

Definitions and Epidemiology of Coronary Functional Abnormalities

Andreas Seitz , Johanna McChord , Raffi Bekeredjian , Udo Sechtem  and Peter Ong 

Robert-Bosch-Krankenhaus, Department of Cardiology and Angiology, Stuttgart, Germany

Abstract

Coronary functional abnormalities are frequent causes of angina pectoris, particularly in patients with unobstructed coronary arteries. There is a spectrum of endotypes of functional coronary abnormalities with different mechanisms of pathology including enhanced vasoconstriction (i.e. coronary artery spasm) or impaired vasodilatation, such as impaired coronary flow reserve or increased microvascular resistance. These vasomotor abnormalities can affect various compartments of the coronary circulation such as the epicardial conduit arteries and/or the coronary microcirculation. Unequivocal categorisation and nomenclature of the broad spectrum of disease endotypes is crucial both in clinical practice as well as in clinical trials. This article describes the definitions of coronary functional abnormalities with currently accepted cut-off values, as well as diagnostic methods to identify and distinguish endotypes. The authors also provide a summary of contemporary data on the prevalence of the different endotypes of coronary functional abnormalities and their coexistence.

Keywords

Epidemiology; coronary functional abnormalities; angina; vasomotor abnormalities

Disclosure: PO is a regional editor on the *European Cardiology Review* editorial board; this did not influence peer review. All other authors have no conflicts of interest to declare.

Received: 28 April 2021 **Accepted:** 4 September 2021 **Citation:** *European Cardiology Review* 2021;16:e51. **DOI:** <https://doi.org/10.15420/ecr.2021.14>

Correspondence: Peter Ong, Robert-Bosch-Krankenhaus, Department of Cardiology and Angiology, Auerbachstr. 110, 70376 Stuttgart, Germany. E: Peter.Ong@rbk.de

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

Although coronary functional abnormalities have fascinated cardiologists for more than 50 years, their existence has long been neglected.¹ Before the advent of percutaneous coronary intervention (PCI), there were a high number of scientific publications regarding coronary functional abnormalities in general and coronary artery spasm in particular. However, after the introduction of PCI, the interest in this topic declined which was accompanied by a reduction in scientific publications on the subject. In recent years interest has grown again and the topic has been receiving more and more attention in the clinical arena. This is why the Coronary Vasomotion Disorders International Study Group (COVADIS) was founded and one of its main aims is to provide unified terminology and definitions for coronary vasomotion disorders.^{2,3} This may not only facilitate comparison of clinical test results from around the world but would also enhance clinical research and help to provide better care for patients. Knowledge about the definitions and epidemiology of coronary functional abnormalities is essential in this context.

Definitions of Coronary Functional Abnormalities

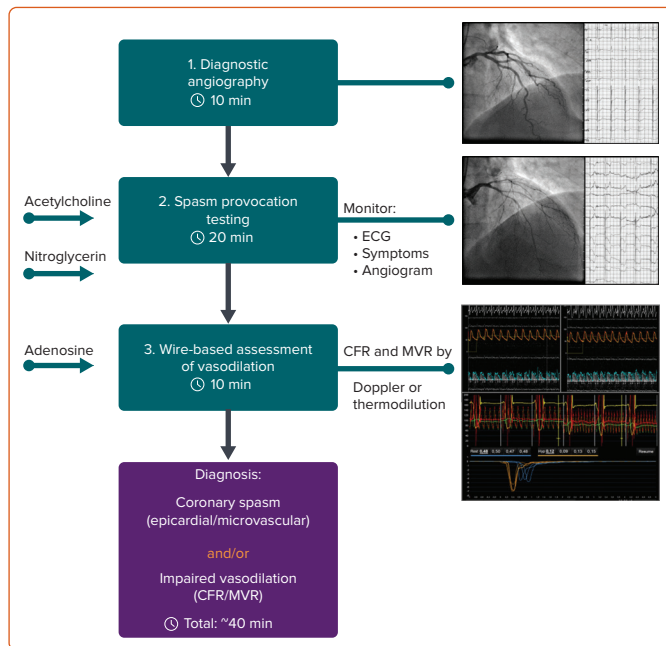
Although functional coronary abnormalities may occur in the presence or absence of epicardial stenoses they are particularly associated with patients with angina and unobstructed coronary arteries (ANOCA).⁴ Such patients are often labelled as having 'non-cardiac chest pain' and frequently have impaired quality of life.⁵ However, a significant proportion of these patients suffer from coronary functional abnormalities (for more details, see the below paragraph on epidemiology) and establishing a diagnosis of coronary functional abnormalities followed by stratified medical therapy can significantly improve quality of life.⁶ Patients with ANOCA may also include patients with angina in whom the haemodynamic

relevance of moderate epicardial stenoses has been ruled out by using a pressure wire, for example. Several invasive investigations in patients with ANOCA are recommended by the European Society of Cardiology Guidelines for the diagnosis and management of chronic coronary syndromes.⁷ Intracoronary provocation testing in search of coronary spasm holds a Class IIa recommendation and wire-based investigations for measuring coronary flow reserve (CFR) and microvascular resistance in search of abnormalities of microvascular dilating function are equally recommended with a Class IIa recommendation. The comprehensive invasive assessment of coronary function is often referred to as interventional diagnostic procedure (IDP) (*Figure 1*). In the following section, we will focus on definitions of coronary functional abnormalities in patients with ANOCA.

Functional abnormalities of the coronary circulation can be divided into those occurring in the epicardial arteries and those affecting the coronary microcirculation – a constellation also referred to as microvascular angina (*Table 1*). Usually, the latter is defined by a vessel diameter of <500 µm. It is also possible that vasomotion disorders affect the epicardial and the coronary microvessels in the same patient and a progression from microvascular to epicardial spasm over time has recently been suggested.⁸ However, data on the frequency of such a constellation are sparse.^{8–11}

The two main mechanisms of functional coronary abnormalities are enhanced vasoconstriction and impaired vasodilatation.¹² The former can be diagnosed during intracoronary provocation testing in search of coronary spasm using acetylcholine or ergonovine.^{4,13} The latter can be

Figure 1: Comprehensive Assessment of Coronary Function Using an Interventional Diagnostic Procedure



Following diagnostic angiography, intracoronary acetylcholine spasm provocation testing is performed in search of epicardial and/or microvascular coronary spasm. Next, microvascular dilatory function is measured invasively using either Doppler or thermodilution technique. This comprehensive interventional diagnostic procedure allows the assessment of structural and functional coronary disorders within a total time of about 40 minutes. CFR = coronary flow reserve; MVR = microvascular resistance.

Table 1: Criteria for Microvascular Angina According to the COVADIS Group

1. Symptoms of MI
 - Effort and/or rest angina
 - Angina equivalents, such as shortness of breath
2. Absence of obstructive CAD
 - Coronary CTA
 - Invasive coronary angiography
3. Objective evidence of MI
 - Ischaemic ECG changes during an episode of chest pain
 - Stress-induced chest pain and/or ischaemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4. Evidence of impaired coronary microvascular function
 - Coronary microvascular spasm, defined as reproduction of symptoms, ischaemic ECG shifts but no epicardial spasm during acetylcholine testing
 - Impaired CFR (cut-off values depending on methodology use between ≤ 2.0 and ≤ 2.5)
 - Abnormal coronary microvascular resistance indices (e.g. $IMR > 25$ or $HMR > 2.5$ mmHg/cm/s)
 - Coronary slow flow phenomenon defined as TIMI frame count > 25

Definitive MVA is only diagnosed if all 4 criteria are present. Suspected MVA is diagnosed if criteria 1 and 2 plus either 3 or 4 are present. CAD = coronary artery disease; CFR = coronary flow reserve; CTA computed tomographic angiography; HMR = hyperaemic microvascular resistance; IMR = index of microcirculatory resistance; MVA = microvascular angina TIMI = thrombolysis in MI. Source: Ong et al. 2018.² Adapted with permission from Elsevier.

diagnosed by non-invasive techniques or invasively when CFR is measured with a dedicated wire (Doppler or thermodilution technique) using adenosine. The CFR is defined as the ratio between maximal coronary blood flow during adenosine-induced hyperaemia and resting

flow at baseline. Usually, a value of ≤ 2.0 – 2.5 is considered to be abnormal, i.e. impaired CFR, with strong adverse prognostic data in patients with ANOCA.^{14,15} It should, however, be noted that an impaired CFR may be due to several constellations of resting and peak flow. On one hand CFR may be impaired because the microcirculation is unable to sufficiently dilate. In such instances resting flow may be normal but peak flow is impaired. On the other hand, a frequent observation is that resting flow is abnormally high, perhaps due to metabolic autoregulation in the presence of cardiovascular risk factors.¹⁶ This constellation may also lead to impaired CFR despite normal or near-normal adenosine flow. Whether these two different constellations when measuring CFR carry prognostic information is unknown but is currently under investigation.

Another important parameter that can be assessed simultaneously while measuring CFR is the index of microvascular resistance (IMR) when using the thermodilution technique or hyperaemic microvascular resistance (HMR) when using the Doppler technique. Both measurements reflect the coronary microvascular resistance during stimulation with adenosine and it is important to know that its calculation is independent of the resting flow. Impaired vasodilatation of the coronary microcirculation may be associated with structural alterations of the microvasculature, such as arteriolar remodelling and capillary rarefaction.^{17–19} Thus documentation of elevated hyperaemic resistance could be interpreted as indirect evidence of a structural phenomenon with or without an additional functional coronary abnormality. Theoretically, capillary rarefaction should also be associated with increased resistance at baseline. Nevertheless, microvascular structural alterations are frequently neglected and the term functional coronary abnormalities is often used as a distinction from structural epicardial (stenosing) coronary disease.²⁰ In light of the aforementioned conditions, several disease endotypes can be defined (Figure 2). Here are the definitions of the most frequent endotypes based on the available evidence.

Epicardial coronary spasm:

- Reproduction of the patient's symptoms during provocative testing.
- Ischaemic ECG shifts on simultaneous 12-lead ECG during provocative testing.
- Epicardial coronary constriction $\geq 90\%$ diameter reduction during provocative testing.

Microvascular coronary spasm (Figure 3):

- Reproduction of the patient's symptoms during provocative testing.
- Ischaemic ECG shifts on simultaneous 12-lead ECG during provocative testing.
- Absence of epicardial coronary constriction $\geq 90\%$ diameter reduction during provocative testing.
- In some centres, further evidence is generated by abnormal lactate concentrations from coronary sinus blood samples during provocative testing.

Impaired CFR:

- Depending on the Doppler or thermodilution technique, CFR is calculated based on average peak flow velocity (APV) or mean transit time (Tmn), respectively, as follows:

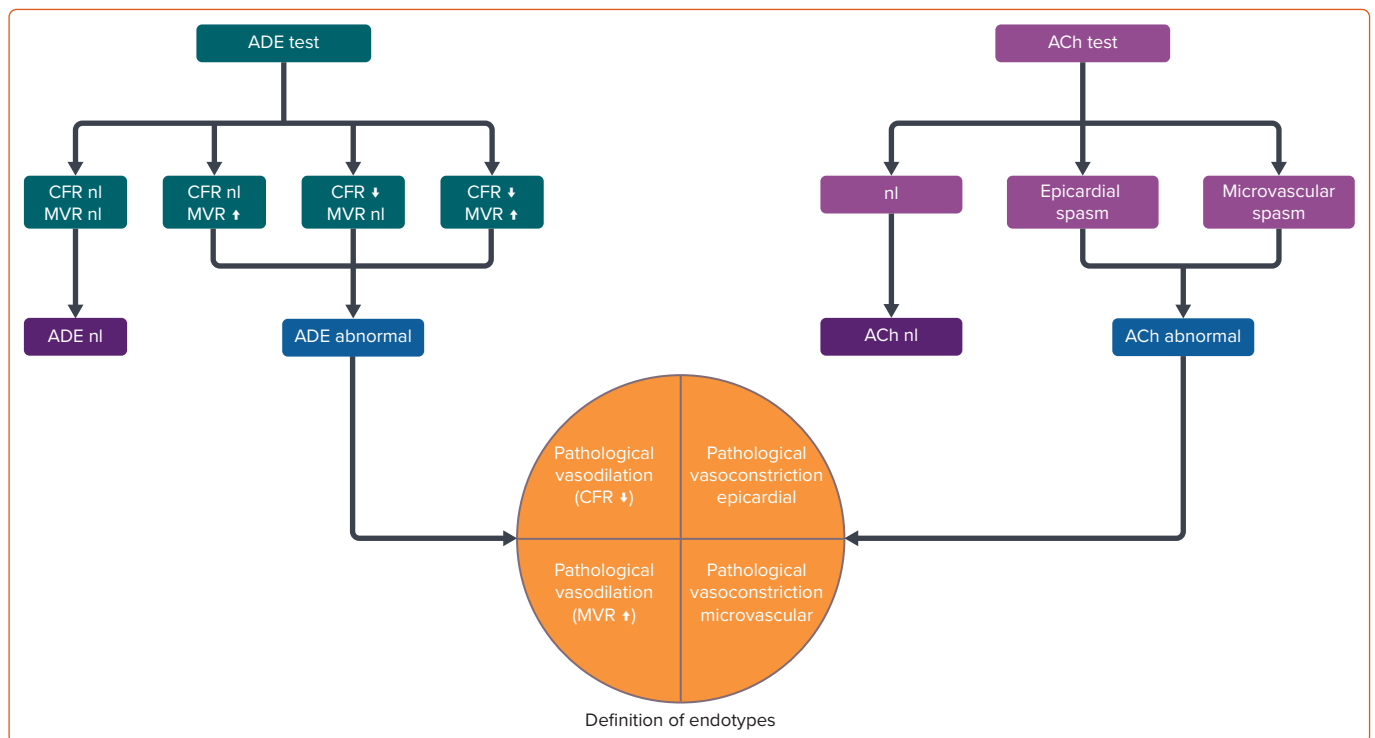
$$CFR_{Doppler} = \frac{APV_{Peak}}{APV_{Rest}}$$

and

$$CFR_{thermo} = \frac{Tmn_{Rest}}{Tmn_{Peak}}$$

- Usually, a CFR ≤ 2.0 – 2.5 during flow measurements using a dedicated wire (Doppler or thermodilution technique) and adenosine infusions (IV or intracoronary) is considered abnormal.

Figure 2: Definition of Functional Coronary Disorder Endotypes as Determined by the Interventional Diagnostic Procedure



Based on the sequential testing of the coronary vasomotor response to acetylcholine and adenosine during the interventional diagnostic procedure different functional coronary disorder endotypes can be distinguished, which can also be observed in combination. ADE = adenosine; ACh = acetylcholine; CFR = coronary flow reserve; MVR = microvascular resistance; nl = normal.

Enhanced microvascular resistance:

- Microvascular resistance is calculated using distal intracoronary pressure and APV or Tmn as follows:
 $HMR = Pd/APV_{Peak}$
 and
 $IMR = Pd * Tmn_{Peak}$
- Different cut-off values for HMR and IMR have been applied depending on the technique and the patient population.
- Frequently an IMR of >25 and an HMR of >2.4 are considered abnormal.

It is important to remember that in a given patient, several of the above-mentioned disease endotypes may be present.^{21,22} This not only leads to a high number of complex endotypes but also means that there may be patients with more than one coronary functional abnormality, e.g. coronary microvascular spasm and impaired CFR.

Consequently, understanding the pathophysiology in an individual patient, as well as creating well-characterised and homogeneous groups of endotypes for clinical trials is challenging.

Epidemiology of Coronary Functional Abnormalities

The true prevalence of patients with coronary functional abnormalities is difficult to determine as there are no reliable non-invasive tests that cover all the endotypes. Novel smart ECG devices may allow detection of ischaemic ECG shifts in patients with chest pain of unknown origin pointing towards a cardiac cause.^{23,24} It is currently unknown how often these symptoms are caused by stenosing coronary disease or a functional coronary abnormality. While common in patients with coronary artery spasm, the frequency of ischaemic ECG changes in patients with impaired

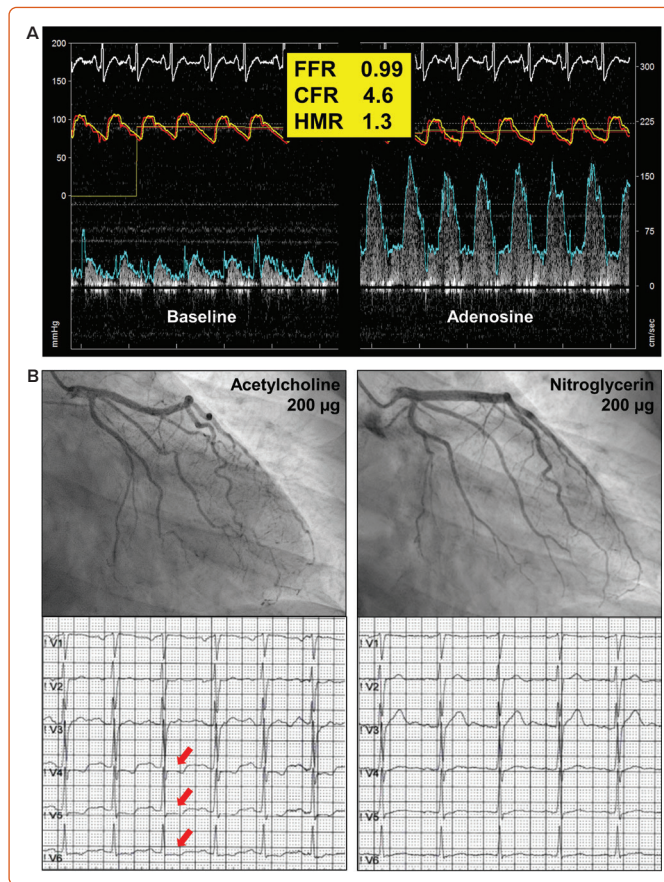
CFR and/or increased microvascular resistance is unknown. Nevertheless, this represents an interesting area of investigation in contemporary precision medicine and upcoming studies are eagerly awaited. The number of patients with ANOCA will most likely further increase due to the fact that current guidelines recommend performing a coronary CT in patients with stable angina.²⁵ However, despite the advantage of providing information on the presence and morphology of coronary plaque, this CT-based anatomical approach does not allow assessment of functional coronary abnormalities. Although few small studies have recently evaluated the feasibility of static or dynamic adenosine-stress CT perfusion examinations in patients with ANOCA, it is unclear whether these methods will enter clinical routine.^{26,27} Unfortunately, testing for functional abnormalities of vasoconstriction is not possible using CT.

Chronic Coronary Syndromes with Non-obstructed Coronary Arteries

It is well known that unobstructed coronary arteries are found in more than 50% of cases when looking at patients with chronic coronary syndromes undergoing elective invasive diagnostic coronary angiography for suspected stenosing coronary disease.²⁸ Although this number may be reduced by better patient selection, the number of patients with ANOCA will remain high and they may even generate higher costs over time compared to patients with obstructive coronary disease.²⁹ This underlines the high burden for our healthcare systems and highlights the need for appropriate diagnostic assessments in search of coronary functional abnormalities.

The frequency of coronary functional abnormalities in patients with ANOCA has been extensively investigated. Most older studies only looked at certain disease endotypes, such as coronary spasm only or impaired CFR only, and reported a prevalence of 50–60% in selected patients with ANOCA for each

Figure 3: Interventional Diagnostic Procedure in a 33-year-old Male Patient with Repeated Episodes of Resting Angina and Unobstructed Coronary Arteries



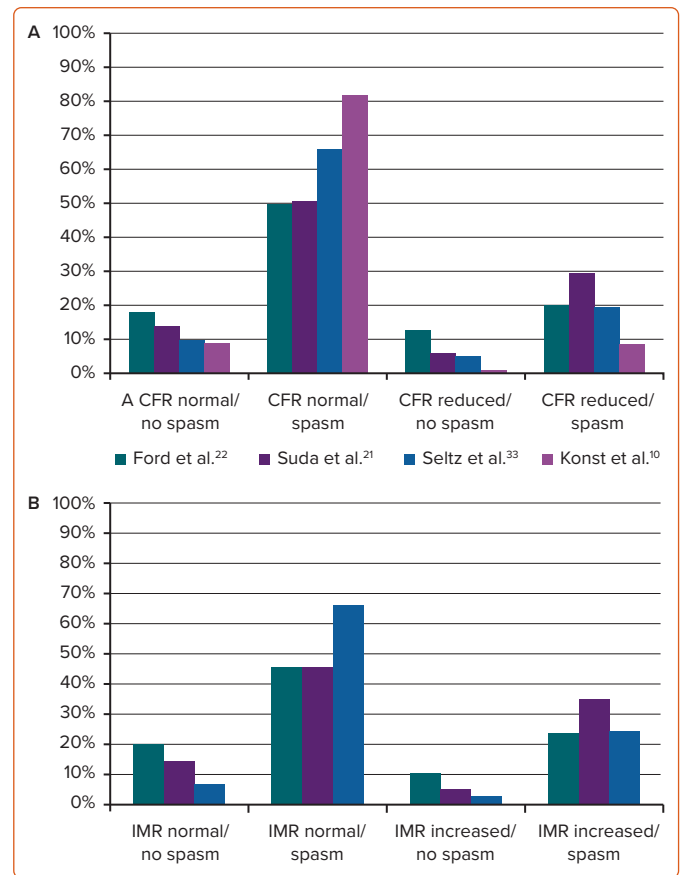
A: Microvascular vasodilatation in response to intracoronary administration of adenosine 200 µg was normal (CFR 4.6, HMR 1.3). B: Acetylcholine spasm provocation testing revealed ischaemic ECG changes (red arrows) but no significant epicardial vasoconstriction (<90%) consistent with microvascular spasm. FFR = fractional flow reserve; CFR = coronary flow reserve; HMR = hyperaemic microvascular resistance.

pathomechanism.^{30–32} Recent studies focused on the comprehensive assessment of coronary function resulting in a growing body of evidence regarding the frequency of enhanced coronary vasoconstriction, impaired microvascular vasodilatation (i.e. reduced CFR or increased microvascular resistance) or a combination thereof (Figure 4).^{10,21,22,33} Notably, these trials unanimously suggest that in patients with ANOCA enhanced vasoconstriction (coronary spasm) is much more frequent than impaired vasodilatation. This has important implications not only for future clinical trials but also for daily practice given that – in contrast to impaired CFR which can be assessed non-invasively using positron emission tomography or MRI – coronary vasoconstriction can only be reliably assessed invasively by spasm provocation testing.

Acute Coronary Syndromes with Non-obstructed Coronary Arteries

While the frequency of obstructive coronary artery disease is higher in patients with acute coronary syndrome (ACS) compared to those with chronic coronary syndromes, up to 25% of patients presenting with ACS are found to have non-obstructed coronary arteries.³⁴ This group comprises patients with MI with non-obstructed coronary arteries (MINOCA), as well as patients with unstable angina. Various pathomechanisms may be responsible for this emergent clinical scenario, including – but not limited to – pericarditis, myocarditis, takotsubo

Figure 4: Frequency of Functional Coronary Disorder Endotypes in Angina and Non-obstructed Coronary Arteries



Microvascular function was stratified according to CFR or IMR (CFR normal = ≥ 2.0 ; spasm = acetylcholine-induced epicardial and/or microvascular spasm; IMR normal = < 25 . CFR = coronary flow reserve; IMR = index of microcirculatory resistance.

syndrome, plaque erosion, spontaneous coronary dissection, valvular heart disease, systemic diseases and functional coronary disorders.³⁵ The prevalence of coronary artery spasm is high in this patient population.^{34,36,37} Although being safe in the acute setting, appropriate testing is rarely performed in clinical practice.^{34,37,38}

Previous Successful Myocardial Revascularisation

Studies have shown that up to 50% of patients with successful PCI complain of ongoing or recurrent angina after the procedure.^{39,40} Such patients represent another important group of patients in whom investigations of coronary functional abnormalities should be performed. Studies have shown that coronary functional abnormalities can be found in ~60–70% of patients who have had previous successful myocardial revascularisation procedures and have ongoing/recurrent symptoms.^{41,42}

Sex-related Differences

Several studies have shown that coronary functional abnormalities are more often found in women compared to men with some trials, such as the WISE study, focusing exclusively on women, however, systematic analyses have found only modest female preponderance.^{31,43,44} Moreover, prognosis in patients with ANOCA and reduced CFR was found to be equally impaired in men and women.⁴⁵ Considering the frequent persistence of symptoms following coronary interventions for obstructive coronary artery disease (CAD) one may speculate that many men with obstructive CAD have

additional functional coronary abnormalities. Thus, the prevalence of functional abnormalities may be the same in both sexes, but it is under-recognised in men because testing is not performed if coronary stenoses are detected. Coronary functional abnormalities should therefore be considered in all patients with angina in daily clinical practice and future studies should provide more evidence regarding sex differences in this field.³²

Conclusion

The high number of patients with ANOCA should prompt further assessments in search of functional coronary abnormalities as suggested by the current guidelines. Knowledge about the current definitions and frequencies of coronary functional abnormality endotypes is essential for appropriate classification and selection of the most effective pharmacological treatments. □

- Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of ischemic heart disease. *Circulation* 2018;138:1463–80. <https://doi.org/10.1161/CIRCULATIONAHA.118.031373>; PMID: 30354347.
- Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018;250:16–20. <https://doi.org/10.1016/j.ijcard.2017.08.068>; PMID: 29031990.
- Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J* 2017;38:2565–8. <https://doi.org/10.1093/eurheartj/ehv351>; PMID: 26245334.
- Ford TJ, Ong P, Sechtem U, et al. Assessment of vascular dysfunction in patients without obstructive coronary artery disease: why, how, and when. *JACC Cardiovasc Interv* 2020;13:1847–64. <https://doi.org/10.1016/j.jcin.2020.05.052>; PMID: 32819476.
- Jespersen L, Abildstrom SZ, Hvelplund A, Prescott E. Persistent angina: highly prevalent and associated with long-term anxiety, depression, low physical functioning, and quality of life in stable angina pectoris. *Clin Res Cardiol* 2013;102:571–81. <https://doi.org/10.1007/s00392-013-0568-z>; PMID: 23636227.
- 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;72:2841–55. <https://doi.org/10.1016/j.jacc.2018.09.006>; PMID: 30266608.
- Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–77. <https://doi.org/10.1093/eurheartj/ehz425>; PMID: 31504439.
- Nishimiya K, Suda A, Fukui K, et al. Prognostic links between OCT-delineated coronary morphologies and coronary functional abnormalities in patients with INOCA. *JACC Cardiovasc Interv* 2021;14:606–18. <https://doi.org/10.1016/j.jcin.2020.12.025>; PMID: 33736768.
- Martinez Pereyra V, Hubert A, Seitz A, et al. Epicardial and microvascular coronary spasm in the same patient? Acetylcholine testing pointing towards a common pathophysiological background. *Coron Artery Dis* 2020;31:398–9. <https://doi.org/10.1097/MCA.0000000000000829>; PMID: 31658150.
- Konst RE, Damman P, Pellegrini D, et al. Vasomotor dysfunction in patients with angina and nonobstructive coronary artery disease is dominated by vasospasm. *Int J Cardiol* 2021;333:14–20. <https://doi.org/10.1016/j.ijcard.2021.02.079>; PMID: 33711394.
- Seitz A, Feenstra R, Konst RE, et al. Abstract: Intracoronary nitroglycerine is more effective in preventing epicardial spasm than microvascular spasm during acetylcholine provocation testing. *Clinical Research in Cardiology* 2021;110:1350.
- Ong P, Safdar B, Seitz A, et al. Diagnosis of coronary microvascular dysfunction in the clinic. *Cardiovasc Res* 2020;116:841–55. <https://doi.org/10.1093/cvr/cvz339>; PMID: 31904824.
- Seitz A, Beck S, Pereyra VM, et al. Testing acetylcholine followed by adenosine for invasive diagnosis of coronary vasomotor disorders. *J Vis Exp* 2021;168. <https://doi.org/10.3791/62134>; PMID: 33616102.
- Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol* 2010;55:2825–32. <https://doi.org/10.1016/j.jacc.2010.01.054>; PMID: 20579539.
- AlBadri A, Bairey Merz CN, Johnson BD, et al. Impact of abnormal coronary reactivity on long-term clinical outcomes in women. *J Am Coll Cardiol* 2019;73:684–93. <https://doi.org/10.1016/j.jacc.2018.11.040>; PMID: 30765035.
- Suppogu N, Wei J, Quesada O, et al. Angina relates to coronary flow in women with ischemia and no obstructive coronary artery disease. *Int J Cardiol* 2021;333:35–9. <https://doi.org/10.1016/j.ijcard.2021.02.064>; PMID: 33662486.
- Broyd CJ, Hernandez-Perez F, Segovia J, et al. Identification of capillary rarefaction using intracoronary wave intensity analysis with resultant prognostic implications for cardiac allograft patients. *Eur Heart J* 2018;39:1807–14. <https://doi.org/10.1093/eurheartj/ehx732>; PMID: 29253131.
- Tsagalou EP, Anastasiou-Nana M, Agapitos E, et al. Depressed coronary flow reserve is associated with decreased myocardial capillary density in patients with heart failure due to idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2008;52:1391–8. <https://doi.org/10.1016/j.jacc.2008.05.064>; PMID: 18940529.
- Sorop O, van den Heuvel M, van Ditzhuijzen NS, et al. Coronary microvascular dysfunction after long-term diabetes and hypercholesterolemia. *Am J Physiol Heart Circ Physiol* 2016;311:h1339–51. <https://doi.org/10.1152/ajpheart.00458.2015>; PMID: 27591223.
- Sechtem U, Brown D, Godo S, et al. Coronary microvascular dysfunction in stable ischaemic heart disease (non-obstructive coronary artery disease and obstructive coronary artery disease). *Cardiovasc Res* 2020;116:771–86. <https://doi.org/10.1093/cvr/cvaa005>; PMID: 31958128.
- Suda A, Takahashi J, Hao K, et al. Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease. *J Am Coll Cardiol* 2019;74:2350–60. <https://doi.org/10.1016/j.jacc.2019.08.1056>; PMID: 31699275.
- Ford TJ, Yli E, Sidik N, et al. Ischemia and no obstructive coronary artery disease: prevalence and correlates of coronary vasomotor disorders. *Circ Cardiovasc Interv* 2019;12:e008126. <https://doi.org/10.1161/CIRCINTERVENTIONS.119.008126>; PMID: 31833416.
- Spaccarotella CAM, Polimeni A, Migliorino S, et al. Multichannel electrocardiograms obtained by a smartwatch for the diagnosis of ST-segment changes. *JAMA Cardiol* 2020;5:1176–80. <https://doi.org/10.1001/jamacardio.2020.3994>; PMID: 32865545.
- Drexler M, Elsner C, Gabelmann V, et al. Apple Watch detecting coronary ischaemia during chest pain episodes or an apple a day may keep myocardial infarction away. *Eur Heart J* 2020;41:2224. <https://doi.org/10.1093/eurheartj/ehaa290>; PMID: 32346733.
- Adamson PD, Williams MC, Dweck MR, et al. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. *J Am Coll Cardiol* 2019;74:2058–70. <https://doi.org/10.1016/j.jacc.2019.07.085>; PMID: 31623764.
- Sugisawa J, Matsumoto Y, Takeuchi M, et al. Beneficial effects of exercise training on physical performance in patients with vasospastic angina. *Int J Cardiol* 2020;328:14–21. <https://doi.org/10.1016/j.ijcard.2020.12.003>; PMID: 33309635.
- Bechsgaard DF, Hove JD, Michelsen MM, et al. Myocardial CT perfusion compared with transthoracic Doppler echocardiography in evaluation of the coronary microvascular function: an iPOWER substudy. *Clin Physiol Funct Imaging* 2021;41:85–94. <https://doi.org/10.1111/cpf.12669>; PMID: 33030280.
- Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886–95. <https://doi.org/10.1056/NEJMoa0907272>; PMID: 20220183.
- Shaw LJ, Merz CN, Pepine CJ, et al. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health–National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Circulation* 2006;114:894–904. <https://doi.org/10.1161/CIRCULATIONAHA.105.609990>; PMID: 16923752.
- Reis SE, Holubkov R, Conrad Smith AJ, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J* 2001;141:735–41. <https://doi.org/10.1067/mhj.2001.141498>; PMID: 11320360.
- Ong P, Athanasiadis A, Borgulya G, et al. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal Coronary Vasomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol* 2012;59:655–62. <https://doi.org/10.1016/j.jacc.2011.11.015>; PMID: 22322081.
- Aribas E, van Lennep JER, Elias-Smale SE, et al. Prevalence of microvascular angina among patients with stable symptoms in the absence of obstructive coronary artery disease: a systematic review. *Cardiovasc Res* 2021. <https://doi.org/10.1093/cvr/cvab061>; PMID: 33677526; epub ahead of press.
- Seitz A, Pirozzolo G, Martinez Pereyra V, et al. Abstract 13340: Microvascular angina is more frequently associated with microvascular spasm than with impaired microvascular vasodilator capacity. *Circulation* 2019;140(Suppl 1):A13340.
- Ong P, Athanasiadis A, Hill S, et al. Coronary artery spasm as a frequent cause of acute coronary syndrome: The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) study. *J Am Coll Cardiol* 2008;52:523–7. <https://doi.org/10.1016/j.jacc.2008.04.050>; PMID: 18687244.
- Niccoli G, Camici PG. Myocardial infarction with non-obstructive coronary arteries: what is the prognosis? *Eur Heart J Suppl* 2020;22(Suppl E):e40–5. <https://doi.org/10.1093/eurheartj/suaa057>; PMID: 32523437.
- Pirozzolo G, Seitz A, Athanasiadis A, et al. Microvascular spasm in non-ST-segment elevation myocardial infarction without culprit lesion (MINOCA). *Clin Res Cardiol* 2020;109:246–54. <https://doi.org/10.1007/s00392-019-01507-w>; PMID: 31236694.
- Montone RA, Niccoli G, Braccasi F, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J* 2018;39:91–8. <https://doi.org/10.1093/eurheartj/ehx667>; PMID: 29228159.
- Probst S, Seitz A, Martinez Pereyra V, et al. Safety assessment and results of coronary spasm provocation testing in patients with myocardial infarction with unobstructed coronary arteries compared to patients with stable angina and unobstructed coronary arteries. *Eur Heart J Acute Cardiovasc Care* 2021;10:380–7. <https://doi.org/10.1177/2048872620932422>; PMID: 32508106.
- Crea F, Bairey Merz CN, Beltrame JF, et al. Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. *Eur Heart J* 2019;40:2455–62. <https://doi.org/10.1093/eurheartj/ehy857>; PMID: 30608528.
- Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31–40. [https://doi.org/10.1016/S0140-6736\(17\)32714-9](https://doi.org/10.1016/S0140-6736(17)32714-9); PMID: 29103656.
- Pirozzolo G, Seitz A, Martinez Pereyra V, et al. Different vasoreactivity of arterial bypass grafts versus native coronary arteries in response to acetylcholine. *Clin Res Cardiol* 2021;110:172–82. <https://doi.org/10.1007/s00392-020-01694-x>; PMID: 32613293.
- Ong P, Athanasiadis A, Perne A, et al. Coronary vasomotor abnormalities in patients with stable angina after successful stent implantation but without in-stent restenosis. *Clin Res Cardiol* 2014;103:11–9. <https://doi.org/10.1007/s00392-013-0615-9>; PMID: 23995322.
- Aziz A, Hansen HS, Sechtem U, et al. Sex-related differences in vasomotor function in patients with angina and unobstructed coronary arteries. *J Am Coll Cardiol* 2017;70:2349–58. <https://doi.org/10.1016/j.jacc.2017.09.016>; PMID: 29096805.
- Vermeltfoort IA, Rajmakers PG, Riphagen II, et al. Definitions and incidence of cardiac syndrome X: review and analysis of clinical data. *Clin Res Cardiol* 2010;99:475–81. <https://doi.org/10.1007/s00392-010-0159-1>; PMID: 20407906.
- Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;129:2518–27. <https://doi.org/10.1161/CIRCULATIONAHA.113.008507>; PMID: 24787469.