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The invasive investigation of INOCA in the coronary catheterization lab

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ABSTRACT

Over half of all patients with angina have no angiographically demonstratable obstructive coronary disease, with a significant proportion of these patients having undiagnosed microvascular dysfunction and/or vasospastic angina. In chronic coronary syndrome, ischemia with non-obstructive coronary artery disease (INOCA) often remains undiagnosed, or uninvestigated. INOCAmay occur due to vasospastic angina and microvascular dysfunction and require invasive assessment in the coronary catheterization lab. To evaluate INOCA coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) are used to assess microvascular dysfunction before acetylcholine provocation testing for coronary spasm. This review provides an overview of the invasive investigation of INOCA in the coronary catheterization lab for patients with angina to be optimally managed.

1. Introduction

Approximately 50–70 % of all patients with angina have no angiographically demonstratable obstructive coronary disease [1,2]. A significant proportion of these patients will have undiagnosed microvascular dysfunction and/or vasospastic angina [2,3]. The microcirculation is not visualized during coronary angiography but is important, patients can have ischemia without demonstratable angiographically visible obstructive macrovascular disease.

While we focus commonly on epicardial coronary artery disease due to obstructive atherosclerosis, other disease phenotypes must be considered. Causes of chronic coronary syndrome may also include myocardial bridging, epicardial vasospasm, endothelial impairment and microvascular dysfunction [3]. In chronic coronary syndromes, ischemia with non-obstructive coronary artery disease (INOCA) often remains undiagnosed, or uninvestigated. INOCA, due to vasospastic angina and microvascular dysfunction requires invasive testing for confirmation in the coronary catheterization lab. To evaluate INOCA coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) are used to assess microvascular dysfunction before acetylcholine provocation testing for coronary spasm. In many cardiac catheterization laboratories these tests are not routinely performed outside of research settings.

Microvascular dysfunction and/or vasospastic angina, collectively known as ischaemia with non-obstructive coronary arteries (INOCA), are not benign conditions, they are associated at long term follow up with high morbidity [4], poor quality of life [5], increased hospitalisation [2], depresson [2], and increased risk of subsequent major adverse cardiac events [6] when compared to people without symptoms of angina.

2. Diagnosing INOCA in the coronary catheterization lab

The measurement of coronary artery function involves invasive coronary artery testing. Guidewire-based measurement of coronary flow reserve (CFR) has a IIa recommendation in ECS guidelines, (level of evidence B) [4]. The accurate diagnosis of INOCA with invasive testing, gives diagnostic clarity to patients and physicians facing ongoing unexplained symptoms of ischaemia. A full diagnostic assessment for INOCA requires invasive angiography, but several non-invasive techniques can be used for the assessment of CFR alone [2]. Non-invasive assessment options include ECHO based assessment of doppler flow in the LAD, magnetic resonance imaging using myocardial perfusion index, or PET. Non-invasive tests of CMR have a class IIb, level of evidence B recommendation in ESC guidelines, while guidewire-based assessment is assigned a class IIa, level of evidence B classification.

The optimal management of INOCA begins with a robust diagnosis. The two main mechanisms for INOCA are vasospastic angina and

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microvascular angina due to microvascular dysfunction, (or a mixed picture of both pathologies). Diagnosing vasospastic angina and microvascular angina involves the use of invasive coronary physiology assessment using pressure/temperature guidewires, adenosine and thermodilution, followed by tests of vasoreactivity, most commonly using acetylcholine. Coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) are used to assess microvascular dysfunction. CFR measures the blood flow in the epicardial arteries and microvasculature, it is not microvascular specific and is influenced by resting haemodynamics. In contrast, IMR is microvasculature specific and is independent of haemodynamic changes.

Algorithms for the evaluation of chronic angina usually recommend a diagnostic coronary angiogram +/− FFR >0.80 in angiographically ambiguous lesions to rule out obstructive coronary disease, followed by CFR and IMR evaluation before considering testing for vasospastic angina by assessing vasoreactivity (with an Acetyl choline test). See Fig. 1.

Both CFR and IMR are measurements captured using thermodilution techniques in conjunction with contemporary pressure guidewires. In a normal population of patients without INOCA IMR is <25 and CFR is ≥2.0. The left coronary artery is usually selected for assessment due to the size and territory of myocardial mass it perfuses. Multiple wires are available for the measurement of coronary function these include wires which use coronary thermodilution via a pressure–temperature sensor guidewire, PressureWire XTM, (Abbott Vascular, Santa Clara, CA, USA0 or a Doppler technique ComboWire XT or Flowire, (Philips Volcano Corporation, San Diego, CA, USA)).

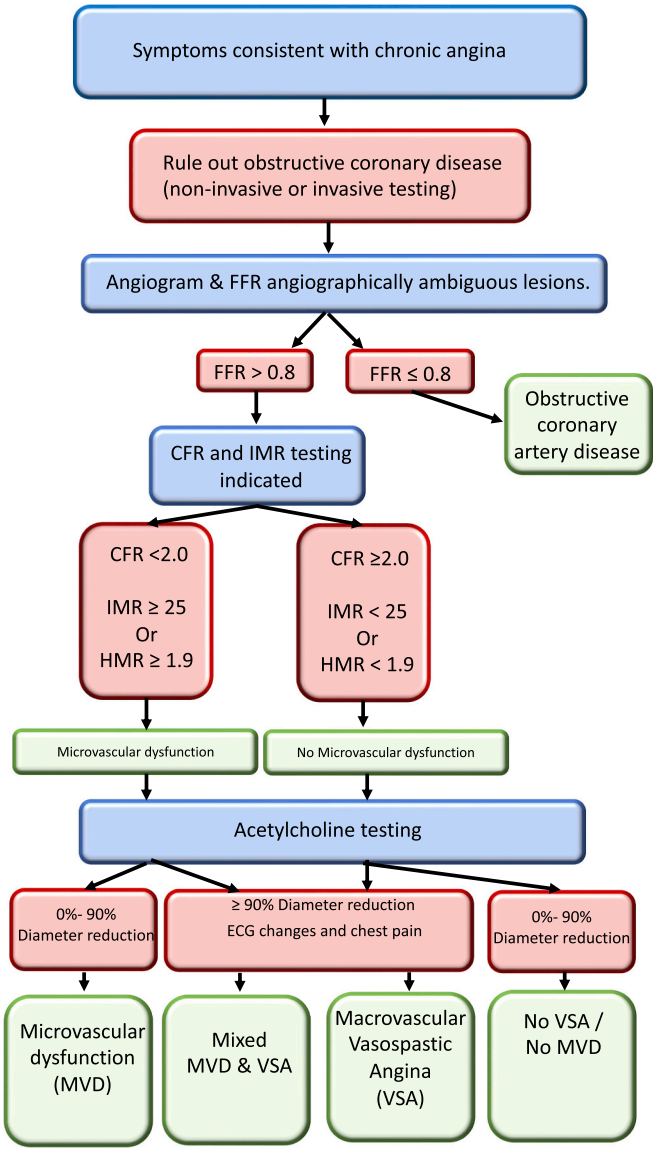

Fig. 1. Algorithm for the investigation of INOCA
This figure shows Diagnostic algorithm and cut off values for the diagnosis of INOCA subtypes.

3. Invasive coronary assessment with CFR AND IMR

3.1. Coronary flow reserve

Coronary flow reserve (CFR) measures flow through both large epicardial arteries and the coronary microcirculation, severe obstructive coronary artery disease needs to be ruled out before CFR can be interpreted, which can be assessed with either an FFR or iFR study. Reduced CFR in the absence of macrovascular stenoses indicates coronary microvascular dysfunction (CMD).

Coronary flow reserve Is assessed by documenting maximum flow in a hyperemic state (MF) and baseline flow (BF) and is the ratio of these two values (MF:BF), a CFR of <2 is abnormal and represents abnormal coronary flow, a value of 2.0–2.5 is consider a grey zone, while normal CFR is 2.5 or greater.

Guidewire based physiology and thermodilution techniques are used. To measure CFR accurately vasodilation is required to generate a hyperemic state, maximal vasodilation is most commonly achieved with the use of an adenosine infusion to achieve endothelium-independent vasodilation, less commonly an alternative intravenous vasodilator regadenoson is used.

3.2. The index of microcirculatory resistance (IMR)

The index of microcirculatory resistance (IMR) is a pressure-temperature sensor guidewire-based measurement of the minimum microcirculatory resistance in a target coronary artery territory and is measured to assess INOCA. IMR is a direct measure of microvascular function and is measure with the same pressure/temperature wire used to assess CFR.

Currently, IMR is regarded as the gold standard for evaluating coronary microcirculatory dysfunction. An increased IMR (≥25) is indicative of microvascular dysfunction, when performed in a vessel without significant coronary stenosis.

IMR is derived by multiplying the distal coronary pressure at maximal hyperemia by the hyperemic mean transit time. To measure IMR, a coronary pressure wire with appropriate software calculates the mean transit time of room temperature saline as it is injected down the coronary artery. Doppler flow-velocity based wire technology can also be used in a similar fashion to calculate hyperaemic microvascular resistance (HMR).

3.3. Vasoreactivity (acetylcholine challenge)

Abnormal coronary vasoreactivity is tested using an acetylcholine provocation test, acetylcholine testing has a class IIb level of evidence B recommendation when coronary angiography is normal or mild-moderate FFR negative stenoses are present. Ergonovine is a less frequently used alternative agent which can be used for provocation testing but is not recommend for non-invasive testing, as it is more likely to produce prolonged multivessel spams which can be fatal. Both agents are considered safe when selectively infused into a single coronary artery, when used in conjunction intracoronary with nitrates used post provocation to relieve spasm. However VT/VF or bradyarrhythmia is reported in 3 % of patients [8].

Coronary spasm can be microvascular or macrovascular (at the level of the epicardial vessel and seen angiographically with provocation).

Diagnostic criteria for microvascular spasm require reproduction of

symptoms and ECG changes with acetylcholine provocation testing but no epicardial spasm seen during acetyl choline testing [2].

Epicardial vasospastic angina (previously referred to as Prinzmetal angina) can also be diagnosed with an acetylcholine provocation test. In the acetylcholine provocation test, incremental boluses of intracoronary acetylcholine are given. If total or subtotal vessel occlusion of >90 % constriction is observed in conjunction with reproduction of angina symptoms and ischemic ST changes on ECG vasospastic angina is confirmed.

Incremental doses of acetylcholine can be used from 20μg, 50μg, 100μg given at 5 min intervals over 20 s in a total volume of 5 ml and, the diagnostic angiogram is performed 1 min after the start of the acetylcholine injection [8]. Alternatively IV infusions at 0.182, 1.82, and 18.2μg/ml at 1 ml/min for 2 min periods using a infusion pump have also been described [8]. The LAD is usually used for provocation testing, these tests can be repeated in the RCA but use of a maximum bolus dose of 80mch is recommended, and some authors also recommend placing a temporary wire before testing the RCA. When performed after IMR testing sufficient time should be allowed for GTN wash out before beginning ACh testing (>5 min). Patients should also be advised to stop any beta, alpha or calcium channel blockers, nitrates, ACE-inhibitors and diuretics for 48 hours prior to the study, and to avoid caffeine for 24 hours prior to testing and nicotine for 4 hours prior to testing.

3.4. Stratified medical therapy using invasive coronary function testing, evidence-based treatment and prognosis of INOCA

The best evidence for invasive investigation guided management of INOCA is provided by the CorMicA study. This 391-patient blinded RCT published in 2018 found 206/391 enrolled patients had obstructive coronary disease as the cause of their angina, patients without obstructive disease 39 % (151/391) were randomized to either intervention with stratified medical therapy based on the findings of invasive CFR, IFR, FFR and acetyl choline test results, vs a sham procedure followed by standard care. The primary endpoint was difference in angina severity at 6 months. The CorMicA trial found a significant reduction of anginal symptoms for patient who were tested invasively and treated based on the results of invasive INOCA testing, compared with conventional, non-guided medical treatment.

These data support other observational findings which have shown that INOCA has an impact on both quality of life and on prognosis [2,3,7–11]. The prognosis of patients with microcirculatory dysfunction in patients with CCS is poorer than originally thought. Recent research studying patients with proven microvascular dysfunction by invasive or non-invasive testing has found microcirculatory dysfunction, is associated with increased risk of future epicardial lesions, particularly in women, and is associated with poor outcomes [7,9,11]. The prognosis for patients with diabetes and INOCA have been found to be similar to patients with prior coronary artery disease [9]. Impaired CFR is associated with an adjusted 3.2- and 4.9-fold increase in the rate of cardiac death for diabetics and nondiabetics [9,10].

The strategy employed in the CorMicA trial [6] provides a stepwise evidence-based treatment plan in keeping with other published guidelines and consensus documents [2,7,8]. CorMicA used baseline therapy of aspirin, statin, and ACE inhibitor for all patients, with GTN as required. Patients with confirmed microvascular angina on invasive testing received first line treatment with beta blocker use (eg. carvedilol), 2nd line was substitution to non-dihydropyridine calcium channel blocker (NDP-CCB) (such as diltiazem or verapamil), 3rd line was the addition of amlodipine (if on betablockers), nicorandil or ranolazine. For patients with vasospastic angina confirmed on invasive testing 1st line treatment was non DHP-CCB, second line treatment was the addition of nitrates such as isosorbide mononitrate, 3rd line treatment replaced nitrates with nicorandil. For those with mixed MVA and VSA 1st line NDP-CCB was used, 2nd line treatment was with nicorandil [6].

4. Conclusions

INOCA is an important diagnosis, it is underrecognized and undertreated. Where conventional evaluation of angina does not yield a diagnosis, further invasive investigation is warranted. Increasing awareness of this condition in patients and healthcare professionals will help to ensure appropriate diagnosis and management for INOCA patients. The use of invasive evaluation measuring CFR, IMR/HFR, and acetylcholine provocation testing for vasospastic angina, are not performed as frequently as they should be. Strategies to facilitate more frequent use of these tests and to decrease barriers to testing are needed if patients with angina are to be optimally managed.

CRediT authorship contribution statement

Sonya N. Burgess: Writing – original draft, revision and editing of final manuscript. **Mamas A. Mamas:** Writing – review & editing.

Declaration of competing interest

The authors confirm no conflict of interest in relation to the manuscript “The invasive investigation of INOCA in the coronary catheterization lab”.

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