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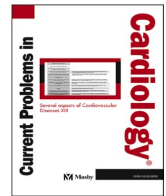

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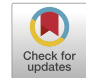

Non-invasive imaging assessment in angina with non-obstructive coronary arteries (ANOCA)

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Abbreviations: ANOCA, (Angina with Non-Obstructive Coronary Arteries); CAD, (Coronary Artery Disease); CAS, (coronary artery spasm); CCTA, (Coronary Computed Tomography Angiography); CFVR, (Coronary Flow Velocity Reserve); CMD, (coronary microvascular dysfunction); CMR, (Cardiac Magnetic Resonance); CTP, (Computed Tomography Perfusion); ECG-EST, (electrocardiogram exercise stress test); FFR-CT, (Fractional Flow Reserve – Computed Tomography); ICA, (Invasive Coronary Angiography); LGE, (Late Gadolinium Enhancement); PET, (Positron Emission Tomography); SPECT, (Single-Photon Emission Computed Tomography).

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ABSTRACT

Due to its significant prevalence and clinical implications, angina with non-obstructive coronary arteries (ANOCA) has become a major focus in modern cardiology. In fact, diagnosing ANOCA presents a significant challenge. The final diagnosis is often difficult, delayed, and frequently necessitates an invasive assessment through coronary angiography. However, recent improvements in non-invasive cardiac imaging allow a diagnosis of ANOCA using a combination of clinical evaluation, anatomical coronary imaging, and functional testing. This narrative review aims to critically assess various non-invasive diagnostic methods and propose a multimodal approach to diagnose ANOCA and tailor appropriate treatments.

Introduction

Approximately 50-60 % of patients undergoing elective invasive coronary angiography (ICA) for suspected coronary artery disease (CAD) exhibit normal or 'near-normal' coronary arteries (<50 % stenosis in any epicardial coronary artery and fractional flow reserve >0.80).[1] Patients with no documented epicardial atherothrombotic mechanism for their symptoms are commonly referred to as angina with non-obstructed coronary arteries (ANOCA).[2] In these patients, the prevalence of demonstrable ischaemia (INOCA) varies, depending on the stress test performed, between 10 % and 30 %.[3] Several studies and registries have revealed that these individuals often have suboptimal care.[4,5] Identifying the different mechanisms behind the clinical presentation of these patients is essential for a tailored, patient-based approach. Extensive data suggest that most of these patients exhibit abnormalities in the regulation of coronary blood flow (CBF) and coronary vascular resistance, suggesting the presence of coronary microvascular dysfunction (CMD).[5,6]

Some studies have demonstrated that a strategy of adjunctive invasive testing for disorders of coronary function, followed by medical therapy guided by their results, might improve clinical outcomes.[7] Therefore, functional tests during invasive coronary angiography (ICA) represent a key diagnostic tool to assess the underlying pathophysiological mechanisms of ANOCA.[7] However, relevant information about the mechanism(s) responsible for ANOCA might also be obtained in most patients by a systematic, non-invasive diagnostic approach.

This review aims to 1) examine the strengths and limitations of non-invasive methods proposed to assess the pathophysiological mechanisms responsible for ANOCA and 2) propose a systematic stepwise non-invasive approach to achieve the correct diagnosis and apply a tailored treatment in individual patients.

Clinical evaluation

Angina pectoris is described as a discomfort usually located in the chest, with variable radiation to the epigastrium, lower jaw, or arm, and described as pressure, heaviness, or burning.[8] The relationship between typical angina and exercise is characteristic, with chest pain occurring and worsening with increased exertion and resolving with rest. However, patients may often report atypical angina (e.g., angina at rest) or angina equivalents (mainly shortness of breath).[3] In typical chronic coronary syndromes, the level of exertion triggering angina is stable, usually for at least two months, and patients are usually asymptomatic at rest.[3] Although obstructive CAD is the most frequent cause of typical angina pectoris, up to 60 % of patients referred to ICA for suspected obstructive CAD do not show any critical coronary stenosis.[2,9] Notably, up to 90 % of these patients have abnormal coronary function testing, thus suggesting functional coronary abnormalities as a potential cause of angina.[10,11]

Patients with ANOCA are generally younger, more often female, and have lower cardiovascular risk factors compared to those with classic angina due to obstructive CAD.[2] ANOCA patients complain frequent episodes of angina and undergo a multitude of non-invasive and invasive diagnostic procedures, thus representing an economic burden for healthcare systems.[12] Accordingly, an adequate knowledge of ANOCA and diagnostic tools available to reach a definitive diagnosis of pathophysiologic mechanisms is needed to improve the management of these patients.

Electrocardiographic stress tests

An electrocardiogram (ECG) exercise stress test (EST) can be performed to assess exercise tolerance and symptoms, arrhythmias, and blood pressure response and to define the prognosis in various populations of patients.[13] Although recent guidelines suggest that imaging, rather than ECG, stress tests should be the initial non-invasive tests for diagnostic assessment of patients with suspected obstructive CAD,[3] ECG-EST remains the most largely used test to this scope due to its large availability, easy repeatability, and low costs.

Importantly, ECG-EST has a relevant role in assessing patients with ANOCA. Despite its suboptimal sensitivity, the induction of significant ST-segment depression during the test is indeed highly suggestive of the presence of CMD in these patients in whom obstructive CAD had already been excluded.[14–16] However, without an anatomical coronary evaluation, a positive ECG-EST is unhelpful in distinguishing between angina patients with obstructive CAD vs. those with ANOCA. Yet, in the latter patients, exercise-induced angina and ST-segment/T wave changes tend to have a slower resolution (>10–15 min) after stopping exercise. Similarly, in agreement with the inconstant and slow response to sublingual nitrates of angina pain, the preventive administration of

short-acting nitrates often has no significant effects on EST-induced ischemic ECG changes in ANOCA, in contrast with the marked improvement usually observed in patients with obstructive CAD.[17] Thus, these findings can help orient the diagnosis of chest pain episodes towards microvascular, rather than macrovascular, coronary abnormalities, and are particularly suggestive of microvascular angina when occurring in peri- or post-menopausal women.[18]

In some patients, ECG-EST may induce typical features of coronary artery spasm (CAS), i.e., angina with ST-segment elevation, often in the recovery period, thus allowing the correct diagnosis.[19,20] Importantly, functional tests for CAS, including ergonovine or hyperventilation tests, can also be performed during ECG monitoring when vasospastic angina is strongly suspected. Of note, induction of typical angina with mild ST-segment/T wave changes may strongly suggest coronary microvascular rather than epicardial spasm in ANOCA patients.[21]

An unherent limitation of ECG-EST is that its interpretation is compromised in patients presenting baseline ECG abnormalities (e.g., conduction disorders, Wolff-Parkinson-White pattern, pacemaker rhythm, baseline ST-segment abnormalities, etc.); furthermore, it cannot be performed in individuals unable to exercise. However, these limitations may only partially apply to functional tests for CAS.

Coronary CT angiography

Coronary computed tomography angiography (CCTA) has a considerable potential to play an increasing role in ANOCA patients. CCTA is at present widely used and recommended as a first-line test in the diagnostic work-up of patients with low-to-intermediate likelihood of obstructive CAD,[3,22–24] mainly due to its high negative predictive value in ruling out the disease[25,26] which is also an essential finding for the identification of patients with CMD.[27,28]

Several studies have shown that CCTA may also provide functional information on coronary lesions along with anatomical information. In the ANOCA context, epicardial vessel volume measured by CCTA can help identify patients with CMD, as those with structural CMD and high minimal microvascular resistance have smaller vessels than those with functional CMD and healthy controls.[29] On the other hand, functional tests can now also be applied to assess whether a microcirculatory disorder is present in patients without obstructive CAD. In particular, two CCTA-based functional types of investigation have recently been proposed for CMD detection: Fraction Flow Reserve CT (FFR_{CT}) (HeartFlow, Redwood City, CA) and CT perfusion (CTP).

The FFR_{CT} model is created by applying computational fluid dynamics to simulate maximal hyperemia, estimate myocardial mass, and quantify myocardial blood flow (MBF), ultimately predicting FFR_{CT} along the coronary tree.[30] One of the first FFR_{CT}-derived parameters undergoing investigation has been the ratio of coronary luminal volume to myocardial mass (V/M ratio). Initial studies reported a significantly lower V/M ratio in patients with microvascular angina compared to age-matched asymptomatic controls and an independent association of low V/M ratio with myocardial ischemia in patients with non-obstructive CAD.[31,32] However, a sub-study of the PACIFIC trial found no association between V/M and hyperaemic MBF or coronary flow reserve (CFR) in vessels with non-obstructive CAD on ICA.[33] Accordingly, the V/M ratio is now considered an integrated measure of the balance between myocardial blood supply and demand,[34] rather than a measure of microvascular function. A second FFR_{CT} derived approach consists of generating patient-specific cardiac vascular networks starting from segmented epicardial vessels down to the microcirculation, allowing an estimate of coronary flow and myocardial perfusion.[34,35] In a proof-of-concept paper, MBF derived by this approach correlated with $[^{15}O]H_2O$ PET data.[36] Research is ongoing to also derive coronary microvascular resistance reserve from CCTA (MRR_{CT}) using total left ventricle flow at rest (from the FFR_{CT} model) and stress (from $[^{15}O]H_2O$-PET).

At variance with FFR_{CT},[37] dynamic CTP allows a quantification of MBF and the assessment of differences in myocardial perfusion at rest and after stress (usually, adenosine or regadenoson) between the endocardium and the epicardium.[38] The usefulness of CTP in CMD detection is still under investigation. However, in animal models, MBF quantification by CTP showed a good correlation with microsphere measurements and with cardiac magnetic resonance (CMR).[39–41] Moreover, decreased endocardial over epicardial contrast ratio was shown to be associated with CMD.[42] The ongoing ADVANTAGE II study will elucidate the diagnostic accuracy of CTP in detecting CMD by comparing its data with those obtained by invasive physiological testing.

Peri-vascular adipose tissue attenuation is a non-morphological and non-invasive analysis capable of detecting localized vascular inflammation performed on computed tomography (CT) that can be applied in multiple vascular districts.[43–45] Peri-coronary adipose tissue attenuation (PCAT) is feasible on both CT and CCTA and is a paramount marker associated with all-cause and cardiovascular mortality independently from the presence and degree of CAD.[46–48] In patients with ANOCA undergoing both CCTA and stress echocardiography (SE), PCAT attenuation was independently related to coronary microvascular function by coronary flow velocity reserve (CFVR) in the mid-distal left anterior descending coronary artery.[49] Although PCAT appears to be a promising index, prospective studies conducted on larger populations are needed in patients with ANOCA. Of note, thanks to new technical improvements, like late iodine enhancement, extracellular volume, and spectral evaluation, cardiac CT also gives additional information on tissue characterization, which may help clarify the clinical picture in some patients.[50]

In conclusion, CCTA has the unique potential advantage of providing both anatomical and functional information on coronary circulation. Thanks to technological advances, CCTA is a promising method for the noninvasive assessment of functional abnormalities of the coronary circulation.

The major drawbacks of the method include radiation exposure, iodine contrast usage, and the need for operators' expertise (especially for CTP). Furthermore, common limitations of CCTA use encompass irregular and tachycardic rhythms, large calcific lesions, and severe kidney disease.

Stress echocardiography

Stress echocardiography plays a role in identifying not only patients with obstructive CAD, but also those with epicardial CAS and CMD.

As shown above, epicardial CAS can be induced by intravenous administration of ergonovine, and may result in regional wall motion abnormalities (usually a-dyskinesia). With CAS induced during ICA as the gold standard, the ergonovine echocardiography test has excellent sensitivity and specificity for CAS in patients with typical variant angina.[51] Accordingly, it might also likely reveal CAS as the cause of symptoms also in patients with ANOCA with no clinical/ECG findings of variant angina. The safety of the noninvasive ergonovine echocardiography test is high in properly selected patients exhibiting angiographically non-obstructed coronary arteries.[52] In cases where ergonovine is unavailable, the hyperventilation test (consisting of 5 min of hyperventilation followed by 5 min of post-hyperventilation monitoring) can be applied as a suitable alternative, although its sensitivity is lower.[51] In some patients, as shown for ECG stress test, CAS may occur and cause the typical wall motion abnormalities during an exercise echocardiography stress test performed to detect obstructive CAD, in particular during the early recovery phase of exercise. In some ANOCA patients, CAS may also be revealed during the dobutamine stress test or following aminophylline administration after an adenosine/dipyridamole stress test.[53]

On the other hand, the induction of typical angina and/or ischemic ECG changes during the echocardiography stress test (either with the use of exercise, vasodilators, or vasoconstrictors) without any abnormality in myocardial contractile function strongly suggests CMD (impaired vasodilation and/or increased vasoconstriction). Most importantly, CMD can be diagnosed by assessing CFVR in the mid-distal left anterior descending coronary artery by adenosine/dipyridamole/regadenoson stress test.[51,54] The evaluation of CFVR through vasodilator transthoracic echocardiography demonstrates excellent feasibility and is recommended (class IIb) by current European Society of Cardiology[3] and American College of Cardiology-American Heart Association guidelines.[8] This dysfunction is rarely associated with regional wall motion abnormalities, but is associated with a worse clinical outcome compared to patients with ANOCA with normal CFVR ($\geq$2.0).[54,55]

The detection of a reduction in coronary flow velocity during intravenous ergonovine or hyperventilation in the absence of wall motion abnormalities may suggest the induction of coronary microvascular spasm/constriction.[55,56]

Two-dimensional speckle-tracking echocardiography is a feasible, reproducible, and accurate imaging technique in several clinical settings.[57–59] In patients with coronary microvascular dysfunction undergoing dipyridamole stress echocardiography, showing no wall motion abnormalities, global and layer-specific deformation indices are reduced during vasodilation compared with resting conditions.[60] Also, the presence of a myocardial bridge can be detected through CFVR measurements in the left anterior descending artery during stress echocardiography; in fact, CFVR has indeed been shown to be reduced in these patients,[61] although it is not clear whether this is directly related to myocardial bridging or a simultaneous coexistence of CMD.[62,63]

Considering the growing emphasis on affordability, radiation exposure, and environmental impact in healthcare policymaking, stress echocardiography presents undisputed advantages of low cost, zero radiation, and near-zero carbon dioxide emissions.[64] Although operator- and acoustic window-dependency are major limitations, the integration of artificial intelligence is becoming an attractive and viable option for standardizing data acquisition, simplifying data analysis, and harmonizing data interpretation. While large-scale experience is currently lacking, the SE 2030 study includes a dedicated sub-project named SESPASM (Stress Echo for detection of coronary vasoSPASM) focused on the noninvasive detection of epicardial artery vasospasm and coronary microvascular dysfunction in ANOCA patients.[65]

In the current ESC guidelines[3] contrast myocardial perfusion imaging during stress echocardiography has been given a Class I (level of evidence B) indication for diagnosis of obstructive CAD. Contrast stress echocardiography has also been reported to be reliable for assessment of CFR in ANOCA patients,[66] but recommendations for its use to this scope needs further confirmation in future studies.

Stress cardiac magnetic resonance

Numerous recent studies have underscored the clinical utility of stress CMR in the assessment of patients with CMD. Indeed, stress CMR is a comprehensive tool combining the benefits of myocardial perfusion imaging and stress testing to evaluate coronary microvascular function thoroughly.[66]

Currently, the predominant method for conducting stress CMR involves inducing hyperemia through the administration of vasodilators such as adenosine, regadenoson or dipyridamole.[23] Once hyperemia is induced, a gadolinium-based contrast agent (GBCA) is introduced into a peripheral vein and passes through the left ventricular myocardium with a typical wavefront from the subendocardial to the subepicardial region. The GBCA exhibits a swifter and more pronounced increase in T1-signal within normally perfused myocardial segments compared to those with abnormal perfusion. A sequence of dynamic stress perfusion images is captured, encompassing the basal, mid, and apical levels of the left ventricle during the GBCA infusion. CMR images enable the visualization of the 16 myocardial segments, standardized by the American Heart Association, representing typical coronary artery territories.[67] Subsequently, approximately 10 to 15 min after the acquisition of stress perfusion images, resting perfusion images are obtained using the same technique and slice position, facilitated by the injection of an additional dose of GBCA.

In clinical practice, the identification of GBCA perfusion defects has traditionally relied on qualitative analysis through visual inspection, and CMD is often linked to uniform circumferential inducible ischemia, with main involvement of subendocardial layers.[68] Nevertheless, over the past years, a semi-quantitative assessment of stress perfusion CMR has become available, facilitating the calculation of myocardial perfusion reserve (MPR), which is a non-invasive surrogate for CFR[69] and is calculated as the ratio of hyperemic to resting MBF. Notably, a specific threshold for MPR has recently emerged, with a cutoff value of $<$1.47 identified as the

optimal prognostic indicator for predicting major adverse cardiovascular events during the long-term follow-up of patients with ANOCA.[70] Compared with visual assessment, semi-quantitative perfusion analysis demonstrated superior accuracy in correctly identifying the presence of CMD.[68]

Moreover, a fully quantitative analysis that allows the measurement of MBF is now available. Perfusion maps are automatically generated on the scanner using artificial intelligence, both at rest and under stress.[71] Quantitative perfusion analysis has shown increased accuracy in identifying CMD when utilizing 3-T CMR, thanks to an elevated signal-to-noise ratio that facilitates the acquisition of high spatial resolution series, improves assessment of subendocardial perfusion, and reduces the occurrence of dark-rim artifacts.[72]

Recent technological advances have paved the way for robust and fully automatic quantitative analysis of coronary perfusion,[68] which, given its independence from operator training, will likely become the most accurate method for CMD assessment.

Unlike other non-invasive imaging modalities, CMR offers high spatial resolution, allowing detailed visualization of the myocardium and thus reducing the number of false-positive cases. It also does not involve ionizing radiations, making it a safer option for repeated evaluations compared to radiologic methods.[73]

Alongside these considerations, CMR provides the capability to meticulously assess the morphology, volume, and global and regional contractile function of the left ventricle (LV), allowing for precise tissue characterization.[73] This would make CMR the preferred test for patients in whom accurate structural and functional myocardial evaluation is also indicated.[74–76]

CMR, however, also presents some limitations. First, the equipment and post-processing tools for stress CMR can be expensive, limiting its widespread adoption in clinical practice. Additionally, CMR image quality and visual interpretation can be operator-dependent, requiring skilled personnel for optimal results. Finally, some patients may experience claustrophobia during CMR, and the technique may be contraindicated in individuals with certain implanted devices or severe renal impairment.

Nuclear medicine

Cardiac positron emission tomography (PET) for myocardial perfusion imaging (MPI) is considered the gold standard for the non-invasive assessment of CMD in the absence of obstructive CAD.[77]

All dynamic radionuclide perfusion tests can show reversible myocardial perfusion defects during exercise or pharmacological stress tests, but PET imaging allows a higher spatial resolution and lower radiation exposure compared to single-photon emission computed tomography (SPECT), which uses common sodium-iodide cameras. Furthermore, although stress SPECT is more affordable and available and is highly sensitive in detecting ischemic areas, even related to CMD, it does not allow a quantitative analysis of CMD. Pharmacologic stress PET, instead, allows a direct global and regional quantitative assessment of MBF, giving direct information about the microvascular response to a stressor. The growing diffusion of PET systems and the introduction of PET perfusion radiotracers that do not require an on-site cyclotron might facilitate the use of this diagnostic tool in clinical practice if costs also become acceptable. ^{15}O-water, ^{13}N-ammonia, and ^{82}Rb are the most used PET radiotracers in MPI. ^{15}O-water is the best radionuclide for MBF calculation due to its high diffusion, but its short half-life affects the visual assessment of perfusion abnormalities. Thus, ^{13}N-ammonia is usually the preferred agent for MPI, due to a longer half-life, a higher first-pass uptake and myocardial retention (as ^{13}N-glutamine), although it requires on-site cyclotron. ^{82}Rb, which also requires an on-site generator, on the other hand, is less used at present due to a higher radiation burden.[78]

Dynamic first-pass vasodilator perfusion acquisition protocols have been widely investigated for the assessment of regional and global stress/rest MBF measurements, primarily achieved by post-processing software that performs automated segmentation and radiation measurements. Notably, the strength of PET for MPI is the opportunity to assess not only MPR but also absolute quantitative MBF measurements (in ml/g/min). A homogenous radiotracer uptake, in the presence of reduced absolute hyperaemic MBF and/or MFR in patients with a known absence of obstructive CAD, will also indicate the presence of CMD.[78]

Importantly, the application of cardiac hybrid imaging, combining PET and CT techniques (by either hybrid PET-CT scanner or software-based image fusion), might implement further functional evaluation of coronary perfusion, simultaneously providing an anatomic assessment of coronary circulation.[79] The need for ionizing radiation, high costs, and limited accessibility to the technique, however, remain significant limitations for its widespread adoption in common clinical practice.

The non-invasive multimodal approach to suspected ANOCA

The current guidelines emphasize the importance of a comprehensive stepwise diagnostic approach for patients suspected to have obstructive CAD, but a similar approach can also be suggested in the setting of ANOCA.[3,8] In fact, reaching a final diagnosis of ANOCA can be challenging and may require a stepwise invasive or non-invasive approach, which is essential to guide the subsequent management of patients (Graphical abstract).[2]

In patients with chest pain, the initial step should involve the assessment of the pre-test probability (PTP) of CAD based on age, sex, and reported symptoms, which can be done with pre-specified risk tables.[3] Of note, while risk tables have been created to predict obstructive CAD, some clinical characteristics of patients may suggest a diagnosis of ANOCA. As reported above, these include the higher prevalence of female sex (particularly in the pre-menopausal/ menopausal age), younger age, fewer cardiovascular risk factors, and atypical and/or long-lasting chest pain.[2,12,80] However, additional diagnostic investigation is needed to orient toward a correct diagnosis of obstructive CAD or ANOCA.

In cases of high suspicion of CAD, the initial diagnostic test should be ICA.[3] Subsequently, if obstructive CAD is unexpectedly excluded, a thorough invasive evaluation for a diagnosis of ANOCA should be performed by assessing both microvascular (i.e.,

impaired microvascular dilatation, coronary microvascular spasm) and epicardial (coronary spasm) circulation.[2] Conversely, in the majority of patients with a low/intermediate probability of obstructive CAD, a full non-invasive diagnostic investigation might be applied to identify patients with either obstructive CAD or ANOCA,[3] considering that each diagnostic methodology has its own strengths and limitations (Table 1).

There is currently controversy about the best approach for the initial noninvasive diagnostic evaluation of patients with stable chest pain, including suspected ANOCA. Up to a few years ago, patients with suspected CCS were referred to a functional test of myocardial ischemia (ECG or imaging stress test). Recently, current data have suggested that an anatomy-based approach, focused on the use of CCTA, might be preferred.[22,23,81]

The study group of this document has decided not to recommend one strategy with respect to the other. Both strategies, indeed, may be considered appropriate to achieve the correct diagnosis and management in individual patients, presenting strengths and limitations that should be considered in guiding the choice, which might depend on multiple factors, including the characteristics of individual patients, clinical experience, preferences and expertise in specific tests of individual cardiologists, as well as the availability of diagnostic tests. Accordingly, the main strengths and weaknesses of each of the two approaches are shortly discussed below.

A) Anatomy-based diagnostic approach

The main strengths of the initial assessment of patients with chest pain with an anatomy-based approach relying on CCTA include the following: 1) CCTA allows a rather reliable assessment of the presence/absence of significant coronary stenosis; hence, considering symptomatic patients without evidence of coronary stenosis (suspected ANOCA patients) it would allow rapid identification of those that should be investigated for ischemic functional mechanisms of the patient's symptoms, leading to an established non-invasive ANOCA diagnosis; 2) CCTA may identify patients with left main disease or other high-disease risk findings (e.g., multivessel disease) who should undergo invasive assessment and surgical or percutaneous coronary revascularization;[22,81] 3) in absence of obstructive CAD, CCTA allows the assessment of the presence, characteristics, and extension of non-obstructive atherosclerosis, which identifies patients with increased risk of events, in whom the implementation of aggressive medical therapy of cardiovascular risk factors might result in improvement of prognosis;[22,82–84] 4) finally, new specific tools, including CTP and FFR_{CT}, might enable a comprehensive functional evaluation to confirm or exclude the ischemic origin of symptoms and CMD diagnosis. Thanks to these advancements and combining anatomical and functional data, CT imaging might effectively characterize patients with chest pain, enabling a non-invasive diagnosis of ANOCA with just one examination (Fig. 1).

Nevertheless, these strengths for a diffuse use of CCTA should be weighted against some limitations and caveats: 1) a CCTA-based approach may lead to an increase in ICAs and revascularizations and the prognostic advantage of CCTA over functional tests of myocardial ischemia remains questionable,[85,86] although recent long-term analyses of the SCOT-HEART trial have demonstrated a significant 10-year benefit of a CCTA-based strategy in patients with stable chest pain;[87] 2) it is not clear at present whether CCTA

Table 1
Non-invasive diagnostic tools for the assessment of ANOCA patients.

Methods	Strengths	Weaknesses
Stress-echocardiography	- Widely available - Low cost - No radiation exposure - Cardiac function evaluation - Ischemia detection - CFVR evaluation	- Acoustic window dependency - No coronary anatomy evaluation - Expertise requirement
CCTA	- Anatomical and CAD evaluation - Functional evaluation (FFR-CT) - Ischemia detection (CTP) - Tissue characterization (LIE, spectral evaluation)	- Radiation exposure - Contrast need - Cost - Availability - Expertise requirement
Stress CMR	- Cardiac function evaluation - Tissue characterization - Ischemia detection - Coronary anatomy evaluation - No radiation exposure	- Contrast need - Ferromagnetic devices - Claustrophobia - Exam duration - Costs - Expertise and availability
SPECT/PET	- Cardiac function evaluation - Ischemia detection through perfusion evaluation (PET as the non-invasive gold standard)	- Radiation exposure - Costs - Exam duration - Availability - Expertise requirement

Abbreviations: ANOCA = angina with non-obstructive coronary arteries, CFVR = coronary flow velocity reserve, CCTA = coronary computed tomography angiography, CAD = coronary artery disease, CTP = compute tomography perfusion; FFR-CT = Fractional Flow Reserve – Computed Tomography; LIE = late iodine enhancement, CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement, PET = Cardiac positron emission tomography; SPECT = single-photon emission computed tomography.

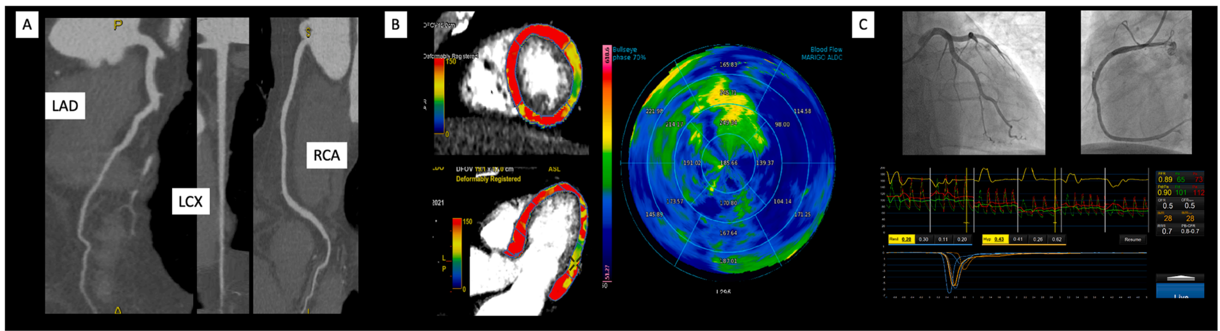

Fig. 1. A case of ANOCA due to coronary microvascular dysfunction.
Male patient, 56-year old, former smoker with angina on effort and positive EKG stress test.
Panel A: CCTA showed no significant stenosis in the epicardial coronary arteries.
Panel B: Stress dynamic CTP showed low diffuse values of myocardial blood flow in the lateral wall. Panel C: ICA confirmed the presence of normal epicardial coronary arteries. During ICA, measurement of IMR was performed, and pathological values were detected on LCX and RCA (IMR measurement in LCX = 28). Abbreviations: ANOCA=angina with non-obstructive coronary arteries; EKG=electrocardiogram; CCTA=Coronary computed tomography angiography; CTP=computed tomography perfusion; ICA = invasive coronary angiography, IMR = index of microcirculatory resistance, LCX = left circumflex artery, RCA = right coronary artery.

might be used to detect coronary artery spasm following provocative tests; 3) finally, some issues of CCTA should be acknowledged, including the small but definite risk associated with ionizing radiation exposure, especially in women of childbearing age or with CTP, the uncertain cost-effectiveness of a CCTA-based strategy for all suspected ANOCA patients, and the expertise and technology required.

B) Ischemia-based diagnostic approach

Based on the recommendations of groups of experts in the field on the assessment of ANOCA patients, documentation of myocardial ischemia is required to achieve a diagnosis of ANOCA in patients with chest pain and non-obstructive CAD, together with the demonstration of coronary functional abnormalities (CMD, CAS) able to cause myocardial ischemia.[28,88,89] Thus, an initial approach to these patients based on functional ECG or imaging stress tests of myocardial ischemia may allow the identification of patients that, together with clinical characteristics (see above), have a high probability of ANOCA rather than obstructive CAD. The exclusion of patients with normal stress tests will avoid unnecessary invasive/non-invasive coronary angiography and, at the same time, might address patients with a high suspicion of obstructive CAD to ICA but those with a high suspicion of ANOCA to CCTA. Accordingly, this type of strategy could be more cost-effective considering that some functional stress tests, such as ECG and echocardiographic stress tests, are widely and readily available, less expensive, and radiation-free. Moreover, at least at present, an advantage of

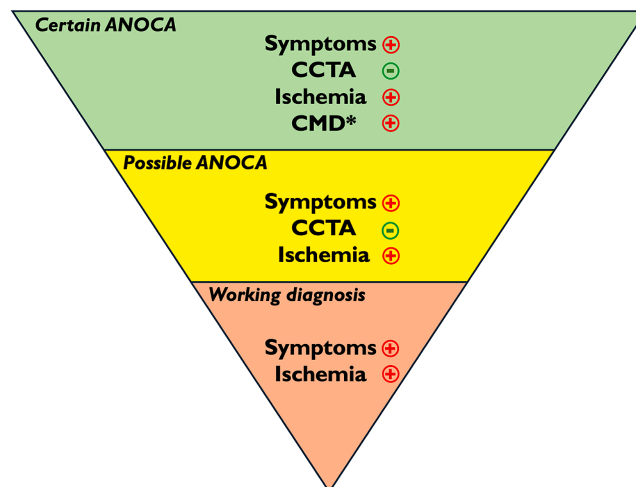

Fig. 2. Non-invasive ANOCA diagnosis.
In the non-invasive diagnosis of ANOCA several key diagnostic steps based on non-invasive evaluations can be identified. The first step (red) involves the working diagnosis of a symptomatic patient with angina and evidence of ischemia detected through non-invasive methods. Possible ANOCA (yellow) is considered when a symptomatic patient shows myocardial ischemia and no obstructive coronary stenosis is found on CCTA. A definitive diagnosis of ANOCA (green) is reached if non-invasive tests also demonstrate the presence of coronary microvascular dysfunction. *CMD diagnosed non-invasively. Abbreviations: ANOCA=angina with non-obstructive coronary arteries; CMD=coronary microvascular dysfunction; CCTA=coronary computed tomography angiography.

ECG/echocardiographic tests is the possibility of identifying a small group of patients with chest pain caused by typical occlusive coronary artery spasm. However, at present there is limited experience about the relation between noninvasive stress test results, invasive coronary physiology assessment and therapeutic implications.[8,85]

As for CCTA, some specific limitations exist for each stress diagnostic test, as previously discussed. Finally, local expertise should always be considered when selecting the optimal non-invasive strategy.

Non-invasive investigation for ANOCA

Regardless of the initial strategy applied, patients with ANOCA might now be identified among those with non-obstructive CAD by performing a careful noninvasive investigation and considering the strengths and limitations of each diagnostic tool, as delineated in the previous paragraphs, Table 1. The **Graphical abstract** summarizes the steps of the non-invasive diagnostic workup to achieve a diagnosis and characterization of ANOCA. In patients in whom a full invasive investigation is believed not indicated, the noninvasive diagnosis of ANOCA is possible by integrating the anatomical data of non-obstructive coronary stenosis and the assessment of the functional mechanisms potentially responsible for angina symptoms. A possible diagnosis of ANOCA is determined if, in symptomatic patients with evidence of non-obstructive CAD on CCTA evaluations, signs of inducible ischemia with coronary functional abnormalities (including CMD and coronary vasoconstriction) are detected (Fig. 2).

However, the diagnostic accuracy and therapeutic implications of a noninvasive approach to ANOCA patients lack proper, correct validation. This validation needs to be obtained by comparing pathophysiologic and outcome data with those obtained with an invasive assessment of coronary functional abnormalities, which remains at present the gold standard for the assessment of CMD and epicardial constriction/spasm.

Conclusions

The diagnosis of ANOCA remains a challenge and an unmet clinical need. Many patients with ANOCA experience diagnostic delays, which negatively impact their quality of life and outcomes. From the clinical scenario, a stepwise non-invasive diagnostic algorithm could aid in the diagnosis of ANOCA and guide management. Future appropriately designed studies, however, should try to establish the reliability of this non-invasive diagnostic approach (as compared with the gold standard of invasive investigation), and determine whether it may effectively guide treatment and improve outcomes in these patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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