Stress Echocardiography in Angina with Nonobstructive Coronary Arteries

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Keywords

Coronary flow velocity reserve · Coronary microcirculation · Global longitudinal strain · Normal coronary arteries

32.1 Definitions and Epidemiology

The clinical syndrome of "angina and no obstructive coronary artery disease" (ANOCA) is defined by two features: (1) Stable, chronic (several weeks or longer) symptoms suggesting ischemic heart disease such as chest discomfort with both classic and atypical features in terms of location, quality, and inciting factors. (2) Absence of flow-limiting obstruction by coronary angiography (invasive or computed tomographic angiography) as defined by any epicardial coronary artery diameter reduction ≥50% or fractional flow reserve <0.8 [1].

This clinical definition is different from ischemia with no obstructive coronary artery disease (INOCA) which requires as a third, obligatory criterion the objective evidence for myocardial ischemia from the ECG or a cardiac imaging study (echocardiography, nuclear imaging, or magnetic resonance imaging) at rest or during stress (exercise, mental, or pharmacological) [1].

A different entity is a myocardial infarction with angiographically normal coronary arteries (MINOCA), which also requires the absence of obstructive coronary artery disease but in presence of the universal acute myocardial

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Table 32.1 Clinical syndromes with chest pain and normal coronary arteries

	ANOCA	INOCA	MINOCA
Chest pain	Present	Present	Present
CAD	Absent	Absent	Absent
Troponin rise	Absent	Absent	Present
Ischemia stress	Absent	Present	Present or absent

infarction criteria with an elevated cardiac biomarker, typically a cardiac troponin >99th percentile of the upper reference level with a rise and fall in the level on serial assessment [1].

The main criteria for differential diagnosis are shown in Table 32.1.

MINOCA is found in 10% of all myocardial infarctions, ANOCA in >50% of patients referred to coronary angiography, and INOCA can be documented in about one-third of patients with ANOCA. Many patients with ANOCA suffer from cardiac extraischemic causes such as pericarditis, or noncardiac causes of chest pain, such as gastroesophageal reflux, asthma, psychiatric causes such as anxiety and panic attack, or osteoarticular disease with costochondritis [2]. In INOCA, the pathophysiology is heterogeneous. A significant central role is possibly played by coronary microvascular disease, coronary vasospasm, and altered cardiac autonomic function with disordered sympathetic innervation. Dynamic intraventricular obstruction increases coronary extravascular resistances and therefore can be considered a cause of functional coronary microvascular disease [3].

32.2 Coronary Microvascular Disease in ANOCA

Coronary microcirculation is a fundamental portion of the coronary artery tree, as it contains most of the coronary blood volume and represents the main regulator of coronary blood flow. Arterioles, capillaries, and venules originating from the major coronary artery branches and extending inside the myocardium, with a diameter of less than 300 μm, constitute the whole coronary microcirculation. Coronary microvascular impairment greatly contributes to the pathophysiology and outcome of many cardiac diseases. Different degrees of coronary microvascular impairment can be found both with and without epicardial obstructive atherosclerosis. Several conditions can be clustered together in the syndrome of microvascular disease (Table 32.2) [3].

Coronary microvascular alterations can be structural, functional, extravascular, and intravascular. In some of these conditions, the abnormalities of the microvasculature represent markers of risk and may determine myocardial ischemia, thus becoming important therapeutic targets [4].

Table 32.2 Clinical cardiac conditions characterized by coronary microvascular impairment

Coronary microvascular impairment in the presence of obstructive epicardial coronary artery disease	It may occur in the context of either stable coronary artery disease or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors
Coronary microvascular impairment in the presence of myocardial diseases	It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular) and is sustained in most instances by adverse remodeling of intramural coronary arterioles
Coronary microvascular impairment in the absence of obstructive coronary artery disease and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, diabetes and insulin-resistant states)
Iatrogenic coronary microvascular impairment	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization

Adapted from Camici and Crea [3]

32.3 INOCA: Not Only Coronary Microvascular Disease

The definition of INOCA has been used to encompass a broad range of conditions (Table 32.3). All ANOCA patients with the documented coronary microvascular disease have INOCA, but INOCA patients can recognize causes of ischemia differently from coronary microvascular disease.

Clinical history, electrocardiogram, and resting transthoracic echocardiogram are therefore essential for identifying patients with true coronary microvascular dysfunction ("cardiac syndrome X") that probably represents no more than 30% of all INOCA patients [5]. The term "syndrome X" (originally the Group X in the 1973 paper by Arbogast and Bourassa) was coined to stress the uncertainty over the pathophysiology of chest pain [6]. It remains unclear whether the chest pain in these patients is ischemic or nonischemic in nature. However, since the unknown factor (X factor) in the original definition was clarified by the evidence of a reduced coronary flow velocity reserve (CFVR) with angiographically normal coronary arteries, we can dismiss the term Syndrome X and define "coronary microvascular disease" for a subset of INOCA patients with reduced ($\leq$2.0) CFVR [7].

Takotsubo cardiomyopathy is clinically indistinguishable from an acute coronary syndrome, but myocardial involvement completely and rapidly recovers in a few days or weeks, making takotsubo cardiomyopathy a unique model of transient and completely reversible myocardial dysfunction, in the absence of significant coronary artery disease [8].

Table 32.3 Myocardial ischemia with "normal" coronary arteries: the spectrum of INOCA

Appropriate nosography	Findings
Minor, initial coronary artery disease (up to 30% stenosis)	Abnormalities of nonsmooth coronary arteries
Early possible cardiomyopathy	HFpEF, LV diastolic dysfunction, left bundle branch block
Variant angina Microvascular vasospasm	Coronary vasospasm of epicardial vessels Coronary vasospasm of small vessels
Secondary microvascular disease	LV hypertrophy, mitral valve prolapse, diabetes, hypertension, high blood cholesterol, amyloidosis
Dynamic LV outflow tract obstruction	LV outflow tract obstruction
Normal coronary microcirculation	Normal CFVR
Microvascular disease (cardiac syndrome X)	Reduced CFVR (< 2.0)
Takotsubo, ACS	Partially reversible acute microvascular damage

ACS acute coronary syndromes, *HFpEF* heart failure preserved ejection fraction, *LV* left ventricle, *CFVR* coronary flow velocity reserve

32.4 The Ischemic Cascade in Microvascular Disease

The typical pattern of microvascular disease during stress testing is the frequent induction of chest pain, ST-segment depression, and perfusion abnormalities without regional wall motion abnormality (RWMA) (Fig. 32.1) [9].

The sequence of events is therefore strikingly different from the ischemic cascade found during stress testing in the presence of coronary artery stenosis (Table 32.4).

In these patients with small coronary vessel dysfunction, focal ischemia in small myocardial regions scattered throughout the myocardium and caused by prearteriolar dysfunction, might explain the paradox of angina and ST-segment depression provoked by physical or pharmacological stress. The site of abnormally elevated resistances (in patients with reduced coronary flow reserve) might be intramural, upstream from the endocardium–epicardium branching point, which is not visualized by coronary angiography [10].

The evidence that, despite ischemic-like stress-induced chest pain and ST-segment changes, left ventricular function remains normal during SE in INOCA patients, is not incompatible with true myocardial ischemia: indeed, it is well known that the presence or absence of abnormal wall motion is related to the amount of a critical mass of ischemic subendocardial tissue, and minor degrees of patchy strictly subendocardial myocardial ischemia [11] are less likely to produce regional wall motion abnormality. A regional dysfunction by two-dimensional echocardiography requires a critical ischemic mass of at least 20% of transmural wall thickness and about 5% of the total myocardial mass. For minimal flow reductions, abnormalities of regional

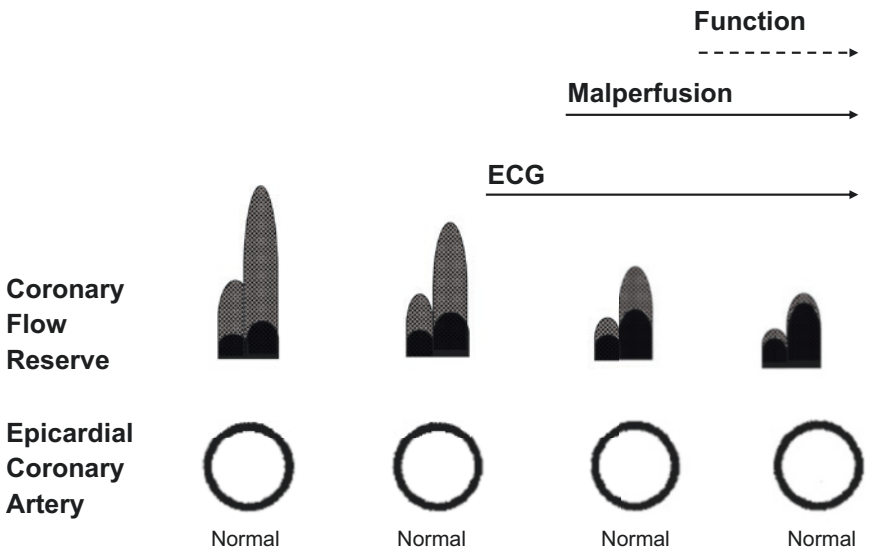

Fig. 32.1 The features of microvascular disease consist of normal epicardial coronary arteries (even when observed by intravascular ultrasound: *lower row*) and reduced coronary flow reserve (by Doppler tracing showing a spectrum of coronary hyperemic responses, from normal—*left* to abolished—*far right*). Chest pain and ECG changes are frequent during stress, especially when flow reserve is reduced, whereas echocardiography changes (*dashed lines*) are only rarely observed. (Modified from Picano E et al. [9])

Table 32.4 Coronary artery disease versus INOCA cascade during stress testing

	Coronary artery disease	INOCA
Clinical models	Coronary stenosis	Microvascular disease
Epicardial coronary anatomy	Stenotic	Normal
Coronary flow reserve	Depressed	Depressed
Stress: Chest pain	Present	Present
Stress: ST depression	Present	Present
Stress: RWMA	Present	Usually absent
Experimental model	Yes	No

RWMA regional wall motion abnormality

systolic function are subtle and certainly below the threshold of detection by echocardiography. Indeed, even under ideal imaging conditions, a subendocardial infarction can be accompanied in 20% of cases by a normal/hyperkinetic regional and global wall thickening [12], for hypercontraction and tethering from subepicardial layer and contiguous segments which may compensate for a limited subendocardial dysfunction.

32.5 SE Patterns in INOCA

In coronary microvascular disease, the peculiar pattern during SE is the regional and global left ventricular hyperkinesia with ST-segment depression and chest pain, consistently observed during dipyridamole [13], exercise [14], and dobutamine [15, 16].

In some patients (<10%) however, an RWMA appears and is not an innocent finding. It is due to angiographically occult coronary artery disease (detectable with intracoronary ultrasound) or initial latent cardiomyopathy which will become manifest in subsequent years [17, 18]. These false-positive results are more frequent in patients with left ventricular hypertrophy and high values of systolic blood pressure during stress, and usually involve the apical region [19].

With last-generation ultrasound technology and advanced expertise, dual imaging (function and flow) SE provides simultaneous insight into regional and global left ventricular function and coronary flow reserve. Coronary flow reserve can be best measured during Doppler transthoracic vasodilator or dobutamine SE in the mid-distal left anterior descending coronary artery, semi-simultaneously with wall motion imaging. A normal (>2.0) CFVR is found in 70% of ANOCA patients (Fig. 32.2).

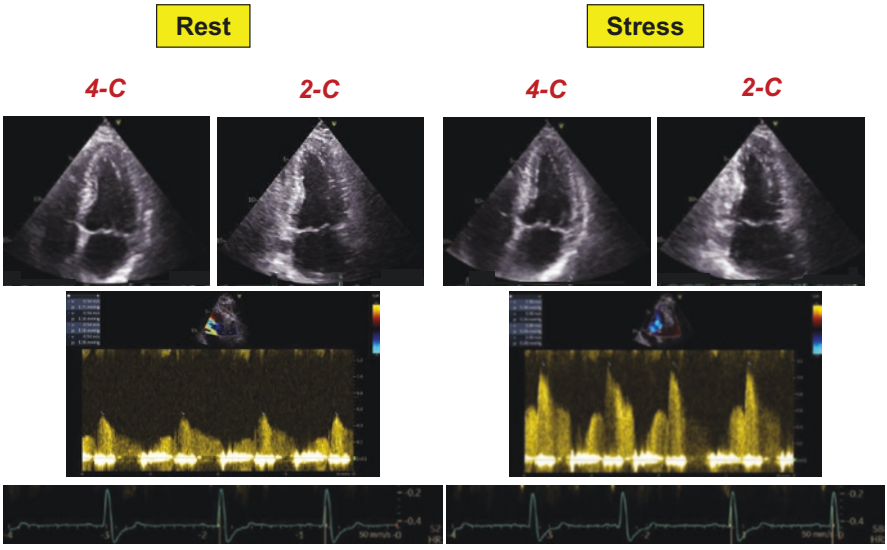

Fig. 32.2 Example of wall motion, coronary flow velocity reserve, and heart rate reserve assessment in patients with normal coronary arteries. Upper panels: end-systolic frames of apical four-chamber and two-chamber views showing normal function at rest and peak stress. Middle panels: Visualization of coronary flow in the mid-distal portion of the left anterior descending artery using pulsed-wave Doppler. Peak diastolic flow velocity was 54 cm s^{-1} under basal conditions (middle left panel) and 116 cm s^{-1} after dipyridamole infusion (middle right panel), with a normal CFVR value of 2.15. Heart rate reserve (lowest panels) is abnormal (rest = 52 beats/min; peak 58 beats/min; heart rate reserve = 58/52 = 1.11, normal values >1.22). (Courtesy of Dr. Lauro Cortigiani)

A reduced (≤2.0) CFVR can be found in 20% of ANOCA patients, in the absence of RWMA. However, the absence of RWMA does not necessarily imply that regional and global left ventricular mechanics are normal since subnormal increases in global longitudinal strain and subendocardial to subepicardial strain ratio can be observed in patients with coronary microvascular disease. Regional thickening and motion express radial function, which can be still normal when global longitudinal strain is impaired during less severe ischemia. When deformation imaging is applied to INOCA patients, an abnormal global longitudinal strain at rest or a reduced strain reserve during stress is observed in concomitance with the reduction in CFVR, suggesting that true ischemia occurs during stress [20–26].

In patients with INOCA, the cause of underlying ischemia can be coronary vasospasm of epicardial coronary arteries, unmasked by exercise, dobutamine, or dipyridamole stress, especially at the interruption of exercise or antidote administration. In these conditions, the diagnosis of vasospasm is easy and obtained by serendipity while testing the patient for coronary artery stenosis [27–29]. Other times, the test can be specifically targeted at vasospasm with ergonovine [30] or hyperventilation [31], eliciting coronary artery vasospasm and transmural ischemia detectable as RWMA.

In patients with left ventricular hypertrophy or young athletes, experiencing symptoms such as chest pain or syncope typically during exercise [32–34], a significant hyperdynamic contraction pattern with left ventricular intraventricular gradient during SE has been observed.

Due to the heterogeneity of underlying mechanisms, it is not surprising that the population of INOCA patients studied mostly under beta-blockers (which may exacerbate vasospasm) and with exercise or dobutamine stress (which may induce vasospasm) showed spontaneous improvements in angina and SE results, but the symptomatic improvement was not correlated with SE findings [35].

32.6 Prognostic Stratification

The prognosis of ANOCA patients is very heterogeneous, and this is not surprising considering the heterogeneity of underlying mechanisms. At long-term (9 years) follow-up, hard events are ten times more frequent in patients with inducible RWMA during SE than in those with negative SE results [36–38]. Within the lower-risk subset of patients with negative SE by wall motion criteria, the risk is higher in patients with reduced CFVR [39, 40].

In patients with ANOCA systematically tested for coronary vasospasm, the prognosis is worse in patients with vasospastic positivity during ergonovine echocardiography despite angiographically normal coronary arteries [41]. Only when all causes of true ischemia have been excluded, the patient can be assigned to a benign, likely noncardiac cause of chest pain. Interestingly, SE can identify an abnormal parameter also through nonimaging heart rate reserve since an abnormal heart rate

reserve identifies a reduced cardiac autonomic balance [42, 43] and offers prognostic information independent and incremental over RWMA and CFVR [44].

32.7 Current Guidelines and Perspectives

Current European Society of Cardiology 2019 and American College of Cardiology/American Heart Association 2021 guidelines on the management of stable coronary artery disease recommend performing SE for the detection of inducible RWMA in association with angina and ischemic ECG changes. Thus, in every patient with sufficiently typical chest pain in whom, despite abnormalities of the electrocardiogram and/or stress test results indicative of myocardial ischemia, coronary angiography fails to show fixed or dynamic obstructions in epicardial coronary arteries, the existence of primary coronary microvascular disease should be suspected. Noninvasive stress testing of CFVR in the left anterior descending artery is now an established option recommended (class 2b) by both European and US guidelines [45, 46]. A CFVR <2.0 strongly suggests coronary microvascular disease. If such criteria are satisfied, more invasive investigations can usually be avoided (Table 32.5).

Although guidelines suggest that testing in the catheterization laboratory may be more comprehensive, it requires separate testing for epicardial artery stenosis (fractional flow reserve <0.8), coronary artery vasospasm (intracoronary acetylcholine testing), coronary microcirculation (coronary flow reserve <2.0), and completely

Table 32.5 Investigations in patients with ANOCA

	COR	Source
Exercise or pharmacological echocardiography *should* be considered to establish whether RWMA occurs in conjunction with angina and ST-changes	2a	ESC 2020 [45]
Transthoracic Doppler echocardiography of the LAD with measurement of diastolic coronary flow velocity following intravenous vasodilators and at rest may be considered for noninvasive measurement of coronary flow reserve	2b	ESC 2020 [45], ACC/AHA 2021 [46]
Intracoronary acetylcholine and adenosine with Doppler measurements may be considered during coronary arteriography, if the arteriogram is visually normal, to assess endothelium-dependent and nonendothelium-dependent coronary flow reserve and detect microvascular/epicardial coronary vasospasm	2b	ESC 2020 [45], ACC/AHA 2021 [46]

ACC American College of Cardiology, *AHA* American Heart Association, *COR* class of recommendation, *ESC* European Society of cardiology

misses the possibility to detect left ventricular obstruction. Noninvasive testing outside the catheterization laboratory by hyperventilation or ergonovine echocardiography testing [41] is by far a more feasible and possibly safer option to identify vasospasm, but not endorsed by current guidelines' recommendations.

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