

Gender differences in coronary functional abnormalities

Kensuke Nishimiya, Hiroaki Shimokawa

Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

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Summary. The ISCHEMIA trial demonstrated that coronary revascularization strategies may not necessarily improve the long-term prognosis of patients with obstructive coronary artery disease, suggesting the significance of the remaining coronary functional abnormalities. Recently, more attention has been paid to ischemia with no obstructive coronary artery (INOCA) disease, due to the poor prognosis as showed in several cohorts. Coronary microvascular dysfunction (CMD) and epicardial coronary spasm have been proposed as the main causes of INOCA. While gender difference was not significant in the prognosis of patients with epicardial spasm, a poor prognosis was identified in women with CMD. In the last decade, efforts have been made to clarify the connection between these coronary functional abnormalities and an impaired prognosis. In this article, we will briefly review the recent advances in gender medicine regarding coronary functional abnormalities, including CMD and epicardial spasm.

Key words. Coronary microvascular dysfunction, microvascular spasm, coronary artery spasm, vasospastic angina.

Differenze di genere nelle anomalie funzionali coronariche

Riassunto. Lo studio ISCHEMIA ha dimostrato che le strategie di rivascularizzazione coronarica non necessariamente migliorano la prognosi a lungo termine dei pazienti con malattia coronarica ostruttiva, suggerendo l'importanza delle anomalie funzionali coronariche. Recentemente è stata prestata maggiore attenzione all'ischemia con malattia coronarica non ostruttiva (INOCA) a causa della prognosi sfavorevole che ha dimostrato in diverse coorti di pazienti. La disfunzione microvascolare coronarica (CMD) e lo spasmo coronarico epicardico sono stati proposti come le principali cause di INOCA. Sebbene la differenza di genere non fosse significativa nella prognosi dei pazienti con spasmo epicardico, nelle donne con CMD è stata identificata una prognosi sfavorevole. Nell'ultimo decennio sono stati compiuti sforzi per chiarire la connessione tra le anomalie funzionali coronariche e una prognosi compromessa. In questo articolo esamineremo brevemente i recenti progressi nella medicina di genere per quanto riguarda le anomalie funzionali coronariche, tra cui CMD e spasmo epicardico.

Parole chiave. Disfunzione microvascolare coronarica, spasmo microvascolare, spasmo dell'arteria coronaria, angina vasospastica.

Introduction

Recently, the Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in Stable Angina (ORBITA)¹ and the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)² trials demonstrated that coronary revascularization strategies may not necessarily improve the clinical manifestations or the long-term prognosis of patients with stable obstructive coronary artery disease (CAD), thus suggesting the significance of the remaining coronary functional abnormalities. Another landmark study, the WISE (Women's Ischemia Syndrome Evaluation) trial, had previously reported that approximately 50-70% female patients with suspected angina had an angiographically insignificant coronary stenosis.³ This disorder, called ischemia with no obstructive coronary artery (INOCA), should be given much attention, because it has been emerging for the poor prognosis demonstrated in several cohorts.⁴⁻⁶ The WISE study estimated that at least 3-4 million patients in the USA are diagnosed with INOCA.^{3,4,7,8} Although multiple mechanisms may be involved in the pathogenesis of INOCA, coronary microvascular dysfunction (CMD) and epicardial coronary spasm are considered to be the leading causes of the disorder.⁹⁻¹³ In particular, CMD is more prevalent in women than in men, with poor clinical outcomes.¹³ In this article, we will briefly review the recent reports on the gender differences in coronary functional abnormalities (Figure).

Gender differences in CMD

Microvascular angina (MVA) is the term that is widely used to describe patients with symptomatic CMD.¹⁴ The consensus document by the Coronary Vasomotor Disorders International Study Group (COVADIS) proposed that MVA is diagnosed based on the following criteria:¹⁴ (1) presence of symptoms suggestive of myocardial ischemia; (2) objective documentation of myocardial ischemia by currently available techniques; (3) absence of obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve (FFR) >0.80), and (4) con-

firmation of a reduced coronary blood flow reserve and/or inducible microvascular spasm (MVS). CMD variably comprises several major pathophysiological mechanisms, including enhanced vascular smooth muscle contraction (MVS), impaired microvascular dilatation, and vascular remodeling associated with structural heart disease.^{10,15} MVS is diagnosed through the reproduction of angina symptoms accompanied by ischemic ECG changes, but with no epicardial spasm during spasm provocation testing.¹³ Additionally, interventional diagnostic approaches with coronary flow reserve (CFR, ≤ 2.0 or 2.5),¹⁶ index of microcirculatory resistance (IMR, >25),¹⁷ or thrombolysis in myocardial infarction frame count (TIMI frame count, >25)¹⁸ are also useful for making a diagnosis of CMD.

Gender differences in the epidemiology and prognosis of CMD

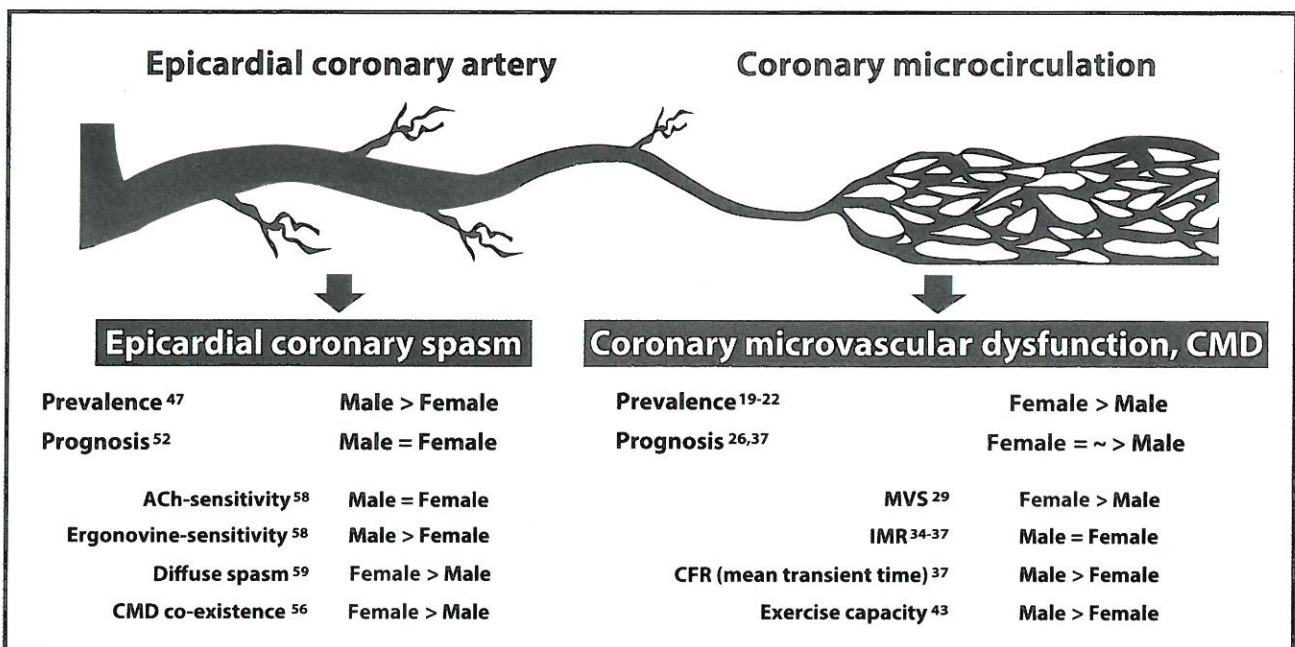
It has been consistently demonstrated that CMD is more prevalent in females than in males, especially in postmenopausal women (Figure).¹⁹⁻²¹ Indeed, in the Coronary Microvascular Angina (CorMicA) study, female sex was more correlated with CMD versus male [odds ratio, 2.7 (95% CI: 0.9-7.9)].²² In the WISE study, with a median of 5.4 follow-up years, CMD (determined by CFR <2.3) was closely associated with Major Adverse Cardiac Events (MACE), including hospitalization for acute coronary syndrome, heart failure, stroke, or cardiovascular death, with 53% of sudden cardiac death.³ Physiological levels of estradiol (E2) exert vasculoprotective and anti-inflam-

matory effects.²³ It has been speculated that women are closely associated with inflammatory markers [eg., high-sensitive c-reactive protein (hs-CRP)], and that inflammatory diseases occur more frequently in menopausal women than in men.²⁴ Sex differences in vasoreactivity to mental stress should also be mentioned. Peripheral vasoconstriction induced by a public speaking stressor is associated with stress-induced myocardial (microvascular) ischemia in women, but not in men.²⁵ Importantly, a positron emission tomography (PET) study showed that both sexes were at high risk for MACE (Figure).²⁶

In general, patients with MVA exhibit better angina summary score than those with vasospastic angina (VSA).²² Regarding the gender variation in the clinical presentation of CMD, young and middle-aged women are more likely to present with 'atypical' angina symptoms.²⁷ These atypical symptoms of MVA could occur at low heart rates, due to mental arousal or palpitation.¹⁰ Although known atherosclerotic risk factors, such as age, diabetes mellitus, hypertension, and dyslipidemia, have been identified as possible causes of CMD,^{11,12} these risk factors are not always predictive.²⁸ Thus, this point still remains to be addressed in future studies.

Heterogeneity of gender differences in the various diagnostic markers of CMD

Regarding the diagnosis of MVS during acetylcholine (ACh) provocation testing,¹⁴ Ong et al. found that the prevalence of female patients was higher in MVS than



Gender differences in coronary functional abnormalities are summarized. Female patients are more likely to have CMD and diffuse epicardial spasm. The prognostic effects of gender differences and the gender-specific treatment for coronary functional abnormalities remain to be elucidated. Numbers represent the corresponding reference numbers.

in VSA [169/205 (82%) in MVS vs 155/283 (55%) in VSA].²⁰ They also demonstrated that female sex was an independent predictor for MVS (OR = 4.2, 95% CI: 3.1-5.5, $p < 0.001$) (Figure).²⁹ In order to make a more precise diagnosis of MVS, we proposed to use the myocardial lactate extraction ratio, which can be calculated as the ratio of coronary arterial vs venous difference in lactate concentration to the arterial concentration during spasm provocative testing.^{9,30-32} In our study, female prevalence was comparable between non-MVS and MVS groups [50/132 (38%) vs 32/66 (49%) patients].³² Ethnicity may also be involved in the gender difference of the prevalence of MVS.

Physiological indexes, such as low CFR and high IMR, have been used as gold standards for the diagnosis of CMD (Figure).¹⁰⁻¹⁴ These indexes are measured in the left anterior descending coronary artery via inserted pressure/temperature sensor-mounted guide wire. Briefly, CFR is calculated using thermodilution as resting mean transit time divided by hyperemic mean transit time, whereas IMR is the product of distal coronary pressure at maximal hyperemia multiplied by the hyperemic mean transit time.³³ Ford et al. clearly demonstrated that female prevalence was higher in the MVA group based on the criteria of either CFR < 2 , IMR ≥ 25 or MVS for MVA [women, 61/78 (78%)].²² Kobayashi et al. reported that no gender difference was noted in IMR, whereas CFR was lower in women than in men (Figure).³⁴ Lee et al. reported that no remarkable gender difference was noted among 230 patients with intermediate coronary stenosis when sorting them into the quadrant according to CFR (a cut-off value of 2) and IMR (a cut-off value of 23).³⁵ We also demonstrated that, among INOCA patients, female sex was not a significant contributing factor to the presence of high IMR ≥ 18 , a prognostic marker for INOCA (OR = 0.51, 95% CI: 0.3-1.0 in the multivariable COX analysis).³⁶ A recent study by Chung et al. showed that, in patients deferred by FFR, CFR related to mean transit time was lower in women than in men, with no differences in IMR.³⁷ However, in this study, long-term clinical outcomes during a 5-year follow-up were better in women than in men (Figure).³⁷

PET allows the CFR quantification of myocardial blood flow (MBF, ml/min/g) of tissue both at rest and during maximal coronary vasodilatation.³⁸ Murthy et al. demonstrated that, among patients with no visual evidence of CAD, CMD determined by CFR < 2 on PET existed equally between men and women (51% and 54%), and showed no gender difference in the long-term prognosis.²⁶ Gupta et al. reported an interesting finding, namely that women were the majority of the discordant group with impaired CFR, but with preserved maximum MBF [608/873 (70%) patients].³⁹ They considered that this discordant group may be a target for the initiation of lifestyle or pharmacological preventive therapies, and

may aid the gender differences in the cardiovascular outcome.³⁹ Cardiac magnetic resonance (CMR) imaging could be an option for making the diagnosis of CMD in women, since it can prevent radiation exposure.⁴⁰

Gender differences in the treatment of CMD

Efforts to establish the optimal medical therapy for CMD have just begun, and several pharmacological strategies are under investigations. The currently proposed anti-anginal agents for CMD include β -blockers, calcium-channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers, nicorandil, ranolazine, ivabradine, and trimetazidine.¹¹ Among them, ACEi have been reported to improve CFR and angina frequency in female CMD patients.¹¹ Despite the high prevalence of menopausal women in CMD,⁴¹ the estrogen replacement therapy is not fully recommended for CMD, because it is possibly associated with increased risks of cardiovascular disease and breast cancer.⁴²

Female patients with INOCA have been reported to have impaired exercise capability (Figure). For instance, it was reported that peak VO_2 was lower in patients with CMD than in controls (17.3 vs 27.3 ml/kg/min).⁴³ Exercise and rehabilitation could improve the clinical manifestations in CMD patients. The COVADIS group started the international prospective cohort study for CMD patients.⁴⁴ This ongoing study is expected to provide novel robust evidence on gender differences in the ethnicity, clinical manifestations, and management of MVA patients in the near future.

Gender differences in vasospastic angina (VSA)

It has been believed for a long time that there are substantial ethnic differences in the prevalence of vasospastic angina (VSA) due to epicardial coronary artery spasm. Indeed, patients with acute myocardial infarction who were positive for spasm provocative testing were more common in Japan than among Caucasians (80% vs 37%).⁴⁵ However, recent studies demonstrated that such ethnic difference in the prevalence of VSA is much smaller than anticipated.^{46,47} In addition to CMD, this coronary functional abnormality by epicardial coronary spasm is important in order to better understand the pathogenesis of INOCA.

Gender differences in epidemiology and prognosis of VSA

A multicentre study conducted in Japan showed that 921 out of 2,251 angina patients were diagnosed with VSA.⁴⁸ In this study, patient distribution peaked at the age of 60-69, but was commonly documented in the under-60s.⁴⁸ Similar trends have been reported in the European

studies.^{29,49} We also have recently addressed this issue of ethnic difference in VSA.⁴⁷ Although female patients with VSA were not prevalent in both Japanese and Caucasians populations (13-22 %), the frequency of women was significantly higher among Caucasians than Japanese (Figure).⁴⁷ The Abnormal COronary VAsomotion (ACOVA) study reported that the epicardial spasm was more frequent in women than in men (77% vs 23%).⁴⁹ Similarly, Ford et al. reported that female patients with VSA accounted for 60%, while female sex was not a significant associate of VSA in multivariable analysis.²² However, in these studies, most of the participants were female, thus caution should be used when considering gender differences in VSA in the real world setting. Although the involvement of genetic factors in VSA is still being debated, Ong et al. reported that, among women with INOCA, a positive family history was more predominant in women than in men (61% vs 45%, $p = 0.0001$).⁵⁰ Furthermore, anginal symptoms of premenopausal female patients with VSA were closely associated with endogenous estrogen levels, where the frequency of angina attack peaked between late luteal and menstrual phases.⁵¹

Through the multicenter registry of the Japanese Coronary Spasm Association (JCSA), we demonstrated that no significant gender difference was noted in the 5-year MACE-free survival (Figure).⁵² We also reported that the hazard ratio of male sex was 1.1 (CI: 0.6-1.8, $p = 0.79$).⁵³ Furthermore, among female patients with VSA, the long-term prognosis was worst in the young female arm with a smoking behavior.⁵² These results indicate the importance of a gender-specific management of VSA. We also demonstrated that a Rho-kinase activity >1.2 could be a prognostic maker for VSA, for which a higher male prevalence was noted among patients with enhanced Rho-kinase activity.^{54,55} Most recently, we revealed that CMD co-existed especially in female VSA patients, a situation in which Rho-kinase activation may substantially be involved (Figure).⁵⁶

Gender differences in the spasm provocation testing of VSA

The Japanese Circulation Society (JCS) guidelines and the latest European consensus document highly recommend spasm provocation testing with ACh when a subject is negative for non-invasive VSA evaluation, but is still suspected to have coronary spasm based on symptoms.^{13,48} Ergonovine provocation testing is another option, when ACh is contraindicated due to comorbid bronchial asthma or severe atrioventricular conduction disorder.⁵⁷ Sueda et al. reported that female patients were unlikely to be sensitive to ergonovine (provocation rate; 96.7% with ACh vs 32.8% with ergonovine) (Figure).⁵⁸ Furthermore, Sato et al. reported that there was a distinct sex difference in the prevalence of diffuse/focal spasm;

60/33% in women vs 40/67% in male, respectively (Figure).⁵⁹ In the JCSA registry study, female sex was an independent factor for provocation testing related to ventricular arrhythmias.⁶⁰ Anatomical anomalies, especially myocardial bridging (MB),⁶¹ are the preferred site of epicardial coronary spasm. Although anatomical MB is more common in men than in women, there was no sex difference in functional abnormalities and flow disturbance due to MB.⁶²

Gender differences in the treatment of VSA

CCBs are the first-line therapy for VSA, since these drugs have been shown to markedly reduce angina symptom⁶³⁻⁶⁵ and suppress coronary spasm.^{63,64} CCBs have been an independent determinant for preventing MACE in VSA.^{63,64} The prognostic effects of nitrates on VSA remain unclear.⁶⁶ Although it has been considered that an insufficient medical therapy could result in a poorer prognosis in female patients, the recent JCSA registry study confirmed that the prescription of CCBs was adequately done in female VSA patients.⁵² The one-year follow-up result of the CorMicA study showed that the gender difference was unclear in the effectiveness of an optimized management for INOCA, based on the interventional diagnostic approaches.⁶⁷ We previously demonstrated that estrogen down-regulates the Rho-kinase activity,⁶⁸ a central molecular mechanism of coronary spasm.^{9,69} The JCS guidelines state that the estrogen replacement therapy is recommended in postmenopausal women as Class 2b.⁴⁸ Coronary plaque erosion has recently attracted more attention than ever before, because this phenomenon is the second leading cause of acute coronary syndrome (ACS),⁷⁰ for which epicardial coronary spasm could be a trigger.⁷¹ In an autopsy study, the prevalence of coronary erosion was higher than that of plaque rupture in female.⁷² Further studies are needed to address the underlying mechanism of this major subset of ACS.

Key messages

- Coronary microvascular dysfunction (CMD) and epicardial coronary spasm have been proposed as the main causes of INOCA.
- The prevalence of female patients is prominent in ischemia with no obstructive coronary artery (INOCA), particularly in CMD.
- There are plausible connections between gender differences and disease manifestations between CMD and epicardial coronary spasm.
- It is important to address gender differences in these coronary functional abnormalities in INOCA patients.

Conclusions

The prevalence of female patients is prominent in INOCA, particularly in CMD. There are plausible connections between gender differences and disease manifestations between CMD and epicardial coronary spasm. While seeking the perfect explanation of the mechanism and the optimization of the management of INOCA, it is important to address gender differences in these coronary functional abnormalities in INOCA patients. An international standardization strategy and expert consensus-based evidence are required for the promotion of women's cardiac health in the future.

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Correspondence to:

Hiroaki Shimokawa
Department of Cardiovascular Medicine
Tohoku University Graduate School of Medicine
1-1 Seiryomachi, Aoba, Sendai
980-8574 Japan
email shimo@cardio.med.tohoku.ac.jp