American Heart Journal Plus: Cardiology Research and Practice 41 (2024) 100389

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Coronary microvascular dysfunction, arrythmias, and sudden cardiac death: A literature review

Razan Dankar, Jad Wehbi, Mohamad Montaser Atasi, Samir Alam, Marwan M. Refaat *

Division of Cardiology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

ARTICLE INFO

Keywords:
Coronary microvascular dysfunction
Ventricular arrythmia
Atrial fibrillation
Repolarization parameters
Sudden cardiac death

ABSTRACT

The coronary vascular system has a unique structure and function that is adaptive to myocardial demand. It is composed of a continuous network of vessels receding in size from epicardial arteries to the microvascular circulation. Failure to meet myocardial demand results in ischemia, angina, and adverse myocardial outcomes. It is evident that 50 % of patients with angina have a non-obstructive coronary disease and 66 % of these patients have coronary microvascular dysfunction (CMD). The impact of CMD on the atria and ventricles is exhibited through its association with atrial fibrillation and distortion of ventricular repolarization. Ultimately, this influence increases the risk of mortality, morbidity, and sudden cardiac arrest. CMD serves as an independent risk for atrial fibrillation, increases ventricular electrical inhomogeneity, and contributes to the progression of cardiac disease. The underlying pathogenesis may be attributed to oxidative stress evident through reactive oxygen species, impaired vasoactive function, and structural disorders such as fibrotic changes. Myocardial ischemia, brought about by a demand-supply mismatch in CMD, may create a milieu for ventricular arrythmia and sudden cardiac arrest through distortion of ventricular repolarization parameters such as QT dispersion and corrected QT dispersion.

1. Background

The coronary vascular system has a unique structure and function which allows for adaptive circulation. Transmural perfusion is almost limited to diastole due to the compressing force present in systole, and as such diastolic abnormalities have a strong effect on myocardial perfusion. Vatner, Chilian, Marcus and their colleagues were among the first to document that epicardial arteries function as capacitance vessels. The myocardium requires a relatively high blood flow and short O2 diffusion distance to accommodate the need for rapid changes in oxygen consumption [1,2].

We can describe three compartments of the coronary arterial system. The first is formed of the most proximal vascular structures, the epicardial coronary arteries, which have a diameter ranging from 500 μm to 5 mm. They are visible using coronary angiography and can maintain a given level of shear stress by endothelial-dependent dilatation. It is followed by the intermediate compartment that is formed of pre-arterioles that are 100 to 500 μm in diameter. The latter is a lower-pressure system without direct vasomotor control, which is regulated by diffusible metabolites that cause them to undergo myogenic constriction. The most distal compartment is comprised of intramural arterioles that are of <100 μm in diameter, offer a considerable drop in pressure along their path and a fundamental role in the metabolic regulation of coronary blood flow [3].

The coronary slow flow (CSF) phenomenon is defined as a microvascular disorder characterized by the slow filling of the opaque material applied during coronary angiography into the distal vasculature in patients with normal or near-normal epicardial coronary arteries [4]. Furthermore, this phenomenon may be explained by endothelial dysfunction, impaired micro-vascularization functions, and atherosclerosis, as they have been directly linked to CSF. Patients with CSF may present with exertional angina, unstable angina pectoris, myocardial infarction, life-threatening arrhythmias, and sudden cardiac death. This suggests another underlying etiology for patients with angina and positive coronary stress test than the classical coronary artery disease (CAD). Vermeltfoort et al. in 2010 defined the term cardiac syndrome X (CSX) to include all patients with typical angina, one or more abnormal cardiac stress tests, and normal epicardial arteries on coronary angiography [5]. Causes might be related to microvascular dysfunction and augmented sensitivity to pain [6].

* Corresponding author.
E-mail address: mr48@aub.edu.lb (M.M. Refaat).

https://doi.org/10.1016/j.ahjo.2024.100389
Received 30 December 2023; Received in revised form 7 March 2024; Accepted 25 March 2024
Available online 28 March 2024
2666-6022/© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

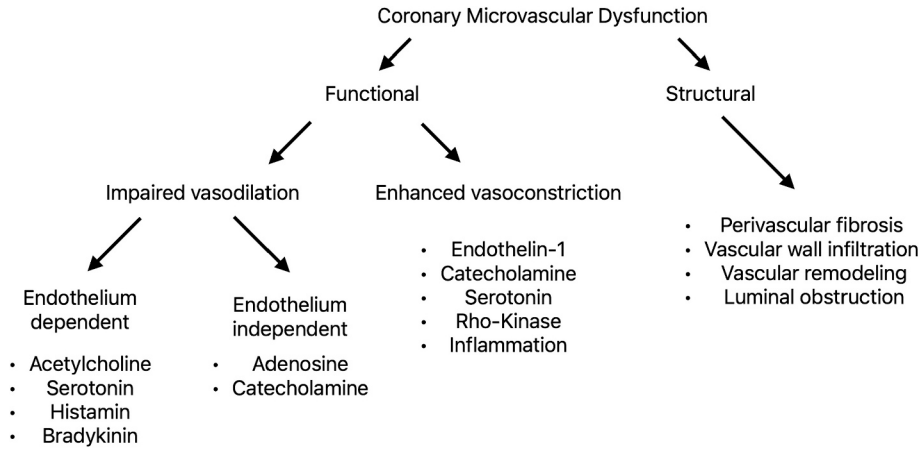

Fig. 1. Classification of CMD.

Patients with microvascular dysfunction are often unable to increase their coronary flow in response to any stressors, putting them at high risk for ischemia, which in turn promotes arrhythmogenesis. There is a scarcity in the literature regarding the underlying link between coronary microvascular dysfunction (CMD), arrhythmias, and sudden cardiac death. In this review, we aim to explore this potential association.

2. Mechanism of coronary microvascular dysfunction

Understanding the pathophysiology of CMD is important for a more targeted approach to therapy. There are two broad classifications of CMD pathological mechanisms, functional and structural. The functional mechanisms are related to enhanced vasoconstriction and impaired vasodilation. Enhanced coronary vasoconstriction reproduces angina and ischemic changes on ECG without apparent changes to epicardial coronary arteries when certain pharmacological agents, such as acetylcholine, are administered [7]. This microvascular spasm is mediated by serotonin, Endothelin-1, Rho-Kinase-induced myosin light-chain phosphorylation, and inflammatory conditions in the small vessels [8]. Secondly, endothelium-derived relaxing factors like vasodilator prostaglandins, nitric oxide, and endothelium-dependent hyperpolarization factor (EDHF) alter the resistance of coronary micro-vessels [8,9]. Hence, diminished production of these endothelium-derived factors contributes to the impairment in vasodilation seen in CMD. Also, this impairment has been associated with endothelium-dependent mechanisms that are linked to diabetes mellitus, obesity, and tobacco smoking among other cardiovascular risk factors, as well as endothelium-independent mechanism such as nitric oxide resistance [10]. Furthermore, structural factors in the coronary microvasculature cause stiffer and thicker walls at the expense of vessel lumen that increases resistance to blood flow. These factors include perivascular fibrosis, vascular wall infiltration, vascular remodeling, and luminal obstruction [10]. Finally, decreased myocardial capillary density in patients with dilated cardiomyopathy correlates with reduced coronary flow reserve and may lead to perfusion abnormalities [11]. It is noteworthy that an increased heart rate, reduced diastolic time, decreased driving blood pressure, and left ventricular inotropism can influence the microcirculation's functional response. Therefore, we need to consider these factors when we assess the microvascular function. Fig. 1. provides a schematic diagram of the classification of CMD.

3. Diagnosis of CMD

Almost 50 % of those with angina exhibit angina with non-obstructive coronary artery disease (ANOCA). This is a broad classification including a variety of vascular illnesses that differ in terms of their underlying mechanisms and long-term outcomes [12]. Among these ANOCA cases approximately 66 % are attributed to CMD [12]. Therefore, the accurate diagnosis of microvascular angina necessitates the exclusion of obstructive CAD. However, due to the current limitations in directly visualizing the coronary microvasculature, diagnostic measures for CMD mainly rely on surrogate markers of myocardial perfusion and microvascular resistance. This involves the assessment of physiological indicators of microvascular function, employing both invasive and non-invasive techniques such as positron emission tomography (PET), cardiovascular magnetic resonance (CMR), and echocardiography [13].

The utilization of invasive coronary angiography helps in assessing patients with CMD due to its capacity to both rule out obstructive CAD and to investigate the physiological aspects of both epicardial and microvascular coronary systems. One crucial parameter used is the coronary flow reserve (CFR), which measures the ratio between maximal hyperemic and baseline coronary blood flow (CBF). It provides insights into the heart's ability to increase blood supply in response to heightened demand, a capacity significantly affected in CMD. CBF is measured both at rest and in the presence of pharmacological agents such as adenosine and acetylcholine (Functional coronary angiography). These measurements help distinguish between endothelium-independent and endothelium-dependent vasodilation, respectively [12–14]. Other indices such as the index of microvascular resistance (IMR) can also be used alternatively. Following the exclusion of obstructive CAD, a diagnosis of endothelium-independent CMD is confirmed when the CFR falls below 2 or 2.5 in response to adenosine, as defined by the COVADIS (Coronary Vasomotion Disorders International Study) group and agreed upon by experts in the field [7,15]. On the other hand, the diagnosis of coronary endothelial dysfunction is confirmed when the acetylcholine flow reserve (AChFR) is impaired, defined as equal to or <1.5 [14].

Coronary microvascular abnormalities are important prognostic factors in many cardiac pathologies. Therefore, considerable research efforts study the most reliable non-invasive diagnostic method, which relies on assessing global and focal blood supply to the myocardium, as well as CFR and resistance in the microvasculature. One of the most validated methods is PET myocardial perfusion stress testing. Such modalities can compare between rest and vasodilator-stress myocardial perfusion studies following the administration of a radiotracer [16,17]. CMR can also be used, by injecting gadolinium contrast, therefore assessing the CFR or the myocardial perfusion reserve index. Also, a gadolinium-free stress CMR can be employed using T1 mapping [18]. Similarly, another modality is using dynamic myocardial perfusion computed tomography (CT) after injecting iodine contrast with prospective electrocardiographic triggering to capture the first pass of the contrast through the heart. CT has better spatial resolution and allows the assessment of both the myocardium and the coronaries at once [17].

Table 1
Summary of studies on the association between AF and CMD.

Reference	Authors	Year of publication	Study	Main findings
[22]	Corban et al.	2020	Patients with chest pain, non-obstructive CAD, and CMD	CMD patients had a 5.8-fold increase in the relative risk for new-onset AF
[23,24]	Pena, A.d.l., et al.; Ozcan et al.	2019; 2021	Patients undergoing invasive coronary studies	CMD was observed in patients with AF, and in patients with AF and concomitant heart failure with preserved ejection fraction
[25]	Ahmad et al.	2021	CMD patients using AI-based ECG algorithm	Successful identification of CMD patients at a heightened risk for long-term incident AF
[26]	Bentea et al.	2023	Patients with persistent AF	All patients with AF had a CFR < 2.5, indicating CMD presence. Low CFR was associated with a higher risk of MACE during 5-year follow-up
[27]	Kochiadakis et al.	2002	Individuals with normal angiographic coronary arteries and experimentally-induced AF	Reduced CFR observed, suggesting inadequate compensation for increased myocardial oxygen demand during irregular ventricular rhythm in AF patients
[28–31]	Byrne et al.; Wijesurendra et al.; Sugimoto et al.; Range et al.	2019; 2018; 2021; 2007	Patients with AF undergoing non-invasive studies	Reduced hyperemic myocardial blood flow observed in AF patients

Finally, measuring the coronary flow velocity reserve index of the left anterior descending artery by Doppler is an operator-dependent technique and it allows for risk stratification [19].

4. CMD and atrial fibrillation

Globally, atrial fibrillation (AF) is the most common sustained arrhythmia [20]. It constitutes a major cause of morbidity and mortality, with a mortality rate twice that of individuals of the same age and sex without AF [21]. Several risk factors have been identified to be associated with AF including advanced age, family history, hyperthyroidism, excessive alcohol intake, and various cardiovascular conditions [20]. CMD is considered one of the etiologies for AF.

A recent study by Corban et al. was conducted to determine the relationship between CMD and AF [22]. The study recruited around 400 patients who suffered from ANOCA, and who were diagnosed with coronary microvascular endothelial dysfunction via invasive evaluation. After >10 years of follow up, it was demonstrated that patients with CMD had a 5.8-fold increase in the relative risk of developing new-onset AF, underscoring CMD as an independent predictor for the incidence of AF. Similarly, abnormal CFR, used as a marker for CMD, has been found to play a significant role in the association between AF, CMD, and heart failure with preserved ejection fraction (HFpEF) [23,24]. CMD was highly observed in patients with AF independent of HFpEF status. However, there were more unfavourable clinical outcomes in cases of their co-existence [24]. In 2021, Ahmad et al. implemented an artificial intelligence (AI)-based ECG algorithm to detect paroxysmal AF in patients with CMD. Despite its limitations, the study was able to identify CMD patients who were at a heightened risk of developing long-term incident AF, thus providing future insights for the potential uses of AI in the field [25].

Several studies have suggested an association between endothelial dysfunction and AF, but they failed to determine which was a consequence of the other. In a recent prospective study that included patients with persistent AF, Bentea et al. concluded that all studied patients with AF had a CFR of <2.5 and a mean value of 1.74, indicating the presence of CMD [26]. After 5 years of follow-up, it was also observed that such patients with low CFR values were at higher risk for major adverse cardiovascular events (MACE). A similar study done by Kochiadakis et al. using invasive coronary physiology testing provided evidence of reduced CFR in individuals with normal angiographic coronary arteries who were experiencing induced atrial fibrillation (AF) [27]. This was hypothesized to be a result of insufficient compensation for the increase in myocardial oxygen demand due to the irregular ventricular rhythm during AF. Such findings of aberrant CFR in patients with AF also align with prior research documenting reduced hyperemic myocardial blood flow in AF using non-invasive techniques [28–31]. Table 1. summarizes the main findings of studies describing the association between AF and CMD.

4.1. Pathophysiology and biomarkers linked to AF and CMD

There are several underlying pathophysiological factors and biomarkers that might explain the correlation between AF and CMD, which is marked by endothelial dysfunction and increased coronary vasoconstrictive reactivity [32].

The involvement of oxidative stress in the pathogenesis and association between AF and CMD has been suggested as being of paramount significance. Research has demonstrated that acute episodes of AF have the capacity to generate oxidative stress in the left ventricular myocardium, hence compromising microvascular blood flow [33–35]. The administration of dronedarone has been shown to effectively eliminate ventricular microcirculatory abnormalities generated by rapid atrial pacing (RAP) [34]. This was determined to be achieved through the reduction of oxidative stress and downregulation of the expression of genes and proteins associated with ventricular ischemia, proving the role of oxidative stress in compromising coronary flow [34]. In fact, a potential link of this association is angiotensin II (ANG-II). In 2009, Goette et al. demonstrated that RAP causes ANG-II-mediated Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase activation, leading to oxidative stress and resulting in microvascular flow abnormalities [33]. Administering irbesartan, an angiotensin II receptor type 1 (AT1), could prevent the expression of NADPH oxidase in this pig model. ANG-II has been proven to initiate the activation of NADPH oxidase, resulting in the production of reactive oxygen species (ROS). These ROS can quickly interact with nitric oxide (NO), leading to the generation of peroxynitrite, a reduction in the availability of NO, and subsequent endothelial dysfunction [36,37].

The role of potential biomarkers in the context of CMD and AF is also critical in providing insights into the underlying pathophysiological mechanisms. Among the most studied CMD biomarkers are asymmetric dimethylarginine (ADMA), NO and endothelin-1. ADMA, an inhibitor of

NO synthesis, has been found to be significantly higher in individuals with CMD as compared to controls, contributing to a marked decrease in NO levels, impaired vasodilation, and flow abnormalities [38–41]. This NO imbalance is similarly observed in AF, as demonstrated in both animal and human studies. For instance, in a pig model with AF, it was demonstrated that AF is associated with a decrease in NO synthesis and bioavailability [42]. Similarly, patients with AF have been found to have significantly lower levels of nitrite and nitrate (NOx) than healthy controls [43,44]. Interestingly though, after cardioversion, a normalization of the NOx levels was observed within 30 days of regaining a sinus rhythm [43].

Endothelin-1 is also suggested in the association between CMD and AF. Endothelin-1 is a potent vasoconstrictor peptide produced by endothelial cells. Endothelin-1 levels have been found to be markedly increased in individuals with CMD versus controls, indicating abnormal coronary vasomotor responses [45–47]. Similarly, plasma endothelin-1 has been positively associated with AF and linked to worse clinical outcomes, all-cause mortality, and cardiovascular death in patients with AF [48–50].

In 2022, Dixit et al. studied the plasma proteomic profile of 18 individuals with concomitant AF, CMD and HFpEF, to identify novel biomarkers involved in the association between the conditions [51]. The research identified 35 potential biomarkers, and it was found that in the coexistence of the 3 conditions, there were elevated levels of serum amyloid A1 (SAA1), Leucine-Rich α-2-Glycoprotein-1 (LRG1), and apolipoprotein C3 (APOC3) proteins [51]. These proteins are found to be linked to inflammation, oxidative stress, and coagulation. This sheds light on the underlying molecular pathways in the concomitant presence of AF, CMD, and HFpEF [51].

5. CMD and ventricular arrhythmia

Changes in ventricular repolarization (VR) noted on surface ECG are linked to ventricular arrhythmias and sudden cardiac death in patients with underlying cardiac disease. The latter includes CAD, idiopathic dilated cardiomyopathy, and mitral valve prolapse, among others [52–56]. Although studies with a direct focus on microvascular dysfunction and sudden cardiac death or ventricular arrhythmias are lacking, a relationship can be inferred from its effect on repolarization parameters. This hypothesis is supported by the finding that patients with CXS and CAD exhibit an increase in QT dispersion (QTd), corrected QT dispersion (QTcd), and adjusted QT dispersion (AdQTd) when compared to reference ranges [57]. Another study noted a greater QTcd at rest in women with CXS and CAD compared to healthy subjects, and this dispersion was augmented by exercise [58]. However, these studies failed to differentiate between the two disorders based on these parameters [58].

Hence, it is possible that a common underlying pathological mechanism to microvascular dysfunction and CAD results in the congruent effect on repolarization parameters. Myocardial ischemia augments the inhomogeneity of VR, which is reflected by an increase in QTd [55,59]. Patients with acute myocardial infarction exhibit a rise in QTd compared to those who are healthy, which drops following revascularization [55]. Similarly, the stress of atrial pacing in patients with CAD shows an increase in QTd, which correlates with coronary sinus lactate levels [60,61]. This further solidifies the effect of ischemia on repolarization parameters. However, this pathological mechanism is not limited to macrovascular changes, as coronary microvascular dysfunction has been depicted as a major cause of ischemic heart disease [62,63]. This negative impact on the myocardium is exerted through a demand-supply mismatch, which results in hypoperfusion and ischemia [62]. The effect of myocardial ischemia can be seen in patients with microvascular dysfunction through a dynamic rise in QTd during peak exercise [58,59]. Also, those with CSF, an angiographic phenomenon indicative of microvascular dysfunction, show higher values of QTcd in the absence of significant coronary obstruction [64]. Although another study

Table 2
Summary of studies on the effect of CMD on repolarization parameters.

Reference	Authors	Year of publication	Title	Main findings
[57]	Lutfi MF et al.	2016	QT Interval Derived Measurements in Patients with Cardiac Syndrome X Compared to Coronary Artery Disease	Comparable QT intervals and QTd in CAD and CSX patients even after adjustment for the possible variations in gender, age and body mass index of the studied groups. Patients with CXS and CAD exhibit an increase in QTd, QTcd, and AdQTd when compared to reference ranges
[58]	Tomkiewicz-Pajak L et al.	2001	[Changes in QT dispersion during the exercise test in women with syndrome X]	At rest QTcd is significantly greater in women with CXS and CAD in comparison with control subjects. Exercise causes an increase in the value of QTd and QTcd both in women with CXS and CAD. The value of QTd and QTcd cannot differentiate between women with CXS and women with CAD.
[59]	Alıcı G et al.	2011	Measurement of the QT dispersion in patients with cardiac syndrome X for the investigation of ischemia as an etiological factor	No difference in QTd noted at rest between patients with CXS and controls Peak exercise QTd was found to be higher in patients with CSX compared to the control group, especially when peak exercise QTd $\geq$ 60 msec
[63]	Sara JD et al.	2016	Coronary microvascular dysfunction is associated with baseline QTc prolongation among patients with chest pain and non-obstructive coronary artery disease	In a linear regression model adjusting for age and sex, CMD was associated with an increase in QTc QTc was significantly longer in those with an

(continued on next page)

Table 2 (*continued*)

Reference	Authors	Year of publication	Title	Main findings
				abnormal CFR response to adenosine Patients in the lowest quartile of CFR had a significantly longer QTc compared to those in the highest quartile
[64]	Atak R et al.	2003	Effects of slow coronary artery flow on QT interval duration and dispersion	QTcd was found to be significantly higher in patients with slow coronary artery flow
[65]	Karahan MZ et al.	2023	The effect of coronary slow flow on ventricular repolarization parameters	Patients with CSF had significantly longer QTmax duration, QTd, Tp-Te interval, and higher iCEB score, wider frontal QRS-T angle when compared to controls

QTd, QT dispersion; QTcd, corrected QT dispersion; AdQTd, adjusted QT dispersion; QTmax, maximum QT; CAD, coronary artery disease; CXS, cardiac X syndrome; CMD, coronary microvascular dysfunction; CFR, coronary flow reserve; CSF, coronary slow flow; iCEB, index of cardiac-electrophysiological balance.

indicated a greater QTd rather than QTcd in these patients, the fact remains that the impact of CSF is evident on repolarization [65].

Furthermore, microvascular dysfunction is implicated in both the pathogenesis and progression of several cardiac diseases, including hypertrophic cardiomyopathy (HCM). These patients are at an increased risk of ventricular arrhythmia and sudden cardiac death. This could be explained by repolarization inhomogeneity, as they exhibit greater QTd and QTcd dispersion when compared to healthy controls [62,66,67]. Also, patients with HCM seem to show coronary microvascular dysfunction that colocalizes to fibrotic scars within the myocardium and exhibit fibrotic changes in the perivascular space of small arteries and arterioles [68,69]. This can also explain their propensity for arrhythmia through fibrotic substrates that serve as re-entry sites and are the result of chronic ischemia inflicted by microvascular dysfunction [69,70]. Table 2. provides a summary of the studies assessing the repolarization parameters in CMD. In the setting of a paced surface ECG, many parameters can still be analyzed including the QTc interval [71,72].

6. Conclusion and perspectives

Coronary microvascular dysfunction is a complex pathology with numerous underlying factors that contribute to abnormal coronary circulation. While substantial progress has been made in unraveling the mechanisms of CMD and its association with arrhythmia and sudden cardiac death, much remains to be explored. It is important to also note that no specific treatment agent has yet been identified for CMD and that clinical management primarily involves addressing the contributing risk factors. Therefore, it is crucial to develop more specific therapeutic strategies, moving beyond risk factor control. The progression in knowledge and the integration of innovative and more targeted treatment approaches holds great promise in providing patients with more tailored and effective therapeutic options, and in protecting them from arrhythmic outcomes.

Funding

No funding source was used in the writing or submission of this review.

Submission declaration/verification

We confirm that this review has not been submitted to other journals.

CRediT authorship contribution statement

Razan Dankar: Writing – original draft, Conceptualization. **Jad Wehbi:** Writing – original draft, Conceptualization. **Mohamad Montaser Atasi:** Writing – original draft, Conceptualization. **Samir Alam:** Writing – review & editing, Conceptualization. **Marwan M. Refaat:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.A. Young, S.F. Vatner, Regulation of large coronary arteries, Circ. Res. 59 (6) (Dec 1986) 579–596.
[2] Goodwill, A.G., et al., Regulation of coronary blood flow, in Comprehensive Physiology. p. 321–382.
[3] A. Sinha, H. Rahman, D. Perera, Coronary microvascular disease: current concepts of pathophysiology, diagnosis and management, Cardiovasc. Endocrinol. Metab. 10 (1) (2021) 22–30.
[4] M.Z. Karahan, et al., The effect of coronary slow flow on ventricular repolarization parameters, J. Electrocardiol. 78 (2023) 39–43.
[5] I.A. Vermeltfoort, et al., Definitions and incidence of cardiac syndrome X: review and analysis of clinical data, Clin. Res. Cardiol. 99 (8) (2010) 475–481.
[6] J.R. Panting, et al., Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging, N. Engl. J. Med. 346 (25) (2002) 1948–1953.
[7] P. Ong, et al., International standardization of diagnostic criteria for microvascular angina, Int. J. Cardiol. 250 (2018) 16–20.
[8] F. Crea, R.A. Montone, Pathophysiology of coronary microvascular dysfunction, Vasc. Pharmacol. 153 (2023) 107239.
[9] Y. Kokusho, et al., Hydrogen peroxide derived from beating heart mediates coronary microvascular dilation during tachycardia, Arterioscler. Thromb. Vasc. Biol. 27 (5) (2007) 1057–1063.
[10] P.G. Camici, G. D'Amati, O. Rimoldi, Coronary microvascular dysfunction: mechanisms and functional assessment, Nat. Rev. Cardiol. 12 (1) (2015) 48–62.
[11] E.P. Tsagalou, 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. 52 (17) (2008) 1391–1398.
[12] D. Perera, 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 109 (2) (2022) 88–95.
[13] V.R. Taqueti, M.F. Di Carli, Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review, J. Am. Coll. Cardiol. 72 (21) (2018) 2625–2641.
[14] H. Rahman, et al., Optimal use of vasodilators for diagnosis of microvascular angina in the cardiac catheterization laboratory, Circ. Cardiovasc. Interv. 13 (6) (2020) e009019.
[15] K.L. Gould, N.P. Johnson, Coronary physiology beyond coronary flow reserve in microvascular angina: JACC state-of-the-art review, J. Am. Coll. Cardiol. 72 (21) (2018) 2642–2662.
[16] A. Gupta, et al., Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease, Circulation 136 (24) (2017) 2325–2336.
[17] A. Feher, A.J. Sinusas, Quantitative assessment of coronary microvascular function: dynamic single-photon emission computed tomography, positron emission tomography, ultrasound, computed tomography, and magnetic resonance imaging, Circ. Cardiovasc. Imaging 10 (8) (2017).
[18] M. Doyle, 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 3 (10) (2010) 1030–1036.
[19] F. Rigo, et al., Prognostic value of coronary flow reserve in medically treated patients with left anterior descending coronary disease with stenosis 51% to 75% in diameter, Am. J. Cardiol. 100 (10) (2007) 1527–1531.
[20] D. Bonhorst, et al., Epidemiology of atrial fibrillation, Rev. Port. Cardiol. 29 (7–8) (2010) 1207–1217.
[21] A. Laupacis, T.E. Cuddy, Prognosis of individuals with atrial fibrillation, Can. J. Cardiol. 12 (Suppl A) (1996) 14a–16a.
[22] M.T. Corban, et al., Coronary endothelial dysfunction is associated with increased risk of incident atrial fibrillation, J. Am. Heart Assoc. 9 (8) (2020) (p. e014850).
[23] A.d.l. Pena, et al., Abstract 16208: coronary microvascular dysfunction and atrial fibrillation, Circulation 140 (Suppl_1) (2019) A16208.
[24] C. Ozcan, et al., The relationship between coronary microvascular dysfunction, atrial fibrillation and heart failure with preserved ejection fraction, Am. J. Cardiovasc. Dis. 11 (1) (2021) 29–38.
[25] A. Ahmad, et al., Coronary microvascular dysfunction and the risk of atrial fibrillation from an artificial intelligence-enabled electrocardiogram, Circ. Arrhythm. Electrophysiol. 14 (8) (2021) (p. e009947).
[26] G. Pintea Bentea, et al., Particularities of coronary physiology in patients with atrial fibrillation: insights from combined pressure and flow indices measurements, Front. Cardiovasc. Med. 10 (2023) (p. 1206743).
[27] G.E. Kochiadakis, et al., Effect of acute atrial fibrillation on phasic coronary blood flow pattern and flow reserve in humans, Eur. Heart J. 23 (9) (2002) 734–741.
[28] C. Byrne, et al., Myocardial perfusion during atrial fibrillation in patients with non-ischaemic systolic heart failure: a cross-sectional study using Rubidium-82 positron emission tomography/computed tomography, Eur. Heart J. Cardiovasc. Imaging 20 (2) (2019) 233–240.
[29] R.S. Wijesurendra, et al., Myocardial perfusion is impaired and relates to cardiac dysfunction in patients with atrial fibrillation both before and after successful catheter ablation, J. Am. Heart Assoc. 7 (15) (2018) (p. e009218).
[30] Y. Sugimoto, et al., Impaired coronary flow reserve evaluated by phase-contrast cine magnetic resonance imaging in patients with atrial fibrillations, Heart Vessel. 36 (6) (2021) 775–781.
[31] F.T. Range, et al., Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation, Eur. Heart J. 28 (18) (2007) 2223–2230.
[32] S. Godo, et al., Endothelium in coronary macrovascular and microvascular diseases, J. Cardiovasc. Pharmacol. 78 (Suppl. 6) (2021) S19–s29.
[33] A. Goette, et al., Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles, Eur. Heart J. 30 (11) (2009) 1411–1420.
[34] A. Bukowska, et al., Dronedarone prevents microcirculatory abnormalities in the left ventricle during atrial tachypacing in pigs, Br. J. Pharmacol. 166 (3) (2012) 964–980.
[35] A. Goette, et al., Oxidative stress and microcirculatory flow abnormalities in the ventricles during atrial fibrillation, Front. Physiol. 3 (2012) 236.
[36] A.K. Doughan, D.G. Harrison, S.I. Dikalov, Molecular mechanisms of angiotensin II-mediated mitochondrial dysfunction: linking mitochondrial oxidative damage and vascular endothelial dysfunction, Circ. Res. 102 (4) (2008) 488–496.
[37] A. Oudot, et al., Angiotensin II activates NADPH oxidase in isolated rat hearts subjected to ischaemia-reperfusion, Eur. J. Pharmacol. 462 (1–3) (2003) 145–154.
[38] P. Piatti, et al., Acute intravenous L-arginine infusion decreases endothelin-1 levels and improves endothelial function in patients with angina pectoris and normal coronary arteriograms: correlation with asymmetric dimethylarginine levels, Circulation 107 (3) (2003) 429–436.
[39] J.-W. Chen, et al., Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X, Am. J. Cardiol. 90 (9) (2002) 974–982.
[40] K. Okyay, et al., Plasma asymmetric dimethylarginine and L-arginine levels in patients with cardiac syndrome X, Coron. Artery Dis. 18 (7) (2007) 539–544.
[41] N. Sen, et al., Carotid intima–media thickness in patients with cardiac syndrome X and its association with high circulating levels of asymmetric dimethylarginine, Atherosclerosis 204 (2) (2009) e82–e85.
[42] H. Cai, et al., Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation, Circulation 106 (22) (2002) 2854–2858.
[43] D. Nikitovic, et al., Plasma levels of nitrites/nitrates in patients with chronic atrial fibrillation are increased after electrical restoration of sinus rhythm, J. Interv. Card. Electrophysiol. 7 (2) (2002) 171–176.
[44] T. Minamino, et al., Plasma levels of nitrite/nitrate and platelet cGMP levels are decreased in patients with atrial fibrillation, Arterioscler. Thromb. Vasc. Biol. 17 (11) (1997) 3191–3195.
[45] J.C. Kaski, et al., Differential plasma endothelin levels in subgroups of patients with angina and angiographically normal coronary arteries, Am. Heart J. 136 (3) (1998) 412–417.
[46] J.C. Kaski, et al., Concentration of circulating plasma endothelin in patients with angina and normal coronary angiograms, Heart 74 (6) (1995) 620–624.
[47] G. Desideri, et al., Endothelial activation in patients with cardiac syndrome X, Circulation 102 (19) (2000) 2359–2364.
[48] S. Wu, et al., The association between plasma big endothelin-1 levels at admission and long-term outcomes in patients with atrial fibrillation, Atherosclerosis 272 (2018) 1–7.
[49] F. Mayyas, et al., Plasma endothelin-1 levels are increased in atrial fibrillation patients with hyperthyroidism, PLoS One 13 (12) (2018) (p. e0208206).
[50] S.Q. Lyu, et al., Plasma big endothelin-1 levels and long-term outcomes in patients with atrial fibrillation and acute coronary syndrome or undergoing percutaneous coronary intervention, Front. Cardiovasc. Med. 9 (2022) (p. 756082).
[51] G. Dixit, J. Blair, C. Ozcan, Plasma proteomic analysis of association between atrial fibrillation, coronary microvascular disease and heart failure, Am. J. Cardiovasc. Dis. 12 (2) (2022) 81–91.
[52] W. Zareba, A.J. Moss, S. le Cessie, Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease, Am. J. Cardiol. 74 (6) (1994) 550–553.
[53] W. Grimm, et al., QT dispersion and arrhythmic events in idiopathic dilated cardiomyopathy, Am. J. Cardiol. 78 (4) (1996) 458–461.
[54] R.G. Tieleman, et al., Increased dispersion of refractoriness in the absence of QT prolongation in patients with mitral valve prolapse and ventricular arrhythmias, Br. Heart J. 73 (1) (1995) 37–40.
[55] S.H. Hohnloser, Effect of coronary ischemia on QT dispersion, Prog. Cardiovasc. Dis. 42 (5) (2000) 351–358.
[56] J.B. Conti, et al., QT dispersion is a marker for life-threatening ventricular arrhythmias after atrioventricular nodal ablation using radiofrequency energy, Am. J. Cardiol. 79 (10) (1997) 1412–1414.
[57] M.F. Lutfi, QT interval derived measurements in patients with cardiac syndrome X compared to coronary artery disease, Front. Physiol. 7 (2016) 422.
[58] L. Tomkiewicz-Pajak, et al., Changes in QT dispersion during the exercise test in women with syndrome X, Przegl. Lek. 58 (3) (2001) 117–119.
[59] G. Alıcı, et al., Measurement of the QT Dispersion in Patients with Cardiac Syndrome X for the Investigation of Ischemia as an Etiological Factor, 2011.
[60] S.C. Sporton, et al., Acute ischaemia: a dynamic influence on QT dispersion, Lancet 349 (9048) (1997) 306–309.
[61] U. Stierle, et al., Relation between QT dispersion and the extent of myocardial ischemia in patients with three-vessel coronary artery disease, Am. J. Cardiol. 81 (5) (1998) 564–568.
[62] J. Gao, et al., Global trends and frontiers in research on coronary microvascular dysfunction: a bibliometric analysis from 2002 to 2022, Eur. J. Med. Res. 27 (1) (2022) 233.
[63] J.D. Sara, et al., Coronary microvascular dysfunction is associated with baseline QTc prolongation amongst patients with chest pain and non-obstructive coronary artery disease, J. Electrocardiol. 49 (1) (2016) 87–93.
[64] R. Atak, et al., Effects of slow coronary artery flow on QT interval duration and dispersion, Ann. Noninvasive Electrocardiol. 8 (2) (2003) 107–111.
[65] M.Z. Karahan, et al., The effect of coronary slow flow on ventricular repolarization parameters, J. Electrocardiol. 78 (2023) 39–43.
[66] C.T. Kaya, et al., The relationship between angiotensin converting enzyme gene I/D polymorphism and QT dispersion in patients with hypertrophic cardiomyopathy, J. Renin-Angiotensin-Aldosterone Syst. 11 (3) (2010) 192–197.
[67] K.E. Bockstall, M.S. Link, A primer on arrhythmias in patients with hypertrophic cardiomyopathy, Curr. Cardiol. Rep. 14 (5) (2012) 552–562.
[68] H. Suzuki, et al., Small vessel pathology and coronary hemodynamics in patients with microvascular angina, Int. J. Cardiol. 43 (2) (1994) 139–150.
[69] S. Aguiar Rosa, et al., Coronary microvascular dysfunction in hypertrophic cardiomyopathy: pathophysiology, assessment, and clinical impact, Microcirculation 28 (1) (2021) (p. e12656).
[70] M.I. Bittencourt, et al., Role of myocardial fibrosis in hypertrophic cardiomyopathy: a systematic review and updated meta-analysis of risk markers for sudden death, Arq. Bras. Cardiol. 112 (3) (2019) 281–289.
[71] M. Refaat, et al., Electrocardiographic characteristics in right ventricular vs biventricular pacing in patients with paced right bundle-branch block QRS pattern, J. Electrocardiol. 44 (2) (2011) 289–295.
[72] S. Chakravarty, et al., Corrected QT in ventricular paced rhythms: what is the validation for commonly practiced assumptions? Cardiology 130 (4) (2015) 207–210.