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RESEARCH LETTER
Imaging

Perivascular inflammation and the coronary micro-circulation and vasoreactivity—a potential clue to angina with non-obstructive coronary artery disease

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Perivascular inflammation and coronary micro-vascular dysfunction

Between 60 and 70% of patients with angina symptoms have non-obstructive coronary artery disease (<50% luminal stenosis of the epicardial coronary arteries) termed as ANOCA.[1] Invasive assessment of ANOCA relies on the intracoronary physiological detection of coronary flow reserve (CFR), myocardial resistance measurements by thermodilution, or Doppler flow measurements [index of microcirculatory resistance (IMR)/hyperaemic micro-vascular resistance (HMR)[1]]. Due to the lack of invasive capacity to serve ANOCA patients, the attention has turned to explore scalable low-cost and non-invasive alternatives. The recent European guidelines recommend non-invasive tests including stress echocardiography and coronary flow assessment as possible diagnostic tools in the assessment of ANOCA (2b/LOE-C).[2] Multi-parametric stress echocardiography has been used to assess inducible ischaemia by the traditional imaging biomarker of regional wall motion abnormality (RWMA) and the recently validated pulse wave Doppler assessment of the distal left anterior descending (LAD) coronary flow velocity at rest and during maximal vasodilatation (peak stress, both with vasodilator and dobutamine stress echocardiography) as a coronary flow velocity reserve (CFVR).[3] Both RWMA (which requires severe myocardial ischaemia to manifest) and CFVR are independent predictors of outcome and are synergistic when both are combined in patients with and without obstructive coronary artery disease.[4] In the recent case series, we have proposed a fully non-invasive pathway based on anatomical imaging of coronary arteries by cardiac computed tomography angiography (CCTA) and functional assessment by multi-parametric stress echocardiography.[5]

Inflammation and infection had been associated with accelerated coronary atherosclerosis.[6] A recent clinical consensus statement by the European Society of Cardiology Working Group on Coronary Pathophysiology and Micro-circulation highlighted the importance of perivascular adipose tissue (PVAT) as a source of imaging biomarker of inflammation as a predictor of outcome in patients with chronic coronary syndrome.[7] Cardiac computed tomography angiography not only assesses plaque composition and plaque burden of individual coronary arteries but can reliably describe and quantify PVAT and its radiomic profile that serves as a 'sensor' of vascular inflammation (fat attenuation index, FAI).[7] Computed tomography–FAI has been validated in histology, gene expression studies of adipose tissue explants, and against ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18F}FDG PET/CT) imaging.[7] In addition, using external CCTA database, FAI was shown to have a strong predictive value of long-term cardiovascular events and cardiovascular mortality.[7]

The role of perivascular inflammation in the pathogenesis of ANOCA has been lately investigated. Indeed, we found an inverse correlation between CT–PVAT attenuation (inflammation) and CFVR in the distal LAD during vasodilator stress echocardiography, in 202 patients with coronary micro-vascular dysfunction without obstructive coronary artery disease,[8] (*Figure 1A*). Moreover, clinical evidence emerges during routine CCTA of the perivascular inflammation expressed by FAI in patients with ANOCA confirmed by reduced CFVR during dobutamine stress echocardiography (*Figure 1B*). The inflammatory risk and the long-term cardiovascular events in patients with no obstructive coronary artery disease had recently been published, using the biggest cardiac CT database in the world, in the ORFAN multicentre, longitudinal cohort study.[10]

Perivascular inflammation and coronary vasoreactivity (macro-vascular spasm and micro-vascular spasm

Between 15 and 20% of ANOCA patients are suffering from macro- or micro-vascular vasospasm in their coronary arteries, to explain

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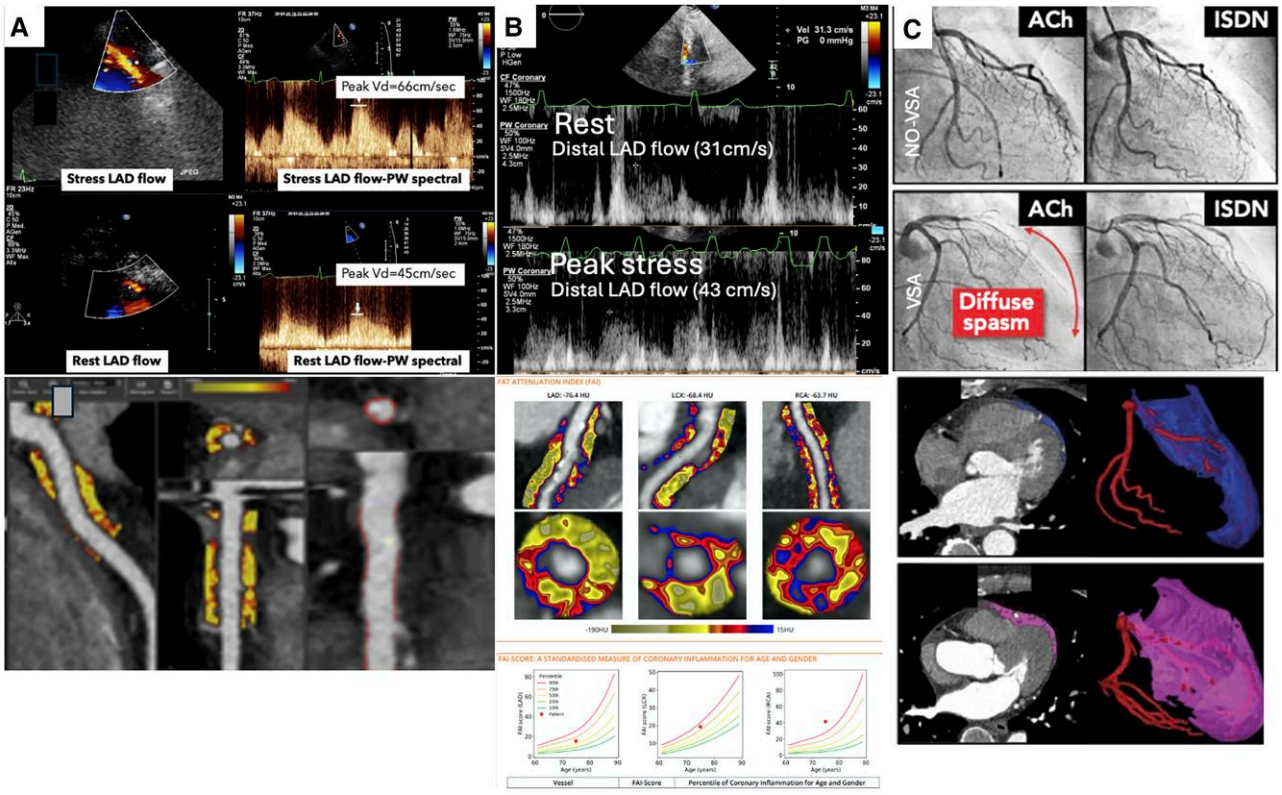

Figure 1 Angina with non-obstructive coronary artery disease endotypes and perivascular adipose tissue. *(A)* Representative example of the Doppler echocardiography-based coronary flow velocity reserve in the distal left anterior descending coronary artery (66/45 = 1.46) during dipyridamole stress echocardiography (*top*) and perivascular adipose tissue by computed tomography imaging in the same angina with non-obstructive coronary artery disease patient (*bottom*; coronary flow velocity reserve normal value >2.0; unpublished image by Pasqualetto *et al.* 2021). *(B)* Representative example of the Doppler echocardiography-based coronary flow velocity reserve in the distal left anterior descending coronary artery (43/31 = 1.38) during dobutamine stress echocardiography (*top*) and fat attenuation index derived from perivascular adipose tissue by computed tomography imaging in the same angina with non-obstructive coronary artery disease patient (*bottom*). Note the high fat attenuation index score in the right coronary artery: 41.4 representing 98th percentile of age- and sex-corrected values (coronary flow velocity reserve normal value >2.0). *(C)* Representative example of the computed tomography–perivascular adipose tissue volume in 2 patients with (*bottom*) and without (*top*) acetylcholine-induced coronary vasospasm. Reproduced with permission from Elsevier.[9] CFVR, coronary flow velocity reserve; FAI, fat attenuation index; PVAT, perivascular adipose tissue; RCA, right coronary artery; LAD, left anterior descending coronary artery; VSA, vasospastic angina; Ach, acetylcholine; ISDN, isosorbide dinitrate; CAG, coronary angiography; CT, computed tomography.

their symptoms.[1] Current recommendation proposes to investigate macro- and micro-vascular vasoreactivity by intracoronary acetylcholine injection to evaluate the degree of vasospasm (luminal diameter reduction), ST changes on 12-lead ECG, and symptoms.[1]

There is a plausible assumption that there is an association between inflammation and coronary artery vascular reactivity. Ohyama *et al.*[9] investigated whether the coronary vasospasm by intracoronary administration of acetylcholine is associated with perivascular inflammation in patients with vasospastic angina using ^{18F}FDG PET/CT. They showed evidence that coronary spasm was associated with perivascular inflammation of coronary adventitia and PVAT in patients with vasospastic angina, but the causal relationship was not explored in humans (*Figure 1C*[9]). However, they previously demonstrated that coronary spasm could be induced in a porcine model with coronary adventitial application of interleukin-1b, which suggested that 'outside–in' signalling has important roles in the pathogenesis of vasospastic angina.[11] In this study, they demonstrated that vascular smooth muscle cell hypercontraction induced by adventitial inflammation through Rho kinase activation, rather than endothelial dysfunction, plays a major role in the pathogenesis of coronary spasm.

The causal relationship of perivascular inflammation and coronary micro-vascular dysfunction and coronary artery vasoreactivity as well as whether reducing perivascular inflammation could help symptomatic improvement and cardiovascular outcome in ANOCA patients would need to be further elucidated. Anti-inflammatory agents, such as statins and immunomodulators, have been assessed and may provide with new treatment strategies to improve cardiovascular outcome in patients with CMD. Indeed, high-intensity statins show promising effect on reducing FAI after >12 months of treatment in prospective observational studies.[12] A randomized clinical trial is currently recruiting to investigate Colchicine Effect on Perivascular Inflammation Index on Coronary CTA (COPIX Trial; *ClinicalTrials.gov identifier (NCT number): NCT05347316).* In addition, preliminary results using Orticumab, first in class monoclonal antibody against oxidized LDL a marker of plaque inflammation, showed a reduction in perivascular inflammation and predicted 50% reduction of risk of cardiovascular mortality.

Author contribution

A.K. and N.G. contributed to the conception or design of the work, interpretation of data for the work, and drafted and critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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Data availability

Data used in this research letter are available at request from the corresponding author.

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