a vasoconstrictor response to acetylcholine (i.e., epicardial spasm and CBF reduction). Interestingly, regional myocardial perfusion abnormalities at SPECT were revealed almost exclusively in these patients, apparently co-localizing (in 54 out of 58 patients, 98%) with the coronary artery showing an abnormal response to

acetylcholine. Conversely, coronary microvascular dysfunction (i.e., impaired response to adenosine) was generally a diffused phenomenon with no significant relationships with regional myocardial perfusion patterns at SPECT imaging. The main conclusion of the study was that selected patients with anginal chest pain and non-obstructed coronary arteries show frequently an altered epicardial coronary vasomotion mainly due to endothelial dysfunction that is able to cause, alone or in association with abnormal microvascular function, downstream perfusion abnormalities on SPECT. Conversely, in this population, coronary microvascular dysfunction alone was a relatively rare condition that generally affected the entire myocardium with no relevant effect on regional myocardial perfusion patterns.

The authors had the great merit to investigate by a comprehensive and complex research protocol some of the major coronary mechanisms leading to inducible myocardial ischemia in patients without obstructive CAD. Using an overall appropriate methodology and an extensive analysis of the data, they reached the conclusion that endothelial dysfunction and abnormal epicardial coronary vasomotion prevail over pure microvascular dysfunction to cause myocardial ischemia in these patients. Based on their findings, the authors advocate for extensive invasive assessment of coronary function in this kind of patients.

While the present study provides interesting pathophysiologic information, some questions remain unanswered. Is epicardial endothelial dysfunction isolated or coexistent with diffuse atherosclerosis? How frequent is this pattern in the more general population of patients with stable chest pain and stress-induced perfusion abnormalities? Should we recommend an invasive coronary functional evaluation in all patients with evidence of ischemia and non-obstructive coronary disease at ICA?

The retrospective selection of the population among patients clinically referred to ICA, mostly unregarding of SPECT results, and the inclusion of subjects with prior acute coronary syndromes, prevented the selection of a homogeneous population of patients. In fact, 30% of the patients had a normal stress myocardial perfusion imaging, only $\approx 34\%$ presented typical angina, and 25% had previous acute coronary syndromes with resting perfusion defects so that the final study population ends up as a mixture of various pathologic conditions. In this respect, the evidence of a relationship between coronary vasomotor dysfunction and resting myocardial perfusion defects, which the authors attribute to repetitive stunning, could be also due to the confounding effect of previous myocardial damage.²⁰

Having used ICA as the reference technique for the definition of a “normal” coronary anatomy, the study

could not evaluate the known impact of diffuse, non-obstructive, coronary atherosclerosis on coronary perfusion parameters.^{21,22} The possible additional effect of abnormal coronary wall structure to the abnormalities of epicardial vasomotricity and coronary perfusion that were attributed by Verna et al to endothelial/microvascular dysfunction could not be excluded.^{15,16} The use of CCTA would have also favored the precise assignment of any myocardial perfusion abnormality to the pertinent coronary artery through hybrid cardiac imaging, allowing a proper per-vessel analysis of the coronary perfusion data.¹²

Nevertheless, the present data underscore the relevance of endothelial dysfunction, possibly not limited to epicardial coronary vessels, over pure microvascular abnormalities in causing myocardial ischemia and angina.^{23,24} Previous studies have demonstrated the functional inter-relationship between the distinct coronary anatomic compartments—*conductive arteries, pre-arterioles, and arterioles*—in determining coronary blood flow abnormalities in cardiac patients.²⁵ Even in the study by Verna et al the most severe perfusion abnormalities occurred in patients with both coronary epicardial vasoconstrictor response to acetylcholine and an altered response to adenosine as signs of global coronary perfusion impairment.¹⁹ Interestingly, while acetylcholine is frequently believed to be a specific test for the evaluation of epicardial endothelium-dependent vasomotion, evidence has demonstrated that it may actually cause diffuse impairment of coronary vasomotricity without apparent epicardial spasms.²⁶ Accordingly, it would have been interesting to know how many patients in the study by Verna et al presented an abnormal CBF response to acetylcholine without appreciable epicardial spasm, as a specific sign of diffuse coronary endothelial dysfunction.

Finally, the present and previous evidence underline the relevant interaction between the specific cardiac stress modality and coronary perfusion parameters, demonstrating that a single stress test (i.e., exercise, vasodilator, vasoconstrictor) may not allow a complete evaluation of coronary vasomotor function, possibly underestimating the effective myocardial ischemic burden.^{23,27} In fact, a consistent proportion of patients may have a strikingly different response to some of the most diffuse cardiac stress modalities, i.e., exercise vs coronary vasodilator, making the interchangeability of those tests rather questionable. In particular, by mainly unmasking the presence of diffuse coronary microvascular dysfunction, coronary vasodilators (i.e., adenosine and dipyridamole) may take particular advantage from the use of imaging techniques that allow the absolute quantification of myocardial blood flow.^{15,16}

In the last decades we have assisted to a radical change of knowledge in the field of chronic ischemic heart disease, with a progressive abandonment of the old belief that linked any relevant coronary perfusion abnormality to the necessary presence of obstructive CAD on ICA. Novel pathologic conditions (i.e., coronary endothelial/microvascular dysfunction, diffuse coronary atherosclerosis, coronary spasm) are now considered relevant mechanisms, either alone or in combination, of inducible myocardial ischemia. Despite these evolutions, a thorough evaluation of the status of coronary vasomotor function is not performed in patients with anginal chest pain, frequently sent to ICA “in the hope” to find an obstructive lesion to treat, and rapidly dismissed as “false-positive findings” in the case of an unobstructed coronary tree. The study by Verna et al further underlines the importance of a multiparametric approach for the assessment of anginal patients, combining anatomical information with the functional data obtained, preferentially, under different stress conditions.¹⁹

Whether such integrated diagnostic approach should be performed invasively or entirely non-invasively (i.e., by means of hybrid PET-SPECT/CCTA cardiac imaging) is a matter of discussion and would require extensive comparative studies including costs and outcome measurements. Most importantly, it would be needed to demonstrate whether a specific treatment targeted to non-invasive or invasive individual characterization could translate into an improvement in health status and final outcome.

Disclosures

The authors have no conflict of interest to be disclosed.

References

1. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. *JAMA*. 2006;295:1556-65.
2. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-16.
3. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886-95.
4. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. ESC guidelines on the management of stable coronary artery disease: The Task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;2013:2949-3003.
5. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: An update. *Eur Heart J*. 2014;35:1101-11.

6. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med*. 1994;330:1782-8.
7. Pupita GS, Maseri A, Kaski JC, Galassi AR, Gavrielides S, Davies G, et al. Myocardial ischemia caused by distal coronary artery constriction in stable angina pectoris. *N Engl J Med*. 1990;323:514-20.
8. Sambucetti G, Marzilli M, Fedele S, Marini C, L'Abbate A. Paradoxical increase in microvascular resistance during tachycardia downstream from a severe stenosis in patients with coronary artery disease: Reversal by angioplasty. *Circulation*. 2001;103:2352-60.
9. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011;124:2215-24.
10. Lanza GA, Camici PG, Galiuto L, Niccoli G, Pizzi C, Di Monaco A, et al. Methods to investigate coronary microvascular function in clinical practice. *J Cardiovasc Med (Hagerstown)*. 2013;14:1-18.
11. Acampa W, Gaemperli O, Gimelli A, Knaapen P, Schindler TH, Verberne HJ, et al. Role of risk stratification by SPECT, PET, and hybrid imaging in guiding management of stable patients with ischaemic heart disease: Expert panel of the EANM cardiovascular committee and EACVI. *Eur Heart J Cardiovasc Imaging*. 2015;16:1289-98.
12. 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.
13. Neglia D, Parodi O. Detecting the impact of emerging cardiovascular risk factors: The role of positron emission tomography. *J Nucl Cardiol*. 2008;15:485-90.
14. Neglia D, Michelassi C, Trivieri MG, Sambucetti G, Giorgetti A, Pratali L, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. *Circulation*. 2002;105:186-93.
15. Liga R, Marini C, Cocceani M, Filidei E, Schlueter M, Bianchi M, et al. Structural abnormalities of the coronary arterial wall in addition to luminal narrowing—affect myocardial blood flow reserve. *J Nucl Med*. 2011;52:1704-12.
16. Naya M, Murthy VL, Blankstein R, Sitek A, Hainer J, Foster C, et al. Quantitative relationship between the extent and morphology of coronary atherosclerotic plaque and downstream myocardial perfusion. *J Am Coll Cardiol*. 2011;58:1807-16.
17. Meijboom WB, Van Mieghem CA, van Pelt N, Weustink A, Pugliese F, Mollet NR, et al. Comprehensive assessment of coronary artery stenoses: Computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. *J Am Coll Cardiol*. 2008;52:636-43.
18. Hadamitzky M, Achenbach S, Al-Mallah M, Berman D, Budoff M, Cademartiri F, et al. Optimized prognostic score for coronary computed tomographic angiography: Results from the CONFIRM registry (COronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry). *J Am Coll Cardiol*. 2013;62:468-76.
19. Verna E, Ghiringhelli S, Provasoli S, Scotti S, Salerno Uriarte J. Epicardial and microvascular coronary vasomotor dysfunction and its relation to myocardial ischemic burden in patients with non-obstructive coronary artery disease. *J Nucl Cardiol*. 2017. doi: 10.1007/s12350-017-0871-6.
20. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med*. 1994;331:222-7.
21. Gould KL, Nakagawa Y, Nakagawa K, Sdringola S, Hess MJ, Haynie M, et al. Frequency and clinical implications of fluid dynamically significant diffuse coronary artery disease manifest as graded, longitudinal, base-to-apex myocardial perfusion abnormalities by noninvasive positron emission tomography. *Circulation*. 2000;101:1931-9.
22. De Bruyne B, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but “Normal” coronary angiography. *Circulation*. 2001;104:2401-6.
23. Cassar A, Chareonthaitawee P, Rihal CS, Prasad A, Lennon RJ, Lerman LO, et al. Lack of correlation between noninvasive stress tests and invasive coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease. *Circ Cardiovasc Interv*. 2009;2:237-44.
24. Ong P, Athanasiadis A, Borgulya G, Vokshi I, Bastiaenen R, Kubik S, et al. Clinical usefulness, angiographic characteristics, and safety evaluation of intracoronary acetylcholine provocation testing among 921 consecutive white patients with unobstructed coronary arteries. *Circulation*. 2014;129:1723-30.
25. Chilian WM. Coronary microcirculation in health and disease: Summary of an NHLBI workshop. *Circulation*. 1997;95:522-8.
26. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol*. 2012;59:655-62.
27. Verna E, Ceriani L, Provasoli S, Scotti S, Ghiringhelli S. Larger perfusion defects with exercise compared with dipyridamole SPECT (exercise-dipyridamole mismatch) may reflect differences in epicardial and microvascular coronary dysfunction: When the stressor matters. *J Nucl Cardiol*. 2007;14:818-26.