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Review Article

Angina with Non-obstructed Coronary Arteries and Invasive Diagnostic Testing in the Cardiac Catheterization Laboratory

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Abstract

More than a third of patients who present to the cardiac catheterization laboratory for elective coronary angiography for a chronic coronary syndrome are found to have normal or nonobstructive coronary artery disease. Angina or ischemia with non-obstructive coronary arteries (ANOCA/ INOCA) is prognostically important and is associated with decreased quality of life and increased cardiovascular morbidity. Chronic coronary syndromes are mediated by atherosclerosis, microvascular disease, and vasospastic disease at the epicardial and microvascular level. The severity of epicardial coronary disease is routinely evaluated with angiography and coronary physiology. A comprehensive invasive diagnostic assessment, however, is rarely pursued in patients determined to have non-obstructive coronary disease. In the modern cardiac catheterization laboratory, patients with ANOCA should be examined with flow assessment, intracoronary imaging, coronary flow reserve, microvascular resistance, and provocative testing to diagnose the mechanism of ischemia. Patients may have one or more endotypes including microvascular angina, microvascular spasm, or vasospastic angina with normal or non-obstructive coronary artery disease. This review provides an overview of the pathophysiology and catheterization lab invasive diagnostic testing that can guide the diagnosis and management of patients with ANOCA and discusses ongoing clinical trials.

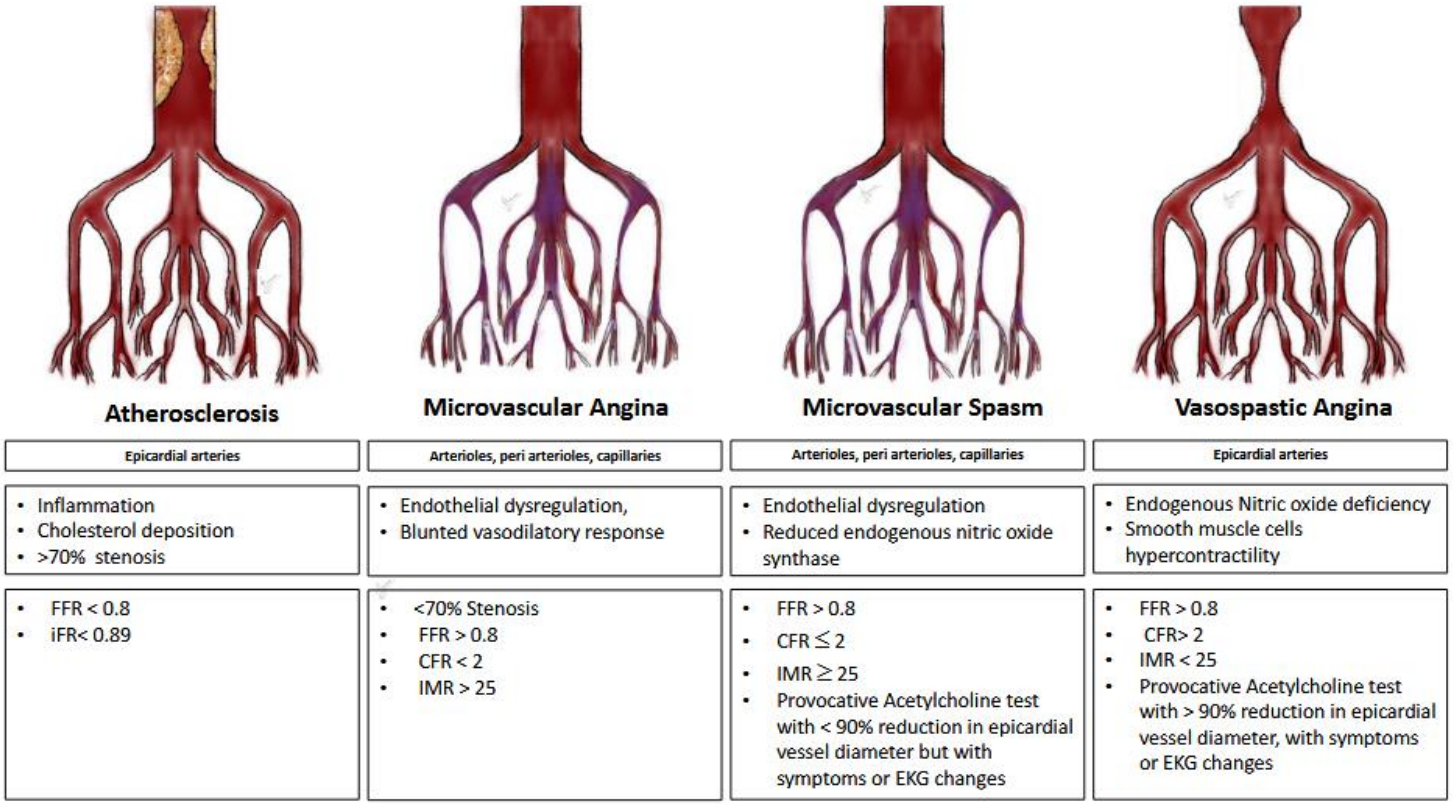
Keywords: INOCA; CAD; angina

1.Introduction

In 1973, Harvey Kemp recognized individuals who had anginal chest pain but had normal coronary arteries angiographically. They were found to have elevated lactate and electrocardiographic changes indicative of myocardial ischemia despite the "normal" coronary arteries. He classified this phenomenon as "Cardiac Syndrome X"[1,2]. In the current era, up to 40% of patients undergoing elective angiography for angina are found to have nonobstructive epicardial coronary artery disease (CAD) [3]. Traditionally nonobstructive CAD has been defined as more than 20%, but less than 50% - 70% stenosis of the epicardial vessels on coronary angiograms [4]. Many of these patients with nonobstructive CAD on angiography are diagnosed with having noncardiac chest pain without a comprehensive evaluation for myocardial ischemia[5]. However, multiple studies have demonstrated that patients with angina or ischemia with nonobstructive coronary artery disease (ANOCA/INOCA, herein ANOCA) have a higher mortality and morbidity as compared to patients with normal coronary arteries; this is irrespective of the modality utilized for structural or functional assessment of the coronary vasculature and myocardium[6-10]. In fact,10 year follow up data from the Women Ischemia Syndrome Evaluation (WISE) study demonstrated that women with stable ANOCA when compared to the controls with normal coronary vasculature had higher all cause (36% vs 13%) and cardiovascular mortality (25% vs 8%) [11]. A meta-analysis of 48 studies also found a higher risk of major adverse cardiac events (MACE) in patients with nonobstructive CAD when compared with patients with normal coronary arteries assessed via cardiac computerized tomography (CT) as well as coronary angiograms[12]. In this paper, we review the pathophysiological processes involved in chronic coronary syndromes and the invasive diagnostic modalities available to evaluate patients with nonobstructive CAD to better diagnose patients with ANOCA.

2. Chronic Coronary Syndromes Mechanisms:

The spectrum of mechanisms and summary of invasive diagnostic criteria for chronic coronary syndromes are summarized in Figure 1.



Legend: FFR: Fractional flow ratio, iFR: instantaneous wave free ratio, CFR: coronary flow reserve, IMR: index of microvascular resistance.

Figure 1. Chronic Coronary Syndromes: Pathophysiological Mechanisms and Invasive Diagnostic Parameters

2.1 Atherosclerotic Disease

The epicardial coronary vessels constitute the macrocirculation of the heart which fulfills the conductance function of the cardiac vascular bed, offering minimal obstruction to flow under normal conditions[13]. The classically described mechanism of chronic coronary syndrome is flow limiting stenoses and impaired flow in the epicardial coronary vessels leading to a supply demand mismatch. This is attributed to atherosclerosis - inflammatory and cholesterol mediated lipid rich plaque buildup in the macrocirculation thereby impairing blood flow to the myocardium[14]. Stenosis more than 70% leads to resting vasodilation and impaired coronary flow reserve[15]. Any increase in oxygen demand, due to exercise or stressors, is not adequately met by increase in blood flow in the affected arteries[15]. This is expressed as anginal symptoms and ischemia.

2.2 Microvascular Dysfunction

An estimated 40% of those with nonobstructive CAD are found to have coronary microvascular dysfunction (CMD)[16]. In contrast to epicardial disease, CMD is caused by changes occurring at the level of the pre-arterioles, arterioles and capillaries, which collectively contribute to 95% of coronary vascular resistance[17,18]. In CMD, the expected increase in coronary blood flow in response to stress is attenuated, creating a supply demand mismatch[17,18]. The two main mechanisms postulated involve structural and functional changes.

The structural changes involve microvascular remodeling, promoted by atherosclerotic narrowing, intimal thickening and perivascular fibrosis, culminating in obstruction of arterioles and capillaries. Here, in contrary to epicardial disease, atheroma is not involved as a primary mechanism for intraluminal obstruction, but more as a stimulus for inflammatory harmful remodeling[19]. Functional changes mainly occur at the level of vascular endothelium, which becomes dysregulated[19]. In response to both physiologic and pharmacological stress, the endothelium will typically secrete vasoactive substances such as nitric oxide and endothelium derived hyperpolarizing factor that will cause vasodilation and help maintain adequate coronary flow[19]. However, in patients with CMD, the vascular endothelium displays a blunted vasodilatory response, where vasodilatory substances are not secreted, which in turn leads to a decrease in coronary blood flow. This effect is most pronounced in patients with other risk factors, such as smoking, obesity, diabetes, dyslipidemia, hypertension, cardiomyopathy or renal impairment[19].

2.3 Vasospastic Disease

Vasospastic angina, first described by Myron Prinzmetal in the late 1950s refers to a disorder where spasm of the epicardial or microvascular arteries leads to sudden coronary flow attenuation and resultant ischemia and angina[20]. The pathophysiology underlying Prinzmetal angina is believed to involve two mechanisms: endothelial dependent; via dysfunctional endothelium and endothelial independent; via vascular smooth muscle hypertrophy. The spasm may be local and affect a certain segment of a coronary artery or may be diffuse and affect multiple coronary arteries[21].

Under normal circumstances, in the presence of shear stress, various vasodilatory substances are released including endothelium derived relaxation factors such as nitric oxide, prostaglandins (mainly PGI2) and endothelium derived hyperpolarizing factor [22]. There is also a concomitant suppression of vasoconstrictive substances such as endothelium I and angiotensin II[23].

In coronary vasospasm however, this balance is disturbed leading to vasoconstriction. The principal mechanism proposed is a deficiency of endogenous NO. This deficiency is in part due to decreased activity of the NO producing enzyme - endothelin NO synthase, supported by the finding that patients with loss of function mutations in eNOS are predisposed to vasospasm[24,25]. Endothelial damage also contributes to deficiency of endogenous NO. In the vessels with intact endothelium, vasoconstrictive agents such as acetylcholine have been shown to induce NO mediated

vasodilation. The same vasoconstrictive agents lead to vasoconstriction in vessels with damaged endothelium via direct action on vascular smooth muscle. This is supported by the improvement of vasospasm with nitroglycerin and the reproducibility of vasospasm with acetylcholine during angiography in vessels with endothelial damage[25].

The second proposed mechanism of coronary artery spasm is vascular smooth muscle hypercontractility. It is hypothesized to be promoted by alterations in the signal transduction cascade leading to downstream effects promoting vasoconstriction. The different mechanisms proposed include: excess myosin light chain phosphorylation leading to downstream muscle contraction; protein lipase C mediated increase in calcium entry into vascular smooth muscle cells and PLC mediated activation of Phosphokinase C, leading to vasoconstriction[20,22].

2.4 Structural Heart Disease:

Structural anomalies such as myocardial bridging, hypertrophic cardiomyopathy, and valvular heart disease such as aortic stenosis can also cause anginal symptoms. When an epicardial coronary vessel courses through the myocardium transiently it is said to be a "tunneled artery" and the overlying myocardium is called the myocardial bridge[26]. Autopsy studies demonstrate a prevalence of 33% - 42% of myocardial bridging in the general population, however the prevalence is reported to be only 2% - 6% on invasive coronary angiography[27]. This typically involves the left anterior descending artery[28]. Myocardial bridging results in symptoms due to dynamic compression of the coronary artery, predominantly in the systolic phase, however the degree of compression and flow limitation can vary by the depth of the tunneled segment, the length of the tunneled segment, sympathetic tone and the heart rate[29]. In some instances, vasospasm and atherosclerosis has also been described in the tunneled segment contributing to the pathology at play[29,30].

Myocardial bridging can be identified by the "milking effect"; systolic narrowing of a segment of artery or an abrupt phasic step-up and step-down phenomenon, in which case care should be taken regarding administration of nitrates which can lead to symptoms due to exacerbation of the flow compromise[29]. Recently, a comprehensive review on the anatomical and functional assessment of myocardial bridging was published[31]. In brief, Intravascular ultrasound can confirm the diagnosis with demonstration of systolic compression. In addition, detection of an echolucent area between the artery and epicardial tissue, "half-moon" sign is highly specific for myocardial bridge. Alterations in coronary physiology can be assessed with intracoronary doppler and include an early diastolic "fingertip" phenomenon, reduction in antegrade systolic flow, and retrograde systolic flow after nitroglycerine administration[32].

3.Chronic Coronary Syndromes Clinical Presentation

In the setting of a supply demand mismatch and resultant ischemia in the cardiac myocytes, there is referred, visceral pain or discomfort; Angina Pectoris[33]. Given its visceral nature, Angina Pectoris is characterized by substernal chest discomfort that is difficult to localize, often associated with or worsened by exertion or emotional aggravation, that builds up gradually and is relieved by rest or nitrates[34]. Women, patients with diabetes mellitus and the elderly can frequently have vague symptoms such as discomfort in the neck, jaw, arms or right side of chest, shortness of breath, lightheadedness, syncope or presyncope, confusion or abdominal discomfort[33,34]. The guidelines recommend taking a thorough history and performing risk stratification before proceeding with non-invasive or invasive evaluation[34].

There are multiple risk stratification tools available for assessment of patients in each clinical setting: outpatient versus emergency room. For patients presenting with stable ischemia or chronic coronary syndrome, the pretest probability proposed by Juarez-Orozco et al has been recommended for optimal utilization of resources and timely evaluation of individuals presenting with symptoms consistent with a cardiac origin[35].

Microvascular dysfunction should be suspected if the patient presents with typical anginal symptoms, or has abnormal noninvasive testing but is found to have either normal or minimally diseased epicardial coronary arteries. It should be noted that there is a gender discrepancy in presentation with angina; with similar symptoms, women are more likely to have CMD as the cause of their presentation[36]. Similarly, it should be suspected in patients who have persistent angina, but have nonobstructive CAD, patent stents and/or slow flow observed on coronary angiogram[5,37].

Vasospastic angina should be suspected in young patients, who are current smokers and who have anginal symptoms occurring at rest. Patients often have preserved effort tolerance and present with attacks that follow a circadian pattern, or have diurnal variation in exercise tolerance which is reduced in early morning[38].

4. Invasive diagnostic testing:

4.1 Invasive Coronary Angiography

Invasive angiography is the first step in investigating etiology of coronary syndromes for patients with high pretest probability or noninvasive testing suggestive of ischemia. It can demonstrate a severe obstructive lesion with stenosis > 70%, moderate obstructive disease (40-70%) or mild disease with lack of any identifiable obstructive epicardial lesions leading to patient's presenting symptoms[39]. Since the qualitative and visual assessment of stenosis severity can vary significantly between providers, objective assessment of flow limitation has been recommended [39,40]. Evaluating flow impairment across the lesion allows for assessment of the hemodynamic significance of a stenotic segment.

4.1.1 *Wire based- Hyperemic parameter:*

Fractional flow reserve (FFR) is the gold standard invasive physiologic assessment parameter which was shown to have significant impact on outcomes; death, nonfatal myocardial infarction, and repeat revascularization at 1 year, as compared to angiography alone[41]. After ensuring appropriate anticoagulation (Activated clotting time ~ 250 s), an FFR specific guidewire is advanced into the pertinent vessel. The system is calibrated with the wire proximal to the lesion, and then the lesion is crossed. Hyperemia is induced with adenosine: either intravenous (IV) or intracoronary (IC). IV adenosine is the preferred method of vasodilator administration and is infused at 180 µg/kg/min for the left coronary artery and 140 µg/kg/min for the right coronary artery for 3-4 minutes. An alternative is IC administration with a dosage of 20-40 µg bolus in the left coronary artery and a 15-30 µg bolus in the right coronary artery42. The mean arterial pressure from the pressure sensor in the guidewire and from the guide catheter in the main vessel is then computed to yield a ratio of the fraction of flow across the stenosis. If the FFR is > 0.8, the lesion is deemed to be not significant and revascularization can be deferred[40]. An abnormal FFR should be further investigated with a pullback: this is important to evaluate two aspects of the assessment: a) the fidelity of the measurement i.e. whether pressure drift (due to the piezoresistive electrical signal deterioration) has occurred; a change of ± 2 mmHg is considered acceptable[43] b) the nature of the disease: whether it is focal or diffuse, focal disease will demonstrate an abrupt loss of pressure across a lesion and offers an appropriate substrate for a percutaneous intervention as compared to the gradual loss of pressure in diffuse disease which is more appropriately treated with medical management[44]. (Figure 2).

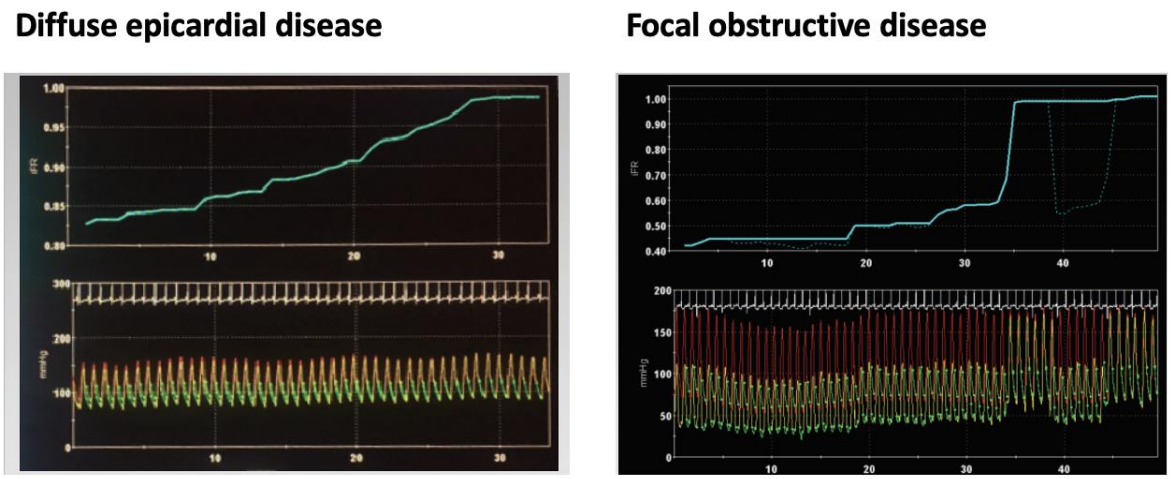


Figure 2: Representative examples of an FFR Pullback in diffuse vs focal epicardial coronary artery disease.

4.1.2 Wire based – non hyperemic parameters:

Given patient discomfort and bradycardia associated with inducing hyperemia, several non-hyperemic pressure ratios (NHPR) have been developed. Among these parameters, only instantaneous wave-free ratio (iFR) has been evaluated in randomized controlled trials: DEFINE-FLAIR and SWEDEHEART, where an iFR threshold of 0.89 has been demonstrated to be noninferior to FFR threshold of 0.8 for major adverse cardiac event (MACE) at 1 year[45-47]. It is important to note that in up to 20% of cases there may be discordance in FFR and iFR[48]. It was shown that FFR+ve /iFR -ve lesions have similar flow characteristics to nonhemodynamically significant lesions however FFR-ve/iFR+ve lesions have flow characteristics similar to hemodynamically significant lesions[49]. This discordance is reflective of the coronary flow reserve, the diffuseness of the atherosclerotic disease and hyperemic response of the microvascular bed which is attenuated in certain disease processes such as diabetes[49].

Other NHPRs such as resting full-cycle ratio (RFR), diastolic hyperemia free ratio (DFR) and resting ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state (Pd/Pa) have been shown to be numerically similar to iFR but have not been validated against FFR[50-52]. The 2019 European guidelines gave a class IIb recommendation for utilization of iFR to investigate nonobstructive or intermediate coronary stenosis (40-70%)[39].

The NHPR evaluation involves instrumenting the lesion with the index specific pressure wire. It utilizes the principle that during diastole, there is a specific wave free period, during which the microvasculature is in a steady state: not effected by the myocardial contractility or relaxation[45,53]. In this period, microvasculature does not contribute to any flow resistance and therefore the ratio of coronary flow proximal and distal to a stenotic lesion is truly reflective of that specific segment (thereby bypassing the need for hyperemia)[53].

4.1.3 Non wire based non hyperemic parameters

The uptake on the wire based hyperemic and non hyperemic parameters for assessment of stenosis significance has been slow. This is due to the reported hyperemia associated discomfort for patients, risks of wire instrumentation, and presumed time and cost associated with the procedure. Therefore, angiography based non-wire technologies have been developed and are commercially available[54]. There are four angiographic non wire based fractional flow reserve methods available which utilize reconstructive three-dimensional models comparing two angiographic views twenty-five to thirty degrees apart to predict the physiological significance of the lesion in question[55].

If epicardial obstructive coronary artery disease is not present or the lesion severity is not sufficient to explain patient symptoms, further testing to diagnose microvascular dysfunction or vasospastic disease can be pursued. Angiographically, sluggish or slow flow in the epicardial arteries (Thrombolysis in myocardial infarction (TIMI) Flow grade 2 or lower), despite absence of significant CAD, known as slow flow phenomenon may be observed which is usually indicative of CMD[56].

4.2 Coronary Flow Reserve

If CMD is suspected, the next step is to pursue the functional assessment of the coronary microvascular bed. Under normal circumstances, the coronary microvasculature can increase the blood flow by up to threefold in response to stress or hyperemic stimuli, which is blunted in the setting of CMD[57]. This can be evaluated with several flow parameters. Coronary flow reserve (CFR) is a measure of the capacity of the microvascular bed to increase the blood flow in response to hyperemic stimuli. This can be measured using two methods: a) doppler wire method: calculating the flow velocity across the area of concern or b) using thermodilution method[58].

In either method, the coronary artery is engaged with a guide catheter, and an intracoronary bolus of 2 00- 300 µg nitrates is administered. Subsequently, the system is calibrated in the proximal vessel, and then the wire is advanced to > 5 cm from the coronary ostium or across a nonobstructive lesion. Measurements are then repeated after induction of hyperemia[58]. Hyperemia is induced by intracoronary or intravenous injection of a vasodilator such as adenosine[59].

In the first method, a doppler wire is utilized to evaluate the ratio of peak velocity in the coronary vasculature under hyperemic conditions to peak velocity at rest[58,60,61].

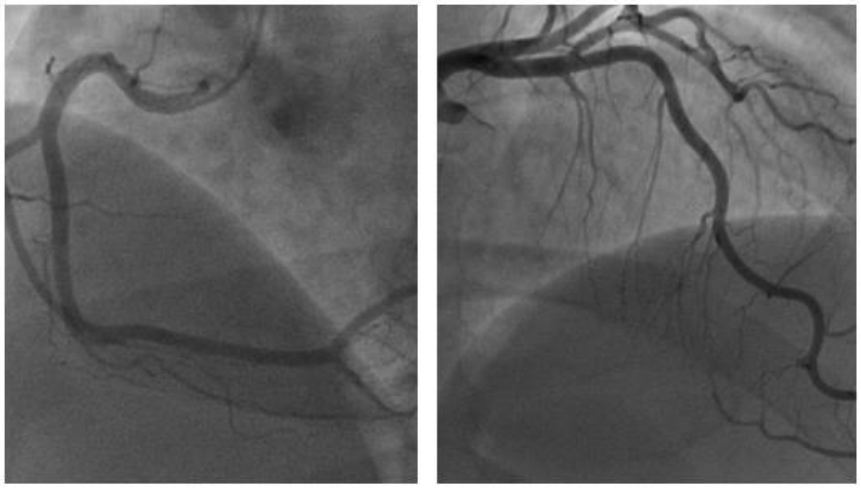
In the thermodilution method, a thermistor tipped guidewire is utilized to calculate the transit time of saline at room temperature and calculating the ratio of transit time at hyperemia to rest[60,62]. A CFR ratio of 3 is considered normal. A ratio ≤ 2 is considered diagnostic of CMD[63]. Although the correlation between doppler and thermodilution CRF is modest, the diagnostic accuracy of the thermodilution method is reasonable using the dichotomous cut-off of ≤ 2.5 [58].

4.3 Index of Microcirculatory Resistance

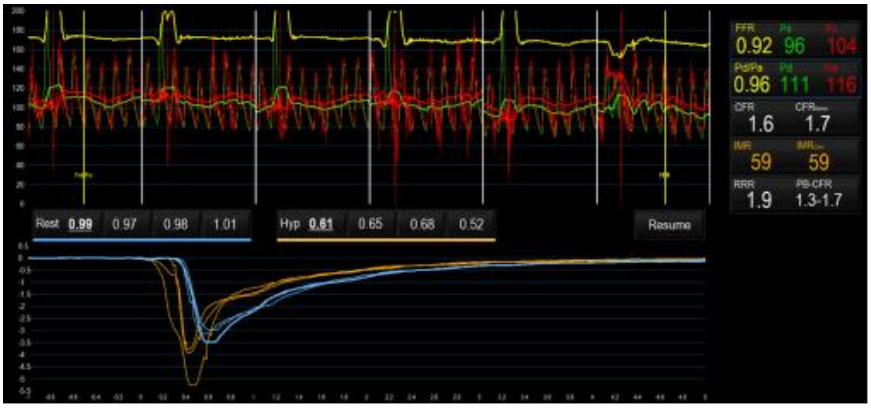
Since the microvascular bed has a capacitance function: assessment of the resistance of the microvascular bed can truly diagnose a diseased microvasculature[17,18]. Index of microvascular resistance is the most specific and reproducible measure of minimal achievable resistance in the microcirculation and thus truly reflective of microvascular function[64-66]. After initial validation in animal models, it has been shown to be independent

of various hemodynamic factors including heart rate, blood pressure and myocardial contractility, thus representing the true microvascular milieu[64].

The procedure involves utilizing a thermistor tipped pressure wire in the coronary arteries. In the absence of any identifiable coronary stenosis, left coronary artery is wired, given the large territory it supplies. After inducing hyperemia with adenosine, saline is injected, and the temperature difference between the proximal and distal sensors is utilized to assess the mean transit time[67]. The product of distal coronary pressure and mean transit time is then computed to yield the IMR[65]. IMR ≥ 25 is considered diagnostic for microvascular dysfunction in the absence of obstructive CAD[65] (Figure 3). IMR has also been shown to have prognostic implications such as predicting the infarct size and recovery of myocardial function[68]. IMR is derived from the thermodilution wire and is most often used to assess microvascular function in ANOCA. If using a doppler wire, the hyperemic microvascular resistance index (HMR), ratio of mean distal coronary pressure and peak velocity during hyperemia, can be determined. A HMR greater or equal to 2.5 mmHg/cs/s is considered abnormal and represents impaired microcirculation[69].



Panel A.



Panel B.

Panel A. demonstrates angiographically normal coronary arteries;
Panel B. shows thermodilution derived CFR and IMR are abnormal.
Figure 3: Case example of patient with microvascular angina

4.4 Vasoreactivity testing: Epicardial and Microvascular spasm

If flow assessments do not yield an adequate diagnosis, then the next step is to evaluate for vasospastic disease: at the epicardial or microvascular level. Endothelium dependent vasospasm- mediated by insufficient endogenous NO or damaged endothelium, can be evaluated with provocative testing[70,71].

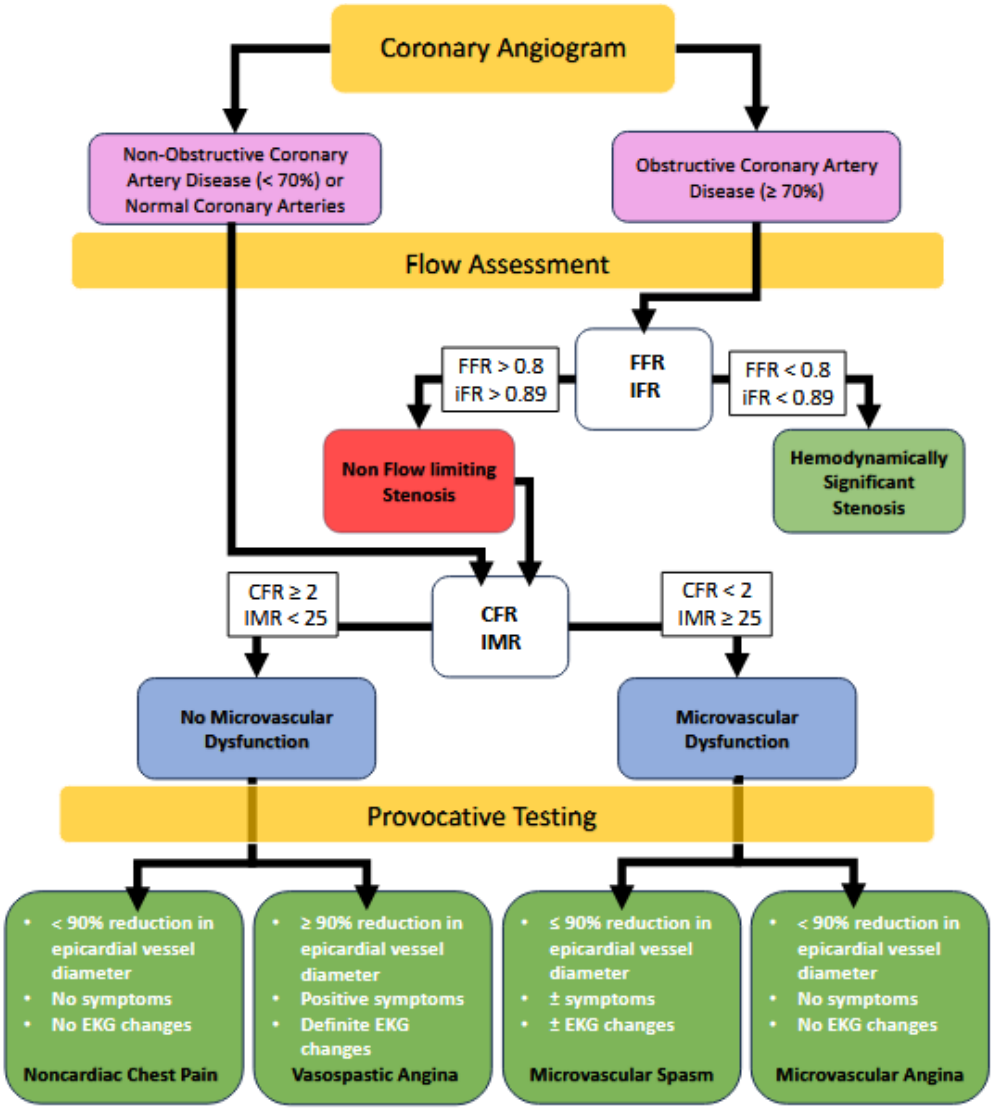
According to the proposed definition by Coronary Vasomotion Disorder International Study Group (COVADIS) coronary artery vasospasm is diagnosed if the following criteria are met: a) *Nitrate responsive spontaneous angina* with at least one episode being at rest or diurnal variation in exercise tolerance or precipitation of the episode with hyperventilation or suppression of episodes with calcium channel blocker but not beta blocker, b)*Transient ischemic EKG changes* during spontaneous episodes including ≥ 1 mm ST segment elevation or depression or new negative U waves c) *Coronary artery spasm* either spontaneous or upon provocative testing with ≥90% transient coronary occlusion[38].

The recommended provocative testing protocol according to the ESC and Japanese guidelines, involves intracoronary injection of acetylcholine in incremental dosage of 20 μg and 50 μg in the right coronary artery and 20, 50 and 100 μg in the left coronary artery with 3 minute intervals between each dose[72-74]. Recent studies have suggested that a dose of 200 μg of Acetylcholine specially in the left coronary artery may have a higher diagnostic yield then a maximal dose of 100 μg[75]. Furthermore, a single center study also reported gender differences in response to acetylcholine, showing that while in males incremental doses provided a higher diagnostic yield, in females a dose > 50 μg led to minimal change in the minimal luminal diameter[76].

In response to provocation subtotal or total occlusion of the coronary artery ≥90% with symptoms and/or EKG changes is diagnostic for coronary vasospasm[77]. If the patient experiences angina, or has significant EKG changes upon provocative testing, without significant epicardial vasoconstriction, microvascular spasm is diagnosed[78]. Long term follow up of patients who underwent provocative testing has demonstrated that epicardial spasm was associated with a higher risk of myocardial infarction and repeat coronary angiography, whereas microvascular spasm was associated with recurrent symptoms[79].

5. Anoca Endotypes and Management

In essence, although ANOCA represents an overlapping spectrum of disease, utilization of the diagnostic measures described can help classify the presenting symptoms into an endotype which can be a target for therapeutic intervention (Figure 4). The CORMICA trial demonstrated significant improvement in angina severity (11.7 units on Seattle Angina Questionnaire summary score) and quality of life with guidewire based invasive assessment and provocative testing of patients with ANOCA and endotype directed management[80].



FFR: Fractional Flow Reserve, iFR: instantaneous wave-Free Ratio, CFR: Coronary Flow Reserve, IMR: Index of Microvascular Resistance.

Figure 4: Diagnostic Algorithm for Assessment of Chronic Coronary Syndrome.

Microvascular Angina is diagnosed in the presence of minimal or moderately obstructive disease when, upon flow assessment with FFR, CFR or IMR, there is flow impairment such that FFR< 0.8, CFR<2 and IMR> 25[5]. (Figure 1) Even with a normal FFR i.e., > 0.8, there is an incremental value in assessment of CFR and IMR. Patients with an FFR > 0.75 but with abnormal CFR have been demonstrated to have a higher rate of MACE at 1 year[81]. Overt microvascular disease; i.e., low CFR and a high IMR despite an FFR > 0.8 was associated with worse outcomes when followed over 5 years in a cohort of 313 patients[63].

If there is some impairment of flow, but the indices are equivocal and provocative testing with acetylcholine demonstrates EKG changes and chest discomfort, without ≥ 90% reduction in the diameter of epicardial vessels, a diagnosis of Microvascular Spasm is established[5].

However, if flow indices are mostly normal and upon provocative testing patient has symptoms, ischemic EKG changes and a ≥ 90% reduction in the diameter of epicardial vessels, Vasospastic angina can be diagnosed[5].

It is important to note, that patients may have an overlap of pathological processes, but the role of this diagnostic approach is to identify the predominant endotype and to target management for the particular endotype.

Furthermore, the establishment of a diagnosis can provide a treatment goal for the patients and physicians to target, prevent unnecessary anxiety and hospital visits for symptoms that are inappropriately classified as being secondary to noncardiac causes.

The CORMICA trial protocol recommendations included addition of beta blockers as a first line therapy for patients with microvascular angina or microvascular spasm and calcium channel blockers for vasospastic angina or mixed CMD and vasospastic disease[80]. It should however be noted that, the first randomized- placebo controlled trial evaluating a calcium channel blocker (diltiazem) for treatment of vasospastic disease showed improvement in epicardial vasospasm but failed to show any improvement in coronary flow testing parameters or symptoms after a period of 6 weeks[82].

Finally, if this exhaustive diagnostic battery does not yield a positive test, then the patient can be diagnosed with having truly non cardiac chest pain[5].

6. Future Directions

CORMICA trial demonstrated the importance of establishing a diagnosis of a particular ANOCA endotype and targeted treatment[80]. This is an evolving field; and with diagnostic integrity, we hope for precise therapies to improve prognosis in patients who have microvascular dysfunction; with or without epicardial coronary disease. Artificial intelligence and refinement of three-dimensional reconstructive models may help in refining flow assessment tools to provide an integrated assessment of epicardial and microvascular flow with the angiogram.

There are already efforts underway to better define and evaluate the prevalence, diagnostic, prognostic and therapeutic approach to ANOCA. Cor CTCA study is an ongoing multicenter, randomized, sham controlled, double blinded study of all patients presenting for coronary CTA; who will undergo invasive flow assessment; thus, help determine the prevalence of ANOCA endotypes[83] (Clinical Trial#NCT03477890). The Inclusive Invasive Physiologic Assessment in Angina Syndromes Registry (ILIAS) is a global prospective study examining comprehensive coronary physiology. The study completed enrollment of 2322 patients and publications are forthcoming (Clinical Trial#NCT04485234). WARRIOR study is currently enrolling patients, and will evaluate intensive statin, ACE inhibitor/ Angiotensin receptor blockers and aspirin against usual care in women with nonobstructive CAD and chronic angina[84] (Clinical Trial#NCT03417388). In the Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) trial, an oral endothelin A receptor antagonist is being investigated for treatment of individuals with microvascular angina; mediated by opposition of the vasoconstriction mediated by damaged endothelium[85] (Clinical Trial #NCT04097314)

7. Conclusion

Chronic coronary syndromes are mediated by atherosclerosis, myocardial bridging, epicardial and microvascular coronary artery spasm and coronary microvascular dysfunction. These pathological mechanisms may sometimes be discrete, but often represent a spectrum of pathology leading to clinical manifestations. Invasive diagnostic techniques are available for definitive diagnosis of ANOCA so that tailored therapies can be employed to accurately diagnose the underlying endotype to optimize treatment and improve outcomes.

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References

1. Kemp HG, Jr. Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am J Cardiol.* 1973;32(3):375-376.
2. Kemp HG, Jr., Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six year experience. *Am J Med.* 1973;54(6):735-742.
3. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med.* 2010;362(10):886-895.
4. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. *Circulation.* 2017;135(11):1075-1092.
5. Kunadian V, Chieffo A, Camici PG, et al. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *EuroIntervention.* 2021;16(13):1049-1069.
6. Doyle M, Weinberg N, Pohost GM, et al. Prognostic value of global MR myocardial perfusion imaging in women with suspected myocardial ischemia and no obstructive coronary disease: results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. *JACC Cardiovasc Imaging.* 2010;3(10):1030-1036.
7. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med.* 2009;169(9):843-850.
8. Schindler TH, Nitzsche EU, Schelbert HR, et al. Positron emission tomography-measured abnormal responses of myocardial blood flow to sympathetic stimulation are associated with the risk of developing cardiovascular events. *J Am Coll Cardiol.* 2005;45(9):1505-1512.
9. Petretta M, Daniele S, Acampa W, et al. Prognostic value of coronary artery calcium score and coronary CT angiography in patients with intermediate risk of coronary artery disease. *Int J Cardiovasc Imaging.* 2012;28(6):1547-1556.
10. Ovrehus KA, Botker HE, Jensen JM, Munkholm H, Johnsen SP, Norgaard BL. Influence of coronary computed tomographic angiography on patient treatment and prognosis in patients with suspected stable angina pectoris. *Am J Cardiol.* 2011;107(10):1473-1479.
11. Kenkre TS, Malhotra P, Johnson BD, et al. Ten-Year Mortality in the WISE Study (Women's Ischemia Syndrome Evaluation). *Circ Cardiovasc Qual Outcomes.* 2017;10(12).
12. Huang FY, Huang BT, Lv WY, et al. The Prognosis of Patients With Nonobstructive Coronary Artery Disease Versus Normal Arteries Determined by Invasive Coronary Angiography or Computed Tomography Coronary Angiography: A Systematic Review. *Medicine (Baltimore).* 2016;95(11):e3117.
13. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol.* 1991;17(2):499-506.
14. Nakahara T, Dweck MR, Narula N, Pisapia D, Narula J, Strauss HW. Coronary Artery Calcification: From Mechanism to Molecular Imaging. *JACC Cardiovasc Imaging.* 2017;10(5):582-593.
15. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. *N Engl J Med.* 1994;330(25):1782-1788.
16. Mileva N, Nagumo S, Mizukami T, et al. Prevalence of Coronary Microvascular Disease and Coronary Vasospasm in Patients

With Nonobstructive Coronary Artery Disease: Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2022;11(7):e023207.
17. Patel B, Fisher M. Therapeutic advances in myocardial microvascular resistance: unravelling the enigma. *Pharmacol Ther.* 2010;127(2):131-147.
18. Herrmann J, Kaski JC, Lerman A. Coronary microvascular dysfunction in the clinical setting: from mystery to reality. *Eur Heart J.* 2012;33(22):2771-2782b.
19. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2018;72(21):2625-2641.
20. Sinha A, Rahman H, Perera D. Vasospastic Angina: A Contemporary Review of its Pathophysiology, Diagnosis and Management. *Heart Int.* 2022;16(2):99-104.
21. Jewulski J, Khanal S, Dahal K. Coronary vasospasm: A narrative review. *World J Cardiol.* 2021;13(9):456-463.
22. Shimokawa H. 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities-from bench to bedside. *Eur Heart J.* 2014;35(45):3180-3193.
23. Rehan R, Weaver J, Yong A. Coronary Vasospastic Angina: A Review of the Pathogenesis, Diagnosis, and Management. *Life (Basel).* 2022;12(8).
24. Nakayama M, Yasue H, Yoshimura M, et al. T-786-->C mutation in the 5'-flanking region of the endothelial nitric oxide synthase gene is associated with coronary spasm. *Circulation.* 1999;99(22):2864-2870.
25. Kugiyama K, Yasue H, Okumura K, et al. Nitric oxide activity is deficient in spasm arteries of patients with coronary spastic angina. *Circulation.* 1996;94(3):266-271.
26. Angelini P, Velasco JA, Flamm S. Coronary anomalies: incidence, pathophysiology, and clinical relevance. *Circulation.* 2002;105(20):2449-2454.
27. Mohlenkamp S, Hort W, Ge J, Erbel R. Update on myocardial bridging. *Circulation.* 2002;106(20):2616-2622.
28. Corban MT, Hung OY, Eshtehardi P, et al. Myocardial bridging: contemporary understanding of pathophysiology with implications for diagnostic and therapeutic strategies. *J Am Coll Cardiol.* 2014;63(22):2346-2355.
29. Sternheim D, Power DA, Samtani R, Kini A, Fuster V, Sharma S. Myocardial Bridging: Diagnosis, Functional Assessment, and Management: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2021;78(22):2196-2212.
30. Uusitalo V, Saraste A, Pietila M, Kajander S, Bax JJ, Knuuti J. The Functional Effects of Intramural Course of Coronary Arteries and its Relation to Coronary Atherosclerosis. *JACC Cardiovasc Imaging.* 2015;8(6):697-704.
31. Ciliberti G, Laborante R, Di Francesco M, et al. Comprehensive functional and anatomic assessment of myocardial bridging: Unlocking the Gordian Knot. *Front Cardiovasc Med.* 2022;9:970422.
32. Ge J, Jeremias A, Rupp A, et al. New signs characteristic of myocardial bridging demonstrated by intracoronary ultrasound and Doppler. *Eur Heart J.* 1999;20(23):1707-1716.
33. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA.* 2012;307(8):813-822.
34. Writing Committee M, Gulati M, Levy PD, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Cardiovasc Comput Tomogr.* 2022;16(1):54-122.
35. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging.* 2019;20(11):1198-1207.
36. Kuruvilla S, Kramer CM. Coronary microvascular dysfunction in women: an overview of diagnostic strategies. *Expert Rev Cardiovasc Ther.* 2013;11(11):1515-1525.
37. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol.* 2018;250:16-20.
38. Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J.* 2017;38(33):2565-2568.
39. Saraste A, Knuuti J. ESC 2019 guidelines for the diagnosis and management of chronic coronary syndromes : Recommendations for cardiovascular imaging. *Herz.* 2020;45(5):409-420.
40. Writing Committee M, Lawton JS, Tamis-Holland JE, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;79(2):e21-e129.
41. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med.* 2018;379(3):250-259.
42. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334(26):1703-1708.
43. Cook CM, Ahmad Y, Shun-Shin MJ, et al. Quantification of the Effect of Pressure Wire Drift on the Diagnostic Performance of Fractional Flow Reserve, Instantaneous Wave-Free Ratio, and Whole-Cycle Pd/Pa. *Circ Cardiovasc Interv.* 2016;9(4):e002988.
44. Scarsini R, Fezzi S, Leone AM, et al. Functional Patterns of Coronary Disease: Diffuse, Focal, and Serial Lesions. *JACC Cardiovasc Interv.* 2022;15(21):2174-2191.
45. Michail M, Thakur U, Mehta O, et al. Non-hyperaemic pressure ratios to guide percutaneous coronary intervention. *Open Heart.* 2020;7(2).
46. Gotberg M, Christiansen EH, Gudmundsdottir I, et al. Instantaneous Wave-Free Ratio versus Fractional Flow Reserve guided intervention (iFR-SWEDEHEART): Rationale and design of a multicenter, prospective, registry-based randomized clinical trial. *Am Heart J.* 2015;170(5):945-950.
47. Davies JE, Sen S, Dehbi HM, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med.* 2017;376(19):1824-1834.
48. Jeremias A, Maehara A, Genereux P, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol.* 2014;63(13):1253-1261.
49. Cook CM, Jeremias A, Petraco R, et al. Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance in Angiographically Intermediate Coronary Stenoses: An Analysis Using Doppler-Derived Coronary Flow Measurements. *JACC Cardiovasc Interv.* 2017;10(24):2514-2524.
50. Van't Veer M, Pijls NHJ, Hennigan B, et al. Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal? *J Am Coll Cardiol.* 2017;70(25):3088-3096.
51. Johnson NP, Li W, Chen X, et al. Diastolic pressure ratio: new approach and validation vs. the instantaneous wave-free ratio. *Eur Heart J.* 2019;40(31):2585-2594.
52. Svanerud J, Ahn JM, Jeremias A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. *EuroIntervention.* 2018;14(7):806-814.

53. Hoffman JI, Spaan JA. Pressure-flow relations in coronary circulation. *Physiol Rev.* 1990;70(2):331-390.
54. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving Routine Standards in Invasive Hemodynamic Assessment of Coronary Stenosis: The Nationwide Italian SICI-GISE Cross-Sectional ERIS Study. *JACC Cardiovasc Interv.* 2018;11(15):1482-1491.
55. Scoccia A, Tomaniak M, Neleman T, Groenland FTW, Plantes A, Daemen J. Angiography-Based Fractional Flow Reserve: State of the Art. *Curr Cardiol Rep.* 2022;24(6):667-678.
56. Fineschi M, Gori T. Coronary slow-flow phenomenon or syndrome Y: a microvascular angina awaiting recognition. *J Am Coll Cardiol.* 2010;56(3):239-240; author reply 240.
57. Kern MJ, Bach RG, Mechem CJ, et al. Variations in normal coronary vasodilatory reserve stratified by artery, gender, heart transplantation and coronary artery disease. *J Am Coll Cardiol.* 1996;28(5):1154-1160.
58. Demir OM, Boerhout CKM, de Waard GA, et al. Comparison of Doppler Flow Velocity and Thermodilution Derived Indexes of Coronary Physiology. *JACC Cardiovasc Interv.* 2022;15(10):1060-1070.
59. De Luca G, Venegoni L, Iorio S, Giuliani L, Marino P. Effects of increasing doses of intracoronary adenosine on the assessment of fractional flow reserve. *JACC Cardiovasc Interv.* 2011;4(10):1079-1084.
60. Pijls NH, De Bruyne B, Smith L, et al. Coronary thermodilution to assess flow reserve: validation in humans. *Circulation.* 2002;105(21):2482-2486.
61. Melikian N, Kearney MT, Thomas MR, De Bruyne B, Shah AM, MacCarthy PA. A simple thermodilution technique to assess coronary endothelium-dependent microvascular function in humans: validation and comparison with coronary flow reserve. *Eur Heart J.* 2007;28(18):2188-2194.
62. Barbato E, Aarnoudse W, Aengevaeren WR, et al. Validation of coronary flow reserve measurements by thermodilution in clinical practice. *Eur Heart J.* 2004;25(3):219-223.
63. Lee JM, Jung JH, Hwang D, et al. Coronary Flow Reserve and Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis. *J Am Coll Cardiol.* 2016;67(10):1158-1169.
64. Ng MK, Yeung AC, Fearon WF. Invasive assessment of the coronary microcirculation: superior reproducibility and less hemodynamic dependence of index of microcirculatory resistance compared with coronary flow reserve. *Circulation.* 2006;113(17):2054-2061.
65. Fearon WF, Kobayashi Y. Invasive Assessment of the Coronary Microvasculature: The Index of Microcirculatory Resistance. *Circ Cardiovasc Interv.* 2017;10(12).
66. Fearon WF, Balsam LB, Farouque HM, et al. Novel index for invasively assessing the coronary microcirculation. *Circulation.* 2003;107(25):3129-3132.
67. Yong AS, Layland J, Fearon WF, et al. Calculation of the index of microcirculatory resistance without coronary wedge pressure measurement in the presence of epicardial stenosis. *JACC Cardiovasc Interv.* 2013;6(1):53-58.
68. De Maria GL, Alkhalil M, Wolfrum M, et al. Index of Microcirculatory Resistance as a Tool to Characterize Microvascular Obstruction and to Predict Infarct Size Regression in Patients With STEMI Undergoing Primary PCI. *JACC Cardiovasc Imaging.* 2019;12(5):837-848.
69. Tas A, Broyd C, Alan Y, et al. Non-hyperaemic coronary flow velocity acceleration indices correlate with hyperaemic microvascular resistance in patients with INOCA. *European Heart Journal.* 2023;44.
70. Boerhout CKM, Beijk MAM, Damman P, Piek JJ, van de Hoef TP. Practical Approach for Angina and Non-Obstructive Coronary Arteries: A State-of-the-Art Review. *Korean Circ J.* 2023;53(8):519-534.
71. Perera D, Berry C, Hoole SP, et al. Invasive coronary physiology in patients with angina and non-obstructive coronary artery disease: a consensus document from the coronary microvascular dysfunction workstream of the British Heart Foundation/National Institute for Health Research Partnership. *Heart.* 2022;109(2):88-95.
72. Okumura K, Yasue H, Matsuyama K, et al. Sensitivity and specificity of intracoronary injection of acetylcholine for the induction of coronary artery spasm. *J Am Coll Cardiol.* 1988;12(4):883-888.
73. Task Force M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J.* 2013;34(38):2949-3003.
74. Group JCSJW. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). *Circ J.* 2014;78(11):2779-2801.
75. Sueda S, Kohno H, Miyoshi T, Sakaue T, Sasaki Y, Habara H. Maximal acetylcholine dose of 200 mug into the left coronary artery as a spasm provocation test: comparison with 100 mug of acetylcholine. *Heart Vessels.* 2015;30(6):771-778.
76. Pargaonkar VS, Lee JH, Chow EKH, et al. Dose-Response Relationship Between Intracoronary Acetylcholine and Minimal Lumen Diameter in Coronary Endothelial Function Testing of Women and Men With Angina and No Obstructive Coronary Artery Disease. *Circ Cardiovasc Interv.* 2020;13(4):e008587.
77. Sueda S, Kohno H, Ochi T, Uraoka T, Tsunemitsu K. Overview of the pharmacological spasm provocation test: Comparisons between acetylcholine and ergonovine. *J Cardiol.* 2017;69(1):57-65.
78. Ohba K, Sugiyama S, Sumida H, et al. Microvascular coronary artery spasm presents distinctive clinical features with endothelial dysfunction as nonobstructive coronary artery disease. *J Am Heart Assoc.* 2012;1(5):e002485.
79. Seitz A, Gardezy J, Pirozzolo G, et al. Long-Term Follow-Up in Patients With Stable Angina and Unobstructed Coronary Arteries Undergoing Intracoronary Acetylcholine Testing. *JACC Cardiovasc Interv.* 2020;13(16):1865-1876.
80. Ford TJ, Stanley B, Good R, et al. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. *J Am Coll Cardiol.* 2018;72(23 Pt A):2841-2855.
81. Meuwissen M, Chamuleau SA, Siebes M, et al. The prognostic value of combined intracoronary pressure and blood flow velocity measurements after deferral of percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2008;71(3):291-297.
82. Jansen TPJ, Konst RE, de Vos A, et al. Efficacy of Diltiazem to Improve Coronary Vasomotor Dysfunction in ANOCA: The EDIT-CMD Randomized Clinical Trial. *JACC Cardiovasc Imaging.* 2022;15(8):1473-1484.
83. Sidik NP, McEntegart M, Roditi G, et al. Rationale and design of the British Heart Foundation (BHF) Coronary Microvascular Function and CT Coronary Angiogram (CorCTCA) study. *Am Heart J.* 2020;221:48-59.
84. Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR). https://clinicaltrials.gov/study/NCT03417388. Accessed 12/7/23, 2023.
85. Precision Medicine With Zibotentan in Microvascular Angina (PRIZE). https://classic.clinicaltrials.gov/ct2/show/NCT04097314. Accessed 12/7/2023, 2023.

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