Research progress regarding the diagnosis and treatment of mental stress-induced myocardial ischemia

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Abstract

Myocardial ischemia resulting from psychological stress [mental stress-induced myocardial ischemia (MSIMI)] refers to the condition wherein psychosocial and psychological stimulations cause myocardial ischemia in patients with coronary heart disease, which is different from drug-induced myocardial ischemia. Therefore, this condition often escapes diagnosis, portends clinical risk, and affects the quality of life of MSIMI survivors. MSIMI is closely related to the poor prognosis of cardiovascular diseases, especially in young women, according to recent randomized, controlled trials (RCTs) on MSIMI. These RCTs involved different sample sizes, interventional measures, and detection techniques. Moreover, differences exist regarding the prevalence rate, distribution characteristics, possible pathogenesis, and clinical significance. Nevertheless, currently, the diagnostic criteria, pathogenesis, and treatment of MSIMI are still in the clinical exploration stage. Hence, considering recent RCTs, this paper summarizes the research status of MSIMI from the aspects of pathogenesis, diagnosis, and treatment strategies to provide a theoretical basis for the follow-up diagnostic methods and treatment guidelines for MSIMI. *(Anatol J Cardiol 2020; 24: 126-36)*
Keywords: mental stress-induced myocardial ischemia, diagnosis, treatment, review

Introduction

Mental stress-induced myocardial ischemia (MSIMI) is a transient myocardial ischemic response to mental stress (1) that can be induced in patients with coronary artery disease (CAD) during a standardized mental stress challenge (2). Notably, patients with CAD are more likely to develop MSIMI under the influence of factors, such as age, sex, and psychosocial characteristics,. Several randomized controlled trials (RCTs) have proven that MSIMI can increase the incidence of adverse cardiovascular events (3). A study by Jiang et al. (4) enrolled patients with CAD with standardized mental stress and revealed that the incidence of MSIMI is as high as 30%–40%. In addition, it has long been confirmed by Sheps et al. (5) that MSIMI has a twofold increased risk of a combined end point of cardiac events or total mortality. Furthermore, the large INTERHEART study performed comprehensive measurements of psychosocial distress and revealed that its attributable risk in women with acute myocardial infarction is 40%, whereas that for men is only 25% (6). Sun et al. (7) demonstrated that the prevalence of MSIMI in patients with ischemic heart disease is as high as 70%. Moreover, for every 5% decrease in left ventricular ejection fraction, the incidence of future adverse cardiovascular events increases by 20% within 6 years, and the risk of mortality associated with cardiac events is tripled. Notably, MSIMI not only affects the quality of life of patients but also leads to the deterioration of clinical prognosis and an increased risk of death. Based on recent RCTs, this paper summarizes the current status and progress of MSIMI research regarding the pathogenesis, diagnosis, and treatment strategies to provide a theoretical basis for the follow-up diagnostic methods and treatment guidelines for MSIMI.

Epidemiological investigation

The most common clinical risk factors for CAD are smoking, hypertension, and hyperlipidemia, but some studies have noted that patients' mental stressors, such as anxiety, depression, anger, hostility, type A personality, and social pressure, are closely related to CAD. Recent RCTs basically considered the psychological stress of public speaking for research. However, after continuous improvements and updates, research was expanded to include subjects with ischemic heart disease (IHD). In addition, some RCTs were based on sex differences, enrolling

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Accepted Date: 11.05.2020 **Available Online Date:** 15.07.2020

DOI:10.14744/AnatolJCardiol.2020.69447

subjects with anxiety and depression who were administered drugs to interfere with MSIMI. The following is a summary of innovations regarding the prevalence and characteristics of the disease. The main content of this article is illustrated in Figure 1, and the relevant RCT content is presented in Table 1.

1. The reduction of left ventricular ejection fraction (LVEF) positively correlated with the risk of future cardiovascular events (death and hospitalization rate) (7).
2. The incidence of MSIMI after myocardial infarction in young women was twice as high as that in men. Moreover, MSIMI occurred easily in women with microvascular lesions. Therefore, hemodynamic and vasoconstrictive responses to mental stress can help predict the risk of MSIMI in patients with CAD (8).
3. The methods to test stress or assess myocardial ischemia are the same, but the prevalence results are different.
4. An acute increase in inflammatory markers was observed during mental stress, but this was unrelated to the occurrence of MSIMI, either at rest or during exercise (9).
5. Women and men have different cardiovascular response mechanisms to MSIMI (10).
6. A correlation was observed between depression and MSIMI, with an increase in depression causing an increase in adverse cardiovascular events (11).
7. CAD severity is related to MSIMI in men, but not in women (12).

Pathological mechanism

Most scientists argue that the pathological mechanism of MSIMI involves sympathetic activity, hemodynamics, microvascular dysfunction, and endothelial dysfunction. The mechanisms deduced by previous studies were further verified and complemented by recent studies. In addition, some RCTs mentioned the possible pathological mechanism of mitochondrial metabolism and inflammatory factors.

Initiation of neuroendocrine regulation mechanism

Patients with MSIMI lack channels to relieve mental stress, which can easily lead to stress accumulation, abnormal body regulation, and occurrence of diseases. Several studies have confirmed that depression, anxiety, and other adverse mental disorders increase the risk of CAD (13-15). Every individual is affected by various social and psychological pressures, but only some, especially young women, are prone to MSIMI. During psychological stress, the cerebral cortex sends messages to the upper brainstem, hypothalamus, and limbic system, and then acts on the hypothalamus-pituitary-adrenal cortex axis, sympathetic-adrenal medullary axis, and adrenal-angiotensin-aldosterone system to produce catecholamines. The secretion of catecholamines increases after repeated or sustained psychological stress. Studies have revealed that patients with certain β1 receptors or serotonin receptors are more sensitive to stress (16). In addition to a patient's susceptibility, the prevalence of MSIMI varies with the type and duration of stress (15). In summary, the sympathetic activity after mental stress could be related to myocardial ischemia.

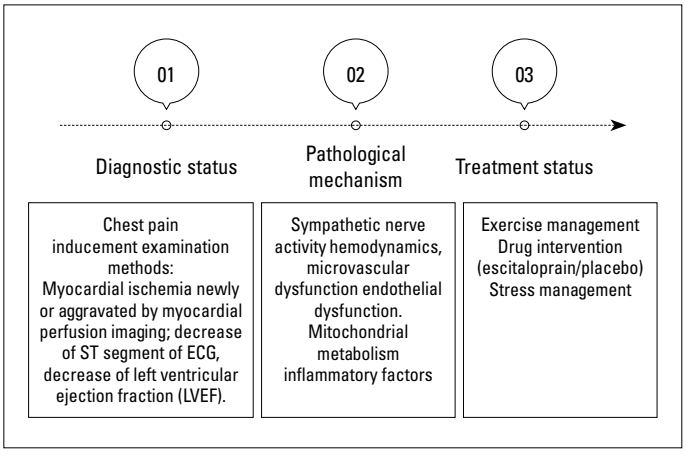

Figure 1. The main content of this article

Sympathetic activity

When sympathetic nerve is excited, the increased secretion of catecholamines and other substances can induce changes in heart rate, blood pressure, vasoconstriction, and vascular resistance. For example, people with depression have a more sensitive sympathetic response, which virtually increases the risk factors for cardiovascular diseases. The stimulation of sympathetic nerve accelerates the process of atherosclerosis, plaque rupture, spasm, and ischemia in coronary arteries by increasing α-2 receptor and TNF-α, releasing endothelin-1 macrophages, and promoting vasoconstriction and pro-inflammatory responses. Ramadan et al. (15) believed that the occurrence of MSIMI is related to the vasoconstriction caused by sympathetic nerve excitation (17). Moreover, under pressure, the activities of cortisol and corticotropin that regulate platelet function play more specific functions like increasing the blood pressure and modulating inflammation. Some studies have unveiled that the release of these hormones change the level of troponin T accumulated at the points of vascular calcification, thereby playing a part in myocardial injury. Hence, the activity of sympathetic nerve increases the occurrence of MSIMI (18). Overall, vasoconstriction and inflammation caused by strengthened sympathetic activity are involved in the pathological mechanisms of MSIMI. The main content of sympathetic activity is presented in Figure 2.

Hemodynamics changes

Hemodynamics reflects the relationship among oxygen consumption, cardiac output, and arterial oxygen content. Notably, hemodynamic changes involve several aspects, such as cardiac output, heart rate, blood pressure, and peripheral vascular resistance. Hammadah et al. (13) evaluated 695 patients with CAD for increases in heart rate, blood pressure, and catecholamine. However, no significant increases in blood pressure and heart rate were observed in the MSIMI group, whereas the ejection fraction was noted to be decreased markedly, without distinct clinical symptoms of MSIMI (19). Therefore, it was suggested that unlike

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DOI:10.14744/AnatolJCardiol.2020.69447

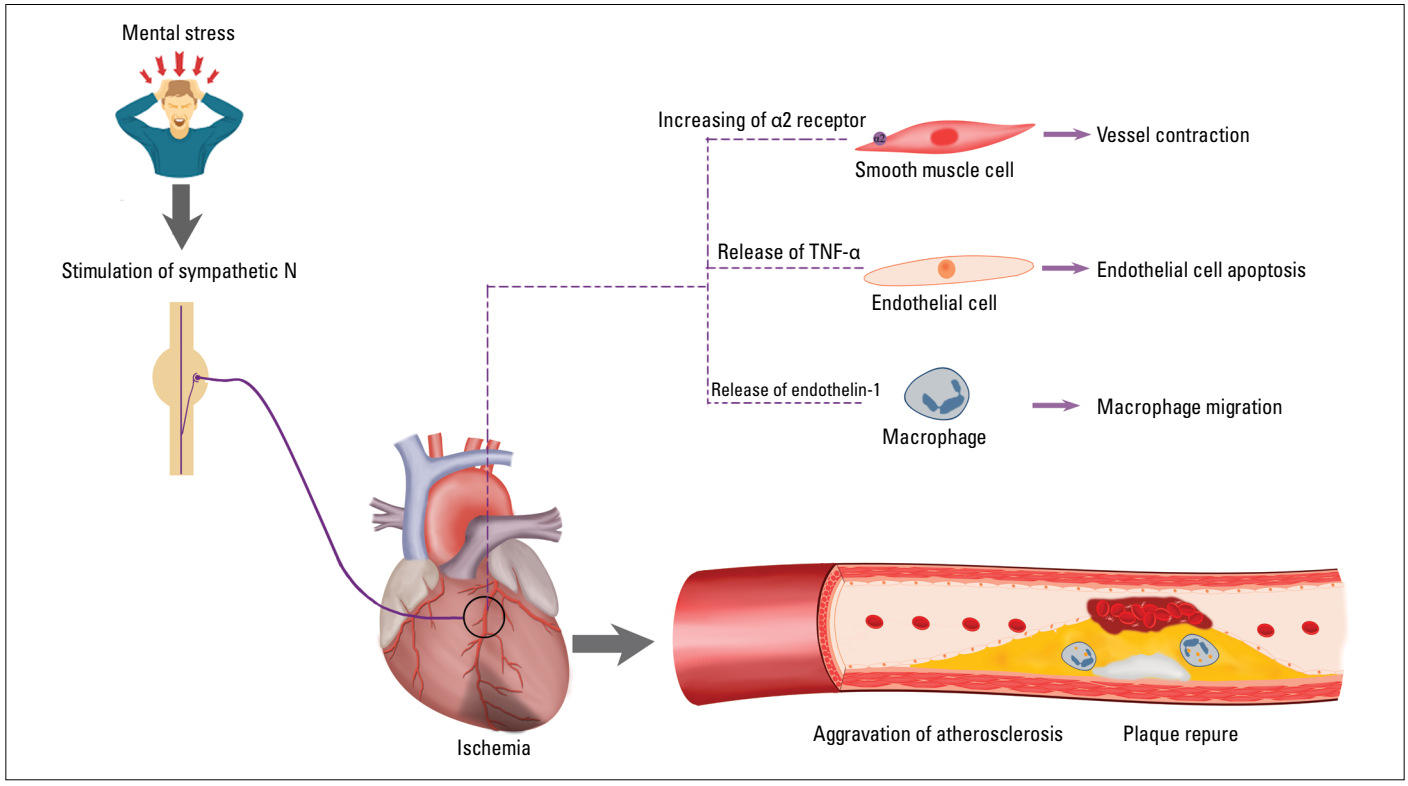

Figure 2. The main content of sympathetic activity

the underlying mechanism of exercise stress-induced myocardial ischemia (ESIMI), MSIMI does not exhibit a typical hemodynamic response, and the proportion of oxygen demand imbalance was small (20). Ramadan et al. (15) observed no imparity in rate-pressure product (RPP) between the MSIMI and ESIMI groups, but the heart rate and diastolic blood pressure were distinct in the ESIMI group, which enhanced the risk of cardiovascular diseases. Hammadah et al. (9) conducted stress tests on 660 patients with CAD and discovered that under psychological stress, a visible increase in RPP (heart rate×systolic blood pressure) and epinephrine were observed, whereas the endothelium-dependent flow-mediated dilation (FMD) and the ratio of peripheral arterial tonometry (PAT) diminished. Compared with the traditional stress group, the RPP value and PAT ratio in 106 patients with MSIMI were altered with mental stress. These findings suggested that people with MSIMI had higher hemodynamic and digital vasoconstrictive responses, and those sensitive to the changes in RPP value and PAT ratio had a higher risk of MSIMI (21). This possibility could be because the mental stress activates the sympathetic nervous system, leading to hemodynamic changes and vasoconstriction. Therefore, hemodynamic changes may not be the primary pathological mechanism of MSIMI, but could be considered a risk factor for predicting MSIMI (22).

Endothelial injury and dysfunction

The main features of endothelial dysfunction are impaired vasodilation, inhibition of platelet aggregation, and thrombosis. Endothelial cells can constrict blood vessels (8, 5). Under mental stress, increased microvascular resistance results in vascular stenosis and decreased perfusion, resulting in myocardial ischemia. On the other hand, microvascular resistance weakens the vasodilation promoted by β_2, which leads to coronary insufficiency. Moreover, the enhancement in systemic vascular resistance strengthens the afterload and myocardial oxygen supply and demand. The release of stress hormones, such as glucocorticoids, pro-inflammatory cytokines, and endothelin-1, as well as the activity of catecholamine lead to an increase in blood pressure and a reduction in nitric oxide production (5). Eventually, vasodilation is hindered and thrombosis is accelerated. Sun et al. (7) scientists determined that LVEF decreased significantly in patients with MSIMI because of the increased vascular resistance under mental stress, abnormal coronary perfusion, and comprehensive reactions, such as pro-inflammatory reaction, platelet aggregation, and increased blood viscosity (23, 24). Jiang et al. (25) detected increased platelet aggregation in patients with MSIMI, which might be related to the activities of collagen, epinephrine, serotonin, and adenosine diphosphate under stress. In conclusion, endothelial dysfunction is one of the pathological mechanisms of MSIMI, and the decrease in LVEF can be used as a diagnostic index of MSIMI.

Microvascular system lesions

Ramadan et al. (15) discovered that the occurrence of MSIMI is not related to the severity of vascular occlusion, but is mainly related to myocardial ischemia caused by microvasoconstriction. This finding is because of the numerous endothelin and catecholamines in cardiomyocytes that are related to vasocon-

striction and play a role in regulating vascular tension by acting on the microvascular system. For example, serotonin, as a vasoconstrictor, can stimulate myocardial arterioles to regulate the capillary flow, thereby slowing down the blood flow (26). Therefore, MSIMI may exhibit transient atypical symptoms.

On the other hand, sympathetic excitement under mental stress causes the adrenal gland of the neuroendocrine system to secrete catecholamines. Epinephrine induces myocardial relaxation by activating stimulative G-protein signaling pathway to bind to myocardial β2 receptor. Upon activating adenylate cyclase, β1-adrenergic receptor activates the calcium channel of myocardial membrane, leading to the enhancement of myocardial contractility and heart rate, and eventually resulting in ischemia because of insufficient diastolic period of coronary artery. Norepinephrine can induce spasm or contraction of peripheral microvascular arteries by activating α-1 adrenergic receptors, and endothelin ET-1-dependent pathway could also be involved in it. Notably, being an endogenous vasoconstrictor, endothelin can maintain the balance and stability of vascular tension. Moreover, myocardial tissue contains abundant endothelial cells. Increased catecholamine activity and angiotensin promote the synthesis and release of endothelin-1, which causes myocardial microvascular contraction. The main content of microvascular system lesions is illustrated in Figure 3.

Evaluation of peripheral vascular function involves digital blood flow, endothelial function, and the measurement of arterial stiffness. The microvascular blood flow PAT, brachial artery FMD, and reactive hyperemia index (RHI) are measured using pulsatile arterial manometry, and arterial stiffness evaluated using SphygmoCor system. Vaccarino et al. (27) observed that under mental and traditional stresses, no intergroup sex-related differences were noted regarding FMD, with RHI of females lower than that of males, thereby indicating the slowing down of peripheral microvascular blood flow. On the other hand, the PAT ratio was higher in females than that in males, indicating its correlation with peripheral vasoconstriction, as well as highlighting the different mechanisms in females and males related to MSIMI. In summary, the mechanism of MSIMI is related to microvascular dysfunction and stress peripheral vasoconstriction in females, rather than increasing hemodynamic workload. Moreover, females have a higher probability of MSIMI (27). Some studies suggested that the mechanism of myocardial ischemia in males depended on hemodynamic changes, but some argued against a correlation.

Other theories

Dorn G and other scientists believed that mitochondria protect cardiomyocytes, and therefore, mitochondrial damage is

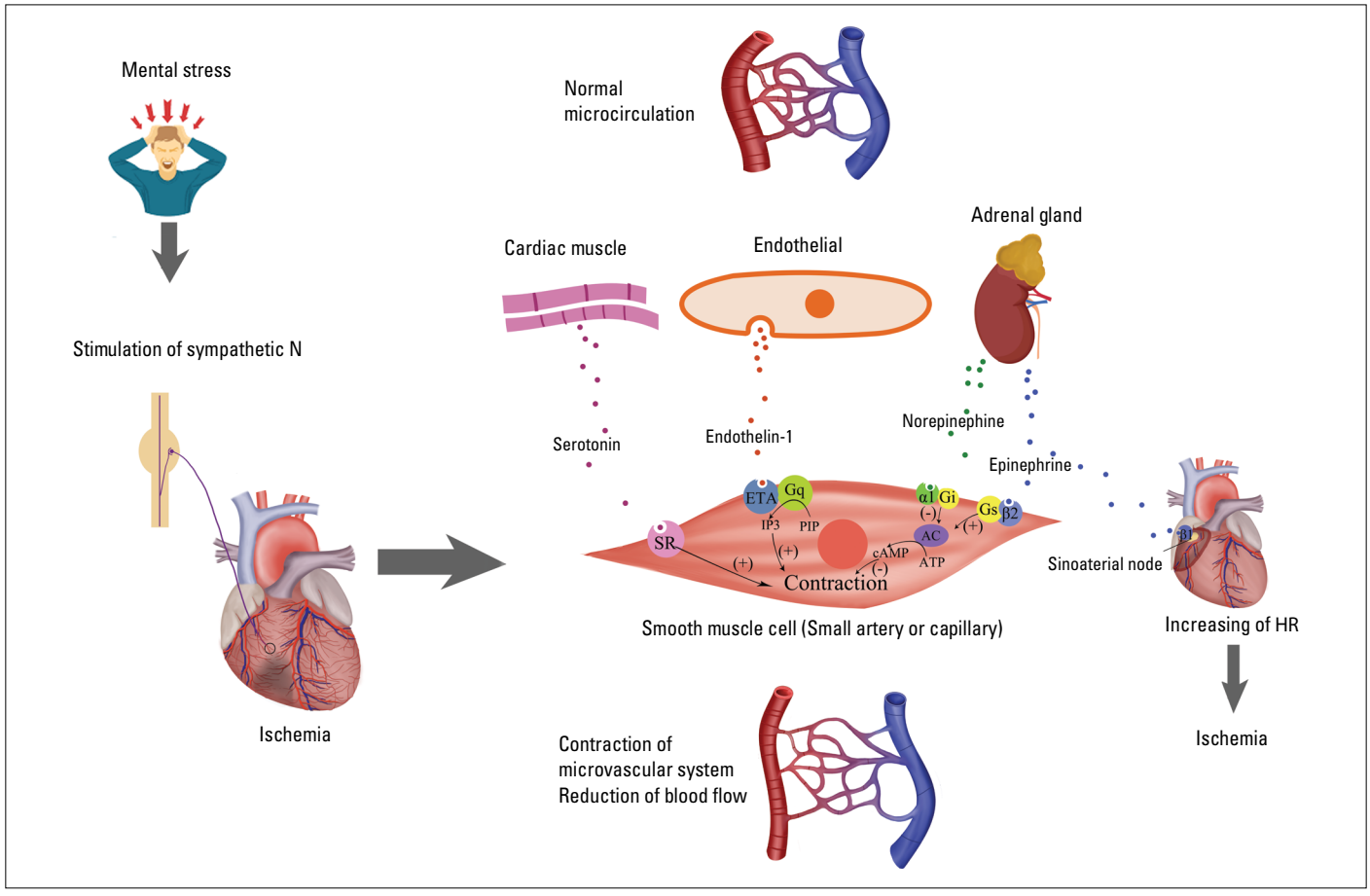

Figure 3. The main content of microvascular system lesions is illustrated

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DOI:10.14744/AnatolJCardiol.2020.69447

Table 1. Summary of randomized, controlled trials

Author	Design/examination methods	Findings
Wei et al. 2014 (3)	A meta-analysis of five cohort studies of patients with CAD was performed to investigate the relationship between MSIMI incidence and cardiovascular end-point events/radionuclide ventriculography/wall motion abnormalities during mental stress, or a reduction in left ventricular ejection fraction	There was a two-fold risk of cardiac events or total mortality among patients with CAD with MSIMI (RR: 2.24, 95% CI: 1.59, 3.15)
Sun et al. 2017 (7)	371 patients with IHD on escitalopram treatment underwent mental stress test and exercise stress test, followed up for 4 years on MACE/assessed for left ventricular wall motion by using 16-segment model/worsening of any wall motion abnormality (WMA), reduction of LVEF ≥8%, or ischemic ST-segment change ≥1mm	The incidence of MACE in MSIMI group was 9.85% higher than those without (*P*=0.08). All-cause mortality was 7.46% with MSIMI and 7.14% with ESIMI (*P*=0.19).
Vaccarino et al. 2018 (27)	Randomized controlled trial of 306 patients with ≤8 months MI and 112 community controls/endothelium-dependent FMD, microvascular reactivity (RHI), digital vasomotor response (PAT), 99mTc-sestamibi myocardial perfusion imaging	Women with post-MI have a two-fold increase of developing MSIMI compared with men. After including resting RPP and resting RHI to the model, the odds ratio (OR) of MSIMI for women compared with men was 2.6 (95% CI, 1.3–5.4). Adding resting FMD to the model did not change the results (OR, 2.6; 95% CI, 1.3–5.3).
Hammadah et al. 2017 (8)	660 CAD patients with speech task and with exercise/pharmacological stress, assess hemodynamic, neuro-hormonal, endothelial, vasomotor and vascular predictors of MSIMI at rest and 30-min after mental stress/99mTc sestamibi myocardial perfusion imaging, FMD, RHI, arterial stiffness (PWV)	106 (16.1%) developed MSIMI and 229 (34.7%) had conventional stress-induced myocardial ischemia (CSIMI). Patients with MSIMI had a 3%, 6%, 5%, and 11% (all *P*<0.05) higher SBP, DBP, HR, and RPP responses to mental stress.
Hammadah et al. 2018 (9)	IL-6, MCP-1, MMP-9, and hsCRP Pci were measured in 607 patients with CAD. MSIMI was determined as impaired myocardial perfusion using a 17-segment model.	Mental stress resulted in a significant increase in levels of IL-6 [33.4%, *P*=<0.0001], MCP-1 [7.2%, *P*=<0.0001], MMP-9 [13.0%, *P*=<0.0001], but a significant decrease in hsCRP [–3.5%, *P*=0.03].
Sullivan et al. 2018 (10)	RPP response and peripheral vasoconstriction by PAT assessed by a cohort study of 678 patients with coronary artery disease underwent myocardial perfusion imaging/MSIMI was defined as percent of left ventricle (LV) that was ischemic and as a dichotomous variable.	Women with MSIMI had a significantly lower PAT ratio (denoting greater vasoconstriction) than women without MSIMI (0.5 vs. 0.8), In adjusted linear regression, each 1,000-unit increase in RPP response was associated with 0.32% (95% CI: 0.22, 0.42) increase in inducible ischemia among men, whereas each 0.10-unit decrease in PAT ratio was associated with 0.23% (95% CI: 0.11, 0.35) increase in inducible myocardial ischemia among women.
Jiang et al. 2015 (17)	Experimental research examining mechanisms of the adverse interplay between mind and heart has led to the discovery of mental stress-induced cardiac dysfunction or myocardial ischemia (MSIMI).	Clinical significance, mechanisms (resting LV dysfunction, peripheral artery resistance, platelet aggregation, and certain metabolites in peripheral blood), effective therapeutics, clinical application

Table 1. Cont.

Author	Design/examination methods	Findings
Almuwaqqat et al. 2019 (12)	276 patients with myocardial infarction underwent myocardial perfusion imaging with mental stress to quantify CAD severity	CAD severity is related to MSIMI in men but not women.
Hammadah et al. 2017 (13)	Psychological stress test and myocardial perfusion were performed on 695 patients with CAD to observe the incidence of adverse events in the next 2 years by measuring digital microvascular flow, endothelial function, arterial stiffness, and blood sample collections indicators.	The prevalence of MSIMI and CSIMI are 16.1% and 34.7%, respectively. Significant increases in epinephrine levels were observed with a median (interquartile) change of 77 (13%–160%). In contrast, norepinephrine levels decreased slightly after mental stress with a median (interquartile) change of −0.02 (−0.17%–0.16%).
Allgulander 2016 (23)	This review examines the possible mechanisms of anxiety in cardiovascular disease.	Anxiety alone or through depression becomes the chief culprit in increasing cardiovascular risk.
Tolentino et al. 2016 (40)	Stress tests were performed on 210 adult patients with IHD using GWBS and depression scale (CES-D) records to assess the effect of stress-induced myocardial ischemia	MSIMI present in 92 (43.8%) and ESIMI present in 64 (30.5%). There was a significant inverse correlation between GWBS-PE (positive emotion subscale) scores and probability of ESIMI (OR=0.55 (95%CI 0.36–0.83), *P*=0.005)
Vaccarino et al. 2016 (36)	Stress tests and myocardial perfusion imaging were performed on 686 patients with CHD to observe sex differences in MSIMI.	Younger women, especially those ≤50 years. The incidence of MSIMI in this group was over three-fold higher than their male counterparts and was also higher than older women and men.

CAD - coronary artery disease; CI - confidence interval; OR - odds ratio; RR - relative risk; Tc - technetium; Tn - troponin; IHD - stable ischemic heart disease; MACE - major adverse cardiovascular event; MSIMI - mental stress-induced myocardial ischemia; FMD - flow-mediated dilation; RHI - reactive hyperemia index; PAT - peripheral arterial tonometry; PWV - pulse wave velocity; IL-6 - interleukin-6; MCP-1 - monocyte chemoattractant protein-1; MMP-9 - matrix metallopeptidase 9; hsCRP - high-sensitivity C-reactive protein; RPP - rate-pressure product; CSMI - conventional stress testing for myocardial ischemia; CHD - coronary heart disease; CES-D - the Center for Epidemiologic Studies Depression Scale; GWBS - General Well-Being Schedule

the cornerstone of cardiomyocyte ischemia. For example, some studies have suggested that several biochemical substances, such as kynurenine, N-acetylserotonin, and tyrosine are produced when left ventricular dysfunction occurs under mental stress, which could be related to mitochondrial function (28, 29). Hammadah et al. (9) evaluated 607 patients with CAD and noted that, regardless of MSIMI occurrence, inflammatory markers, including interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and matrix metallopeptidase 9 (MMP-9) were elevated. This finding proves that increases in inflammatory factors are not specified in MSIMI.

Rooks et al. (30) believed that a relationship existed between MSIMI and prognostic cardiovascular events. On the one hand, it was related to vascular tension. In other words, under mental stress, vascular endothelial dysfunction promotes peripheral vascular dilatation and coronary vasoconstriction, with an increase in blood pressure and heart rate, resulting in an imbalance between myocardial oxygen supply and demand (31). On the other hand, it is also considered to be associated with increased catecholamine secretion and hemodynamic changes (32). The hemodynamic mechanism of MSIMI could be similar to that of MI induced by physical stress, but ESIMI is not related to the secretion of catecholamine, and the peripheral vascular resistance is lessened (23). Because MSIMI can enhance the peripheral vascular resistance and abnormal myocardial perfusion, as well as promote platelet adhesion and aggregation, change coagulation status, and enhance inflammatory responses, it is associated with an increased risk of cardiovascular events in the future. Notably, MSIMI in female patients is mainly related to microvascular dysfunction.

Diagnostic status

According to the results of RCTs, most patients with MSIMI had left ventricular dysfunction, as well as abnormal wall motion and myocardial perfusion. Moreover, these patients were noted to have less chest pain and myocardial ischemic changes

Anatol J Cardiol 2020; 24: 126-36
DOI:10.14744/AnatolJCardiol.2020.69447

on electrocardiography (ECG). Hassan et al. (19) noted that 11% of patients only had MSIMI, without ESIMI, which indicated that they had different myocardial ischemia pathogenesis. The etiology of ESIMI involves visceral stenosis that hinders the increased demand of myocardial blood supply, thereby causing myocardial supply imbalance and ischemia. Some studies have analyzed that the pathological mechanism of MSIMI entails the enhanced vasoconstriction and insufficient dilation of the microcirculatory system rather than coronary artery occlusion (33). In other words, MSIMI is related to vasoconstriction and abnormal vascular movement of coronary artery under mental stress, such as endothelial function and autonomic nerve function. Therefore, it is necessary to study the diagnosis of MSIMI from the aspects of left ventricular wall motion, ejection fraction, and myocardial perfusion imaging. The main content of diagnostic status is illustrated in Figure 4.

Coronary angiography

The degree of coronary artery stenosis detected using coronary angiography is the gold standard for the diagnosis of CAD. Clinically, some patients had transient chest tightness and chest pain under mental stress, but the results of coronary angiography were negative. Based on previous studies, MSIMI may occur in patients with CAD with clear evidence of coronary angiographic obstruction, or in patients with CAD without evidence of coronary stenosis (34). Jain D and other researchers have revealed that patients with MSIMI have no obvious chest pain, and no ischemic changes in the ST segment are detected on routine ECG, thereby indicating that MSIMI could be caused by changes in the microvascular system (35). Notably, patients with no obstruction have slow blood flow and shallow intraluminal pressure, revealing a punctate ischemic distribution, with the vasoconstriction more obvious in female patients. Even though no changes in coronary artery structure is observed, the risk of future cardiovascular events is high (36). The ESC guidelines in 2013 suggested that in addition to coronary artery stenosis, CAD is also related to chest pain caused by microcirculatory disorders or coronary spasm (1).

Echocardiography

Echocardiographic assessment of ventricular function could accurately measure myocardial ischemic flow, such as wall motion and LVEF. The left ventricular wall motion was determined using echocardiography with the 16-segment model recommended by the American Association of Cardiac Echocardiography involving 30–40 frames contraction of the cardiac cycle. The echo image, LVEF, and ECG were performed at rest, under mental stress, and after stress, respectively. MSIMI is defined

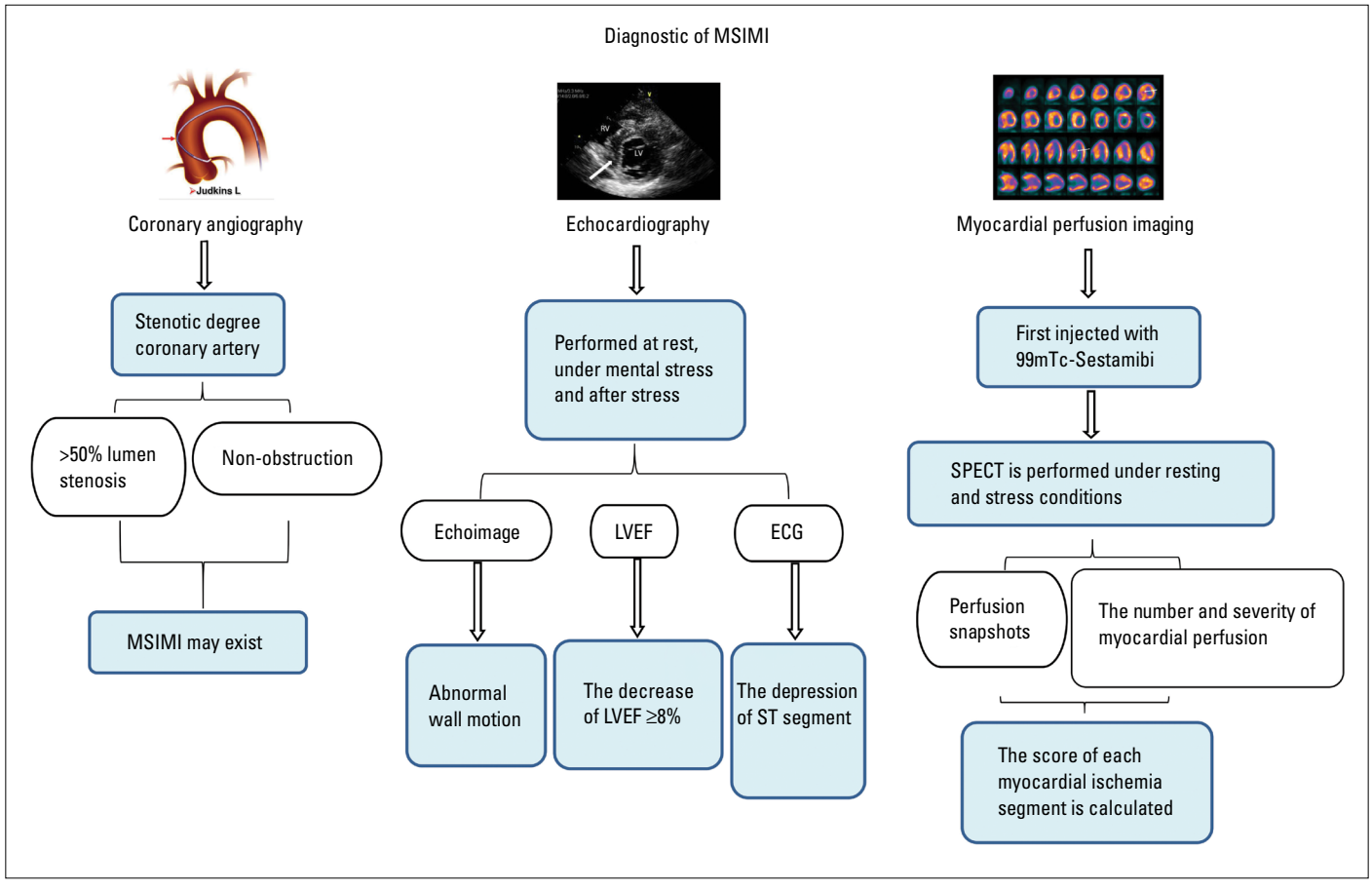

Figure 4. The main content of diagnostic status is illustrated

as abnormal wall motion under psychological stress, a decrease in LVEF ≥8%, a 1-mm in ST segment depression in more than two leads of ECG, and the dynamic evolution of ST segment three times in a row.

In 2013, Boyle et al. (37) adopted left ventricular dysfunction as the basis for the diagnosis of MSIMI. In 2007, Sun et al. (7) defined MSIMI as abnormal ventricular wall motion (16-segment model recommended by American Echocardiography Association for echocardiographic evaluation), LVEF diminished by more than 8%, and changes in the ST segment on ECG. Some researchers have discovered that the incidence of adverse cardiovascular events in patients with left ventricular dysfunction under mental stress is three times higher than that in patients without left ventricular dysfunction, although MSIMI can be evaluated based on left ventricular function. In addition, the study discovered that the reduction of LVEF under mental stress was significant than that observed in ESIMI, and for every 5% decrease in LVEF, the predicted incidence of major adverse cardiovascular event (MACE) increased by 5% in 4 years. In addition, the decrease of LVEF is related to the increase of peripheral vascular resistance. Yeung et al. (7) observed that MSIMI occurs in subendocardial and middle wall regions, which correlates with left ventricular dysfunction prompted by microvascular insufficiency. Therefore, reduced LVEF can be used as an independent predictor of MACE in patients with IHD.

However, there are differences in the criteria for myocardial ischemia in the previous RCTs of MSIMI. The cases diagnosed based on changes in left ventricular function are not considered true myocardial ischemia because mental stress can fortify peripheral vascular resistance, and then increase afterload, resulting in the reduction of left ventricular function. This kind of increased left ventricular pressure cannot represent decreased myocardial blood flow. Follow-up studies noticed that myocardial oxygen consumption and exercise load at the onset of MSIMI were apparently lower than those observed in ESIMI. This finding is associated with the increases in peripheral vascular resistance and the decreases in cardiac output and stroke volume under mental stress. Deanfield et al. (38) observed a significant reduction in myocardial blood flow during the process of mental arithmetic. Microvascular contraction under mental stress could be a dynamic process of coronary artery occlusion, and thus, the measurement of left ventricular dysfunction is not as accurate as myocardial perfusion imaging (MPI).

Myocardial perfusion imaging

MPI refers to a method of obtaining perfusion imaging through radioisotopes injected into cardiomyocytes, which is recommended as the gold standard for the assessment of myocardial ischemia by American College of Cardiology (19). Krantz et al. (33) argued that myocardial ischemia can be detected more precisely by using MPI than based on changes of left ventricular function (4). Typically, the subjects stop taking anti-myocardial ischemia drugs 24 hours before the test. A minute after the start of the stress test, they are first injected with 99mTc-sestamibi (radioisotope). Single photon emission computed tomography (SPECT) is then performed under resting and stress conditions to capture the perfusion snapshots. Myocardial perfusion damage is evaluated using a 17-segment model and the number and severity of myocardial perfusion defects under resting and stress images are compared. The score of each myocardial ischemia segment is calculated. If the score of any segment is ≥2, it represents a new perfusion abnormality. If the score of a single segment is ≥2 or the score of two consecutive segments is ≥1, it represents deterioration of original lesions. Both these are defined as the diagnostic criteria of MSIMI.

Most RCTs rely on MPI for the diagnosis of MSIMI with or without new or aggravated myocardial ischemia. For example, Vaccarino et al. (36) performed MPI by injecting 99mTc-sestamibi, and defined MSIMI in case of the sum difference of myocardial ischemia greater than or equal to 3 and the number of ischemic segments (8). Hammadah et al. (10) made patients undergo three SPECTs and used a 17-segment model to diagnose myocardial ischemia by comparing the number and severity of perfusion defects. Presently, MPI is used as the diagnostic standard of MSIMI in numerous studies. Even though the method of evaluating the ischemic segment varies, it will be constantly updated with the future advancements in detection technology.

Treatment status

Based on the pathological mechanism, interventional measures, and meaningful experimental conclusions summarized by RCTs at present, the treatment modalities involve a combination of exercise, medicine, smoking cessation, and psychological prescription besides the five major goals of cardiac rehabilitation. Notably, MSIMI can be treated based on the following three aspects: drug intervention, exercise management, and stress management.

Drug intervention

Provided the medications for CAD, including anticoagulation, antiplatelets, and modulating drugs, are standardized, the current drug treatments for MSIMI include selective serotonin reuptake inhibitors and benzodiazepines (26). At present, the most widely used drug per the RCTs is escitalopram-a serotonin reuptake inhibitor. Jiang et al. (39) determined that after treating patients in the experimental group with escitalopram for 6 weeks, the incidence of MSIMI was significantly reduced. Sun et al. (7) randomly treated 127 patients with MSIMI using escitalopram or placebo for 6 weeks and observed that the recurrence rate of MSIMI in the experimental group was two times lower than that in the control group. Escitalopram is thought to improve the symptoms of CAD by regulating the transport quantity and binding affinity of platelet serotonin receptors, thereby reducing short-term cardiovascular disease risk by adjusting negative mood. Tolentino et al. (40) reported a patient who had MSIMI and acute coronary syndrome complicated by generalized anxi-

Anatol J Cardiol 2020; 24: 126-36
DOI:10.14744/AnatolJCardiol.2020.69447

ety disorder (GAD). When MSIMI occurred, the LVEF decreased by 10%. The patient was then administered escitalopram 10 mg daily. Upon follow-up a year later, the patient's anxiety symptoms had improved and there was no angina pectoris. Escitalopram has been proven to be effective in reducing the occurrence of MSIMI (40). Furthermore, Sullivan et al. (10) evaluated the pathogenesis of MSIMI in 678 patients with CAD, and deduced that MSIMI in females is related to vasoconstriction and microcirculation disorders, and therefore, in addition to escitalopram, α- and β-receptor blockers could be considered as therapeutic agents (11).

Sports management

In 2016, the Heart Journal proposed that cardiopulmonary endurance is the fifth major sign of life. Improving cardiopulmonary endurance through aerobic exercises can decrease the risk factors of cardio-cerebrovascular diseases, as well as reduce the mortality and hospitalization rates. In addition, exercise training could improve the endothelial function, weaken catecholamine release, and increase peripheral oxygen extraction (41, 42). Blumenthal et al. (43) performed weekly regular aerobic exercises in 134 patients with IHD. The results revealed that exercise could effectively build up LVEF and accelerate the degree of abnormal wall motion (43). A meta-analysis of exercise rehabilitation demonstrated that high-intensity interval training (HIIT) rehabilitation therapy within a safe range can improve cardiopulmonary function (44). However, there is a lack of large-scale RCTs regarding the benefits of exercise intervention in MSIMI. Nevertheless, based on the principle of cardiac rehabilitation, large sample trials are warranted to explore the efficacy of exercise prescription in patients with MSIMI.

Stress management

Allgulander (23) and other researchers have confirmed that anxiety is not only a risk factor for cardiovascular disease, but also aggravates other risk factors, such as depression, smoking, and poor lifestyle. Therefore, a healthy and effective emotional regulation can reduce the adverse effects of stress on the heart. Studies have confirmed that antidepressant therapy can cut down the incidence of MSIMI by 40% (45). Moreover, positive and healthy emotions can weaken the mortality risk in patients with CAD (46). In addition, maintaining good emotional management is conducive to forming healthy living habits. For example, Pressman and Cohen (47) noted that improving the mood can reduce bad living habits, such as smoking and drinking. Gross and John (48) believed that positive mental state can improve the happiness and shorten the risk probability of anxiety and depression. Blumenthal et al. (43) conducted stress management in patients with MSIMI for 4 months, and observed that in these patients the probability of adverse cardiovascular events abated compared with the general nursing group. Bullock-Palmer et al. (49) believed that non-obstructive CAD with myocardial infarction is more likely to occur in females, and the following two mechanisms of myocardial infarction are involved in non-obstructive CAD: MSIMI and spontaneous CAD. Therefore, the diagnosis of the two should be differentiated to prevent misdiagnosis and mistreatment (49).

Advantages of pathogenesis and treatment with traditional Chinese medicine

MSIMI belongs to the category of chest paralysis and heartache per the traditional Chinese medicine. Based on the physiological function of the heart in governing the blood and storing the spirit; the physiological characteristics from the mutual assistance of heart, lung, qi, and blood; as well as the mechanism of the liver in governing the qi function of the whole body to release and regulate emotions, Chinese medicine considers that the pathogenesis of MSIMI is because of the deficiency in the Ben (root) and excess in the Biao (branch). Therefore, the treatment starts with the whole body and syndrome differentiation and treatment, considering the patients' constitution, as well as pathogenesis of spirit, viscera, qi, and blood. The treatment primarily aims to relieve Shaoyang (name of meridian in traditional Chinese Medicine); soothe the liver and relieve depression; unblock the heart, lung, and qi; nourish the blood; and calm the mind. Moreover, combined with the five major goals of cardiac rehabilitation, an individualized rehabilitation prescription should be formulated per the individual suitability to derive the full advantages and characteristics of traditional Chinese medicine. Notably, Chinese herbal medicine prescriptions are aimed at reconciling, nourishing blood, calming nerves, relieving pain. In addition, traditional exercise therapies, such as Baduanjin, Taijiquan, and breathing exercise improve cardiopulmonary endurance, when administered along with balanced food and medicine. Some studies have revealed that Taijiquan, qigong, and Baduanjin exercises play an effective role in reducing the incidence of cardiovascular diseases, reducing the level of blood lipids, and improving the exercise endurance and mood (50, 51).

Clinical significance

All the reviewed studies have adopted different detection indexes and diagnostic methods to explore the potential pathogenesis of MSIMI from the aspects of hemodynamics, sympathetic nerve, microcirculation, and endothelial mechanism. MPI and echocardiography have been proven to be effective diagnostic tools. Moreover, hemodynamic changes, microvascular constriction index, LVEF, and myocardial perfusion ischemia are clinically significant indicators to predict cardiovascular risk factors. For instance, Sun et al. (7) suggested that the change in LVEF can be used as one of the indexes to predict MACE. Hammadah et al. (8) believed that RPP increase and microvasoconstriction are independent predictors of MSIMI in patients with CAD. In addition, analyses determined sex-related differences in the occurrence mechanism of MSIMI, with a high incidence of MSIMI in females, which could be related to the fact that females are easily affected by social environment and emotion.

Therefore, in female patients who have chest pain with anxiety and depression, it is imperative to exclude MSIMI (52).

Conclusion

Previous studies have confirmed sex-related differences in the occurrence of myocardial ischemia under mental stress. However, most RCTs lack research on females and clinical intervention measures. Second, RCTs differed in the evaluation methods of ischemia, stress testing methods, and the characteristics of enrolled population. Third, some RCTs lacked long-term follow-up to determine the future end events of patients. Fourth, there is limited statistical data until date. Therefore, there were different views regarding the pathological process and clinical significance of MSIMI, with no unified standard of clinical detection methods. Moreover, some studies failed to consider factors, such as anxiety, depression, and the disease severity. Hence, several standard trials are further needed to verify the current conclusions before they can be considered as the clinical standard.

Regarding treatment, because of the atypical symptoms of MSIMI, it is imperative to regulate and intervene the process of myocardial microvascular reactions to prevent or reduce the risk of cardiovascular events. In addition, negative emotions can induce myocardial ischemia by interfering with the central nervous system and cardiovascular system. Therefore, further studies are needed that can explore the mechanisms involved in an individual's perception of social, psychological, and environmental pressures.

Conflict of interest: None declared.

Peer-review: Internally peer-reviewed.

Authorship contributions: Concept – N.H.; Design – N.H., C.W.; Supervision – C.W.; Funding – C.W.; Materials – None; Data collection and/or processing – N.H.; Analysis and/or interpretation – N.H., Y.Y.; Literature search – P.W.; Writing – N.H.; Critical review – Y.Y., P.W.

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