

# Invasive functional testing in the cath lab as a routine investigation in INOCA: pros and cons

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## Introduction

While invasive coronary angiography can evaluate epicardial coronary arteries in patients with suspected ischaemia, it may not be sufficient for those with ischaemia and non-obstructed coronary arteries (INOCA). In these cases, a more accurate diagnostic approach involving invasive functional testing can be considered. However, the routine use of invasive functional testing in INOCA patients is still an area of debate due to uncertainties surrounding its diagnostic value, optimal thresholds, cost-effectiveness, and therapeutic implications.

## Pros

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The goal of invasive coronary angiography is to identify the cause of a patient's symptoms that are possibly related to myocardial ischaemia. Yet the epicardial coronary arteries we can "see" on angiography represent only a small portion of the total coronary arterial volume. Accordingly, coronary angiography overlooks several other reasons for myocardial ischaemia and its related

symptoms. When coronary arteries are "non-obstructive" on invasive coronary angiography in patients with anginal chest pain (ANOCA), coronary microvascular dysfunction (CMD) is too often the convenient excuse for treatment failure. Then, without any documentation of microvascular function, the patient is discharged with a shrug of the shoulders and the diagnosis "it's likely the microcirculation", a judgement often as mysterious for the patient as it is for the physician.

Nowadays, there is no reason to deny patients a thorough functional investigation of their entire coronary arterial system, including the microcirculation, especially when their complaints are debilitating, convincing and recurring.

Why?

## VOLUME OF THE MICROVASCULAR COMPARTMENT

The epicardial arteries are the tip of the iceberg<sup>1</sup>, with the microvascular compartment constituting 90% of the volume of the coronary circulation<sup>2</sup>. This alone leads us to believe that it must be the site of pathological mechanisms that contribute to limited myocardial perfusion.

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## FREQUENCY OF THE PROBLEM

The reported prevalence of CMD varies from 15 to 75%, depending on patient selection and the definition<sup>3</sup>. More pragmatically, approximately half of the patients with anginal chest pain and signs of myocardial ischaemia have no evidence of epicardial obstruction on invasive coronary angiography. This mainly illustrates that 50% of patients, while having a sizable pretest likelihood of myocardial ischaemia, leave the catheterisation laboratory without a diagnosis. It is precisely in this cohort of patients that additional testing in the catheterisation laboratory is desirable<sup>4</sup>.

## QUANTITATIVE MEASUREMENTS OF CMD ARE AVAILABLE

Until recently, assessing the microcirculation in the catheterisation laboratory was either difficult, imprecise, or both.

Technical advances have been made that enable quantification of microvascular resistance – the quintessential metric of the microcirculation. The method used is based on continuous thermodilution, measuring volumetric flow (in mL/min) and absolute microvascular resistance (in Wood Units) in a safe and largely operator-independent manner<sup>5</sup>.

Theoretical progress has been made as well. Based on the awareness that microvascular resistance at rest very often does not correspond to true resting resistance, the concept of microvascular resistance reserve has been proposed as a specific index for the microcirculation<sup>6</sup>. At this time, highly precise and comprehensive measurements of this type can only be achieved in the catheterisation laboratory. Therefore, in a medical world touting “precision medicine”, there is no good reason for a patient with debilitating symptoms and no obstructive coronary arteries to leave the room

## Cons

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Despite the recent pioneering studies demonstrating the high prevalence of ischaemia with non-obstructed coronary artery disease (INOCA) and the ability to use intracoronary (i.c.) tests to describe abnormalities of the coronary circulation that are associated with the symptoms and outcomes in these patients, several factors prevent this being appropriate as routine clinical practice at the current time.

First, the available i.c. wire-based tests themselves have important limitations. Specifically, the inter- and intra-test reproducibility for standard parameters is not ideal for a routine investigation. For example, recent data from Demir et al highlight the discrepant output for thermodilution and Doppler-flow methods in terms of coronary flow reserve (CFR) and hyperaemic microvascular resistance/index of microvascular resistance (IMR) values<sup>8</sup>, which is a particular concern given the current concept that there can be binary cut-off values in this clinical context. In particular, the

without a full quantification of the function of his/her coronary circulation.

## MANAGEMENT

Data from the CorMicA<sup>7</sup> trial have demonstrated that patients randomised to receive specific management (including cardiac rehabilitation) guided by a functional testing-facilitated diagnosis of CMD, spastic angina, or both, show robust and clinically relevant improvement in patient-reported angina and quality of life. Equally important, in CorMicA, patients deemed to have non-cardiac symptoms were asked to de-escalate their medications. This type of management should preferably be conducted in the setting of a dedicated “ANOCA clinic”.

In conclusion, as interventional cardiologists, we should recognise that epicardial disease represents only one of several phenotypes in patients with angina and/or signs of myocardial ischaemia. When patients present with no obstructive coronary arteries and debilitating symptoms, it is our responsibility to provide them with as complete a diagnosis as possible.

## Conflict of interest statement

B. De Bruyne has an institutional consulting relationship with Boston Scientific, Abbott Vascular, CathWorks, Siemens, GE Healthcare, and Coroventis Research; has received institutional research grants from Abbott Vascular, Coroventis Research, CathWorks, and Boston Scientific; and holds minor equities in Philips, Siemens, GE Healthcare, Edwards Lifesciences, HeartFlow, Opsens, and Celiad. M. Belmonte has no conflicts of interest to declare.

validity of the cut-off values that are now applied when these tests are used in clinical practice is questionable and demands more investigation: for example, the notion that the dynamic function of the microvasculature could be dichotomised by a single cut-off for CFR and IMR is very challenging and biologically implausible. The complex interaction between the epicardial, pre-arteriole, arteriole and capillary segments is likely to yield a biological spectrum of abnormality, thus, raising concerns that a patient with apparently “normal” CFR and IMR, with negative fractional flow reserve, could be reassured inappropriately based upon these artificial thresholds.

Second, the risk-benefit ratio for such testing on a routine basis remains unacceptable. Despite fascinating preliminary data suggesting that endotypes of INOCA can be identified and therapy “tailored” accordingly<sup>7</sup>, the fact is that, as things stand, the menu for such personalised therapy consists of the same standard pool of tablets that we try routinely for all angina patients anyway. Meanwhile, the introduction of a pressure wire into the distal coronary artery carries a risk of important complications (usually

mediated by dissection) of around 2%<sup>9</sup>. Positive studies of specific pharmacological agents targeting potential mediators of microvascular dysfunction, such as endothelin antagonists<sup>10</sup>, are surely required before it is possible to justify routine tests of this type?

Third, we require more information about the extent of coronary microvascular dysfunction and, specifically, its distribution. For example, based upon current evidence, can we be sure that a “negative” result for INOCA in the left anterior descending artery territory also excludes abnormality in the circumflex and right coronary artery territories in the same individual? The appetite for i.c. wire-mediated testing for INOCA, even among its strongest advocates, is likely to be significantly dampened if a 2- or 3-territory i.c. survey is required in each patient to provide comprehensive reassurance.

Finally, the rapid advance in angiography-derived and non-invasive assessment of the microcirculation<sup>11</sup> may leapfrog current i.c. wire technology into routine practice, simply because of

their potential to offer information on 3 territories in a quicker and safer fashion.

In summary, we are on the (exciting) threshold of providing a personalised approach to the diagnosis and management of the spectrum of conditions lumped together as INOCA, which represents a major step forward for a population who have been routinely mismanaged in the past. However, we need more information about the optimal diagnostic tests and their thresholds for abnormality, and especially regarding the efficacy of bespoke novel therapies, before i.c. wire-based tests are ready and justifiable for routine clinical practice.

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