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Microvascular Coronary Dysfunction in Women-Pathophysiology, Diagnosis, and Management

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Abstract

Women exhibit a greater symptom burden, more functional disability, and a higher prevalence of no obstructive coronary artery disease (CAD) compared to men when evaluated for signs and symptoms of myocardial ischemia. Microvascular Coronary Dysfunction (MCD) defined as limited coronary flow reserve (CFR) and/or coronary endothelial dysfunction is the predominant etiological mechanism of ischemia in women with the triad of persistent chest pain, no obstructive CAD, and ischemia evidenced by stress testing. Evidence shows that approximately 50% of these patients have physiologic evidence of MCD. MCD is associated with a 2.5% annual major adverse event rate that includes death, nonfatal MI, nonfatal stroke and congestive heart failure. Although tests such as adenosine stress cardiac magnetic resonance imaging (CMRI) may be a useful non-invasive method to predict subendocardial ischemia, the gold standard test to diagnose MCD is an invasive Coronary Reactivity Testing (CRT). Early identification of MCD by CRT may be beneficial in prognostication and stratifying these patients for optimal medical therapy. Currently, understanding of MCD pathophysiology can be used to guide diagnosis and therapy. Continued research in MCD is needed to further advance our understanding.

Introduction

Chest pain in the absence of obstructive coronary artery disease (defined as ≥ 50% stenosis in ≥ 1 major coronary artery) is particularly common in women,[1,2] can be associated at times with debilitating symptoms, repeated evaluations and at times false reassurance. For subjects presenting for evaluation of suspected ischemic symptoms, a diagnosis of normal coronary arteries is five times more common in women as compared to men.[3]

A number of studies including the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study, have reported that up to one-half of patients undergoing coronary angiography are found to have normal or non-obstructive epicardial coronary arteries.[4]

Bernard J. Gersh: In general, cardiovascular medicine is less evidence based in women than in men due in part to underrepresentation in clinical trials and the misperception that women are "protected" against cardiovascular disease. One area that is, however, receiving increasing recognition is the entity of microvascular angina, Syndrome X, or

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microvascular coronary dysfunction, and in this respect, studies like the WISE have been invaluable.

MCD, a disorder of coronary resistance vessels is proposed to be one of the key mechanisms for women with persistent signs and symptoms of ischemia in the absence of obstructive CAD.[1] Data obtained from several well conducted cohort studies has demonstrated that prognosis in this condition is not as benign as once thought.[5,6] Currently, despite of extensive investigations, the causal mechanism(s) are far from being fully understood, and accordingly, MCD is still managed using a heuristic approach.

Definition of MCD

There is no universally accepted definition for MCD. Reis et al[7] has defined MCD as disordered function of the smaller (<100–200 μm) coronary resistance vessels. Beltrame et al. defined MCD as "abnormal coronary microvascular resistance (either arteriolar or pre-arteriolar) that is clinically evident as an inappropriate coronary blood flow response, impaired myocardial perfusion and/or myocardial ischemia that cannot be accounted for by abnormalities in the epicardial coronary arteries." [8(p21)] The coronary circulation, responsible for the delivery of oxygen and nutrients to the myocardium, is a coordinated system of capacitance (epicardial coronary artery 500 μm to 5mm) and resistance vessels (pre-arterioles 100–500 μm, intramural arterioles <100 μm and capillaries <7 μm).[9] The smaller coronary arteries (which cannot be visualized by angiography) constitute the coronary microcirculation and regulate coronary blood flow (tone), redox, growth, inflammation, coagulation and permeability.[10] These vessels normally offer significant vascular resistance. Consequently, it is the adaptive properties of these vessels to metabolic stimuli that determine coronary blood flow and thereby the appropriate matching of myocardial oxygen demands with myocardial perfusion.[11]

The traditional definition of MCD requires that maximal hyperemic stimuli (e.g., adenosine) increase coronary volumetric blood flow less than 2.5-fold, which is the lower limit of normal flow reserve in coronary arteries free of significant obstructive CAD.[10] Thus, attenuated epicardial coronary dilation response to adenosine may be a surrogate marker of MCD in women with chest pain and no obstructive CAD.[10]

Assessing the Coronary Microcirculation

MCD is thought to be a key contributory mechanism for myocardial ischemia in patients with signs and symptoms of ischemia but no obstructive CAD, therefore, identification of the role of microvasculature in the presence or absence of obstructive CAD should result in more rational diagnostic and therapeutic interventions for patients with ischemic heart disease (IHD). Unfortunately, current cardiovascular imaging technologies are unable to image the vessels that are smaller than 500 μm in diameter.[8] Endomyocardial biopsy in these patients may reveal pathologic small coronary arteries with fibro-muscular hyperplasia, hypertrophy of the media, swollen endothelial encroaching on the lumen, and myo-intimal proliferation,[12] however it is an invasive test and can not visualize the vessels in between 200–500 μm and may under-represent MCD that may be patchy.[13] Based on this, it is clear that anatomical or morphological approaches to evaluate coronary microcirculation are quite limited; therefore, study of the human coronary microcirculation is indirect and relies on assessing parameters, such as coronary blood flow (CBF) and CFR, which reflect its functional status rather than morpho-histological evaluation. These are primarily regulated by the coronary microcirculation and thus, in the absence of obstructive CAD, their measurement offers an index of coronary microvascular function.[14]

The normal physiologic response to an increase in myocardial demand is enhanced CBF, which is achieved by vasodilation of epicardial and resistance vessels, mediated by endothelium-dependent and non-endothelium-dependent mechanisms, respectively. [15,16] Abnormalities in the coronary circulation and CFR can be divided into endothelial and nonendothelial- dependent mechanisms, as well as into macrovascular (epicardial) and microvascular involvement.

Assessment of non-endothelial dependent microvascular function

The administration of adenosine provides an endothelium independent evaluation of the coronary microvasculature and may reveal abnormal CFR, even in the presence of normal epicardial endothelial function. CFR is a magnitude of an increase in coronary flow that can be achieved in going from basal coronary perfusion to maximum coronary vasodilation.[9] Adenosine predominantly acts on the coronary vessels less than 150 μm in diameter[17] via stimulation of the adenosine A2 receptor on smooth muscle cells by crossing the endothelial barrier and mainly assesses changes in the coronary resistance vessels as reflected by changes in coronary flow.[16]

Bernard J. Gersh: In some patients the intravenous administration of adenosine may provoke chest pain in association with an absence of an increase in subendocardial perfusion as assessed by cardiac magnetic resonance. (Paunting JR, Gatehouse PD, Yanz GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med. 2002; 346:25):1948–1953)

Assessment of endothelial dependent microvascular and macrovascular function

Acetylcholine is a drug commonly used to evaluate endothelium-dependent vasomotor tone regulation. Stimulation of acetylcholine receptors produces a uniform endothelium-dependent dilation of both micro and macrovasculature.[18] Normal coronary endothelial function is characterized by coronary vasodilatation and an approximate 3- to 4-fold increase in coronary blood flow in response to acetylcholine. Coronary endothelial dysfunction (CED) may be manifested by a significant attenuation of the increase in CBF in response to intra-coronary acetylcholine, no change or even a decrease in CBF.[16]

Assessment of non-endothelial dependent macrovascular function

The administration of nitroglycerine provides an endothelium independent evaluation of the coronary macrovasculature. Nitroglycerine is a vasodilator which acts directly on vascular smooth muscle. Since the coronary microvaculature lack the enzyme needed to convert nitroglycerine to its active form, nitric oxide, nitroglycerine produces a dose-related dilation of coronary vessels greater than 200 μm in diameter and has no effect on smaller coronary vessels.[16,17]

Impaired coronary vasomotor tone regulation in patients with angina and non-obstructive CAD may involve one or several pathways. Typically, a > 50% increase in CBF above baseline in response to acetylcholine and a CFR ratio of > 2.5 in response to adenosine is considered normal.[16] A patient with impaired response to acetylcholine and adenosine can be considered as having dysfunction of epicardial and resistance vessels involving endothelium-dependent and non-endothelium-dependent mechanisms respectively. An abnormal response to adenosine with a normal response to acetylcholine indicates MCD involving a non-endothelium-dependent pathway. An attenuated response to acetylcholine with a normal response to adenosine indicates endothelium-dependent disease. Lastly, a lack of response to nitroglycerine suggests non-endothelium dependent dysfunction of epicardial

arteries.[16] The categorization of the testing of the microvascular coronary pathways by CRT is shown in Table 1.

Bernard J. Gersh: Other tests used primarily in a research environment in patients with microvascular dysfunction or measurement of high energy phosphates with exercise using NMR spectroscopy and measurements of coronary sinus oxygen saturations during atrial pacing. (Cannon RO 3rd, Watson RM, Rosing DR, Epstein SE. Angina caused by reduced vasodilator reserve of the small coronary arteries. J Am Coll Cardiol. 1983; 1(6):1359–1373)(Buchthal SD, Hollander JA, Merz CN, Rogers WJ, Pepine CJ, Reichek N, Sharaf BL, Reis S, Kelsey SF, Pohost GM. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. N Engl J Med. 2000; 342(12):829–835).

Pathological Classification of MCD

MCD can be classified based pathological findings and proposed pathogenetic mechanisms. Kansra and Sircar divided microvascular angina (MVA), the symptomatic manifestation of MCD, into 'primary' caused by abnormal constriction of coronary microvasculature and 'secondary' caused by anatomical restriction of vascular cross-section or reduced vasodilator capacity. [19(p69)] Lanza and Crea [13(p2317)] classified MVA into 2 major groups, including primary MVA vs secondary MVA occurring in the setting of specific diseases. Listing of a classification of MCD based on pathogenic mechanism in Table 2. [9]

Pathophysiology of MCD

Cardiac Syndrome X (CSX), Microvascular Angina (MVA), MCD

For the last several decades, clinicians and researchers have investigated mechanistic causes of signs and symptoms of ischemia experienced by patients with CSX. The term CSX was popularized by Kemp et al[20] in 1973 to distinctly label patients with a triad of angina pectoris, a positive exercise test for myocardial ischemia and angiographically normal coronary arteries.

Bernard J. Gersh: The incidence of normal coronary arteries (stenoses less than 20%) in patients referred for coronary angiography was 41% among women and 8% among men in one series. (Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham, D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. BMJ. 1994; 308(6933):883–886) Diagnosis of CSX requires that both cardiac and non-cardiac causes of angina-like chest pain have been ruled out.[21] More recent findings suggest that a plausible mechanism for the triad is MCD resulting in reduced CBF reserve and MVA.[22–24]

While research has been carried out to facilitate understanding of the symptoms associated with CSX, there have historically been no definitive conclusions regarding the existence of myocardial ischemia in this condition.[9] The main hurdle for this conclusion is because of frequently lack of regional myocardial wall motion abnormalities[25], and typical metabolic changes[26] during cardiac stress test in patients with CSX, which are considered the most dependable finding of myocardial ischemia [22,27]. Several studies found no differences in myocardial blood flow either at rest or after dipyridamole, when patients with CSX are compared with control subjects. [28,29] Contrary to these findings, more direct evidence of ischemia associated with MCD in CSX patients comes from studies showing an impaired response of CBF to primarily non-endothelium dependent stimuli, including adenosine, dipyridamole and papaverine, using either invasive (intracoronary doppler recording) or non-invasive (thermodilution, positron emission tomography and CMRI) diagnostic techniques.[14,30–38]

Abnormal pain perception is an additional proposed mechanistic pathway for CSX.

Bernard J. Gersh: The possibility that enhanced pain sensitivity could be important in the pathogenesis of chest pain in these patients is somewhat indirectly supported by studies that failed to demonstrate objective evidence of ischemia in response to stressors such as dobutamine, exercise, and dipyridamole. Adenosine and potassium release as well as altered central neural modulation of afferent pain signals possibly contribute to the abnormal pain perception.[39] Despite this, the cause of neural abnormality in CSX is poorly understood. Crea and colleagues hypothesized that repeated episodes of myocardial ischemia might stimulate functional alterations in cardiac afferent nerve endings, resulting in increased reactivity to usually inoffensive stimuli, notably metabolic and inflammatory.[40]

Bernard J. Gersh: It has been suggested that increased pain sensitivity may be the result of altered autonomic tone, regional cerebral cortex activiation, and/or reduced activity of the endogenous opioid system. (Fedele F, Agati L, Pugliese M, Cervellini P, Benedetti G, Magni G, Vitarelli A. Role of the central endogenous opiate system in patients with syndrome X. Am Heart J. 1998; 136(6):1003–1009)(Pasceri V, Lanza GA, Buffon A, Montenero AS, Crea F, Maseri A. Role of abnormal pain sensitivity and behavioral factors in determining chest pain in syndrome X. J Am Coll Cardiol. 1998; 31(1):62–66) Kaski[41] proposed that interrelations between chest pain and MCD are important in the pathogenesis of CSX and are likely to determine the patient's clinical presentation. Figure 1 demonstrates the hypothesized variable interactions between MCD and pain threshold and can explain the heterogeneous pathogenesis of CSX.

Altered Regulation of Coronary Microcirculation

Coronary Endothelial Dysfunction

An endothelium with normal structure and function is required for appropriate dilatation of coronary vasculature during stress.[42] Endothelial function can be accessed centrally or peripherally by brachial artery flow-mediated dilation and it is impaired in hypertensive, hyperlipidemic, smoking, and diabetic women[43]. The vascular endothelium secretes factors that not only adapt blood vessel tone, but also contribute in the development and progression of atherosclerosis through their effects on platelet adhesion and aggregation, cell proliferation, and thrombogenicity.[44] CED in the coronary microcirculation, mainly the arterioles is said to be the trigger for pathogenesis of IHD.[45] Intact endothelium has a vital role in the regulation of vascular tone by releasing nitric oxide (NO) and thus matching myocardial perfusion with oxygen consumption.[45] Clinical studies have demonstrated that CED appears to have unfavorable functional consequences such as inadequate tissue perfusion, particularly during stress, contributing to myocardial ischemia.[46] Furthermore, CED could trigger an imprecise augmentation of the response to all vasoconstrictor stimuli. Inability to release endothelium-dependent NO shifts a net dilator response to sympathetic stimulation to a net constrictor response.[47] Myocardial ischemia may occur with impaired endothelium-dependent coronary flow reserve of the coronary epicardial and microcirculation, supporting a role for the coronary epicardial and microcirculation endothelium in regulating myocardial perfusion.[48]

CED, which is potentially restorable, has been suggested as a contributor to cardiovascular morbidity and mortality and is an independent predictor of adverse cardiovascular outcome.[49]

Bernard J. Gersh: This is a key point. Microvascular angina is not a benign condition and endothelial dysfunction may not only play a role in the pathophysiology of

symptoms, but can have a negative effect on prognosis in addition. (Rubinstein R, Yang EH, Rihal CS, et al. Coroanry microcirculatory vasodilator function in relation to risk factors among patients without obstructive coronary disease and a low to medium Framingham Risk Score. European Heart J. 2010; 31:936–942) This finding is further supported by a study in which Halcox et al[50] found that better coronary microvascular response to acetylcholine is associated with improved survival. These findings were in the perspective of both obstructive and non-obstructive CAD and support the hypothesis that CED is cornerstone in both the development and progression of CAD.

Cardiac Autonomic Nervous System (ANS) Imbalance

Altered coronary microvascular tone due to cardiac ANS imbalance has been implicated in MCD. In particular, elevated adrenergic tone may contribute to elevated microvascular constrictor at rest as well as sensitize the resistance arterioles to vasoconstrictor stimuli. In a study, Lanza et al reported that 75% of patients with CSX have defects in global and/or regional cardiac MIBG uptake, indicating an abnormal cardiac adrenergic nerve function.[51] Other work however has demonstrated that among patients with a positive exercise test there was no sign of ANS dysfunction, although the patients had altered coronary vascular resistance indicative of MVA.[52] Adamopoulos et al. has suggested that patients with CSX have an altered autonomic control of the cardiovascular system characterized by impaired baroreceptor sensitivity and reduced heart rate variability.[53] Conversely, Gulli and colleagues[54] found that among almost two thirds of CSX patients, symptoms could be related to the attenuated parasympathetic tone, rather than to an enhanced sympathetic activity.

Bernard J. Gersh: One study has suggested that patients have an increased response to beta-adrenergic stimulation. (Madaric J, Bartunek J, Verhamme K, Penicka M, Van Schuerbeeck E, Nellens P, Heyndrickx GR, Wigns W, Vanderheyden M, De Bruyne B. Hyperdynamic myocardial response to beta-adrenergic stimulation in patients with chest pain and normal coronary arteries. J Am Coll Cardiol 2005; 46(7):1270–1275)

Vasodilator and Vasoconstrictor Imbalance

Disruption of the balance between endothelial derived vasodilator NO and vasoconstrictor endothelin-1 (ET-1) has been suggested as one of the mechanism for MCD. Endothelin (ET) is a potent vasoconstrictor peptide produced by vascular endothelium which appears to play a crucial role in regulation of coronary blood flow. Plasma immunoreactive ET concentrations are raised in patients with angina pectoris and normal coronary arteriogram.[55] Selective blockage of vascular endothelin receptors is a promising new approach for the treatment of MCD.

Viscosity and Blood Rheology

When the normal coronary vasculature is maximally dilated with adenosine, the capillaries (which do not vasodilate due to absence of smooth muscles) are the “bottleneck” to hyperemic flow.[56] In addition, although the capillaries provide only one-quarter of the total microvascular resistance at rest, they offer three-quarters of the total MVR during hyperemia, despite the fact that total MVR decreases significantly during hyperemia from arteriolar and venous vasodilation.[57] Thus, capillaries play a key role in the regulation of CBF. The individual capillary offers very high resistance to blood flow by virtue of its small diameter, however, as the capillaries are arranged in parallel fashion there is acceptable drop in total resistance across the capillary bed.[57] Both capillary diameter and myocardial capillary density are directly proportional to CFR. (Figure 2) Because flow is related to the fourth power of diameter, a decrease in capillary diameter affects CFR more than does a decrease in myocardial capillary density.[57]

Smooth Muscle Dysfunction and Vasospastic Angina

Reduced CFR to intracoronary adenosine is observed in many women with chest pain and non-obstructive coronary arteries, suggesting impaired microvascular smooth muscle relaxation.[58] It may be challenging to differentiate Vasospastic /Prinzmetal's angina from MVA.

Bernard J. Gersh: This may be even more complex or perhaps mute in patients in whom the mass of the "non-obstructive plaque" on angiography is underestimated since vasospasm at the site of the non-obstructive plaque is well documented. The differentiation can be more complex because of the fact that both of these may co-exist. In a study, Sun and colleagues[59] demonstrated myocardial ischemia, most probably due to coronary microvascular spasm, in one-fourth of the studied patients with angina due to angiographically documented epicardial spasm suggesting that MCD might also contribute to angina in patients with vasospastic angina.

Inflammation

Systemic inflammation plays a vital role in atherosclerosis. Studies have shown increased markers of inflammation in CSX patients when compared with age matched control.[60] Whether inflammation of the coronary microvasculature results in altered physiology causing MCD is unknown. In a study Tomai and colleagues[61] found that in patients with CAD, evidence of systemic inflammation in the form of raised C-reactive protein levels is independently associated with endothelium-dependent and endothelium-independent MCD. Pavlov et al demonstrated that efferent vagus nerve inhibits pro-inflammatory cytokine release and protects against systemic inflammation, and phrased this vagal function "the cholinergic anti-inflammatory pathway."[62]

Aging

Age is a recognized risk factor for cardiovascular disease, and senescence is associated with functional and morphological changes in the coronary microvasculature.[56] Aging is associated with progressive endothelial dysfunction.[63] The age-related impairment in endothelial function, however, appears to occur earlier in men than women.[64] In a study, Chauhan et al. demonstrated that the CBF response to acetylcholine (an endothelium-dependent vasodilator) decreased significantly with aging, whereas that in response to papaverine and glyceryl trinitrate (endothelium-independent vasodilators) was unaffected by aging[65], furthermore, they established that this impairment can be restored by administration of L-arginine, a precursor of nitric oxide. The mechanisms of the attenuated coronary blood flow response to acetylcholine may involve age-related decreases in release of endothelium-derived relaxing factor (EDRF) dependent relaxing factors, inactivation of EDRF or the concomitant release of constricting factors by microvascular endothelial cells.[65] Aging may decrease the atrial natriuretic peptide (ANP)-induced relaxation and ANP-stimulated increase in cyclic GMP (cGMP) level by decreasing the ability of endothelial cells to produce EDRF, by decreasing guanylate cyclase activity, and by enhancing cGMP-phosphodiesterase activity.[66] Impaired endothelial function with aging may result in adverse clinical events as a result of alterations in the interaction of the vessel wall with neutrophils, macrophages and platelets.[65] It can also alter the regulation of myocardial perfusion and facilitate small-vessel platelet aggregation because of decrease in inhibitory effects of EDRF on platelet adhesion and aggregation.[67]

Bernard J. Gersh: It is interesting, however, that this occurs primarily in middle-aged women as opposed to the elderly. What is the role between aging, endothelial dysfunction, and hormonal status in women with microvascular coronary dysfunction?

MCD Secondary to Systemic Diseases

MCD can be associated with more obvious cardiovascular or systemic diseases. Symptoms and signs of myocardial ischemia are often found in patients with hypertrophic cardiomyopathy (HCM), a genetic disease despite angiographically normal coronary arteries.[68] MCD is also associated with diseases such as dilated cardiomyopathy[69], aortic stenosis[30,70], hypertensive heart diseases with or without left ventricular hypertrophy[71,72], hypercholesterolemia[73], post cardiac catheterization[74,75] and infiltrative heart disease such as Anderson–Fabry disease.[76] Studies have shown that MCD is also associated with diabetes mellitus[77,78] however, In a study, Shivu et al.[79] demonstrated that young subjects with uncomplicated type 1 diabetes mellitus have impaired myocardial energetics which may result from metabolic dysfunction rather than microvascular impairment.

Bernard J. Gersh: An association with the anti-phospholipid syndrome has been suggested. (Single SR, D'Cruz DP. Syndrome X (angina pectoris) with normal coronary arteries and myocardial infarction in patients with anti-phospholipid (Hughes) syndrome. Lupus 2008; 17:82–85)

Diagnosis and Clinical Evaluation

Compared to patients with obstructive CAD, those with signs and symptoms of ischemia but no obstructive CAD are more commonly mid-life women. Angina may be either typical or atypical and may occur with exertion or at rest. Based on clinical presentation alone, however, it is quite difficult to differentiate MCD from obstructive CAD, although, some clinical features provide clues such as episodes of chest pain lasting longer and poor response to sublingual nitrates particularly in patients with CSX [80]

Bernard J. Gersh: There are reports of an association between syndrome X (microvascular coronary dysfunction) and psychiatric disorders such as panic attacks and anxiety. (Kaski JC, Rosano GM, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA. Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study. J Am Coll Cardiol. 1995; 25(4):807–814)

Objective indicators of myocardial ischemia include ST-segment depression on electrocardiogram (EKG), abnormal stress imaging studies, or abnormal biomarkers of myocardial damage, such as troponin levels. Noninvasive imaging with echocardiography or nuclear perfusion stress testing may be not sufficiently sensitive to detect ischemia, and the EKG does not reliably demonstrate ST-segment depression during chest pain episodes in these patients.[81]

Currently, the gold standard for the diagnosis of MCD requires the exclusion of obstructive CAD by coronary angiography[13], followed by evaluation of microvascular coronary function by Doppler guide-wire in the cardiac catheterization laboratory for endothelial function testing in response to intra-coronary acetylcholine (Figure 3), and CFR testing in response to adenosine (Figure 4) by CRT. CFR is defined as the ratio of near maximal to basal myocardial flow, has been proposed as an indirect variable to evaluate the function of the coronary circulation[82], is considered as an amalgamated measure of CBF through both epicardial coronary arteries and the coronary microcirculation[83], therefore, decrease in CFR can be attributed to either obstructive epicardial CAD or MCD.[84]

Bernard J. Gersh: It should be emphasized that coronary endothelial dysfunction is commonly found in patients with cardiovascular risk factors, and its identification does not necessarily mean that the patient has microvascular angina or syndrome X. This entitiy requires for diagnosis a clinical history with/without definitive measures of

ischemia on stress testing in addition to documentation of abnormal coronary flow reserve in a patient without demonstrable obstructive coronary disease. CED can be diagnosed by no change or decrease in CBF in response to intra-coronary acetylcholine.[16] In another method, volumetric blood flow is directly measured in coronary sinus based on thermodilution technique during cardiac catheterization.[85] A Corrected Thrombolysis in Myocardial Infarction frame count is also used for quantitative measurement of CBF; its utility is limited because of subjective nature.[86]

Non-invasive Testing for MCD

Multiple modalities are available nowadays for detecting the presence of hemodynamically significant CAD such as treadmill testing, stress echocardiography and nuclear imaging each test has its own advantages and disadvantages. Stress studies are often sub optimal, as treadmill testing does not detect the site of ischemia, while using echocardiography the image quality and reproducibility are moderate. CMRI is a relatively new and promising technology to assess myocardial perfusion defects. CMRI can be used to measure global and regional myocardial function, the presence of ischemia and myocardial scar tissue. It is a noninvasive technique in which all these parameters can be acquired in one imaging session and has the advantage of using relatively safe contrast material without the use of radiation.[87] Several other non-invasive techniques have been suggested to determine myocardial perfusion such as positron-emission tomography (PET) using metabolic tracers[88], myocardial perfusion scintigraphy[89], and contrast echocardiography.[90] Magnetic resonance spectroscopy is relatively a new technique that enables to study inter-relations among cardiac structure, function, myocardial perfusion, and metabolism; however, it is not widely used because of low spatial and temporal resolution.[91] Doppler 2D–echocardiography can also be used to access CFR non-invasively.[92] Table 3 summarizes different invasive and non-invasive techniques used to assess functional abnormalities in coronary microvasculature.[8]

Prognosis of MCD

MCD patients face a 2.5% annual adverse cardiac event rate, which includes myocardial infarction, congestive heart failure, stroke, and sudden cardiac death.[93] Data from the NHLBI– sponsored WISE study has shown that women with no obstructive CAD and evidence of myocardial ischemia have a relatively poor prognosis compared with women with no obstructive CAD and no myocardial ischemia.[94]

Bernard J. Gersh: In the past, it is my impression that this syndrome was thought to have an excellent prognosis, but this is not the case as shown by the WISE and other studies. Not only is this condition a cause of considerable morbidity, it should also be considered as a harbinger of future cardiac events and a stimulous for aggressive control fo risk factors. Furthermore, among the women with no obstructive CAD, an abnormal coronary microvascular response to adenosine is associated with relatively greater increased risk for major adverse outcomes[95], suggesting that endothelial independent microvascular response predicts outcome. The endothelium-dependent component on the microvasculature has also been linked to risk factors and pro-inflammatory processes promoting atherosclerosis[11] as well as adverse clinical outcomes.[49,50,94] A study demonstrated that about 30% women with non-obstructive CAD and coronary endothelial dysfunction progressed to obstructive CAD during a 10 year follow-up.[2]

Management of MCD

Treatment of MCD can be challenging due to a current lack of uniform diagnostic criteria, multiple mechanistic pathways contributing to the pathophysiology, and often unsuccessful

empiric therapies. The goals of treatment are to control debilitating symptoms and improve quality of life, to reduce incidence of hospitalization/repeated invasive testing, and to improve event-free survival. A multidisciplinary approach is often required in most cases. Anti-atherosclerotic and anti-ischemic treatment strategies based on mechanistic pathways is demonstrated in Table 4.

Anti-Atherosclerotic Therapy

ATP Therapeutic Lifestyle Change (TLC)—Due to a high burden of cardiac risk factors and coronary atherosclerosis in subjects with angina[93], evidence of ischemia and no obstructive CAD, lifestyle changes to aggressively modify risk factors using TLC is a cornerstone of treatment. Cardiac rehabilitation can be recommended for the many patients who have limited their physical activity to minimize their symptoms, has been demonstrated to be effective in these subjects for increased exercise capacity and symptom relief.[96]

Bernard J. Gersh: Many patients with microvascular dysfunction/angina are deconditioned and may benefit from exercise training and cardiac rehabilitation. This also offers an opportunity to monitor modification of risk factors and lifestyle. (Eriksson BE, Tyni-Lenn R, Svedenhag J, Hallin R, Jensen-Urstad K, Jensen-Urstad M, Bergman K, Selvin C. Physical training in syndrome X: physical training counteracts deconditioning and pain in syndrome X. J Am Coll Cardiol. 2000; 36(5): 1619–1625)

Lipid-lowering Therapy and Anti-platelet Agents—Therapy with statins can be particularly useful in patients with presence of risk factors, evidence of atherosclerosis and/or endothelial dysfunction. Target LDL should be lower than 100 mg/dL, and even as low as 70 mg/dL with co-morbidities. Statins may improve endothelial function by lipid-independent mechanisms by their anti-inflammatory and antioxidant properties and ability to restore vascular NO availability.[97] The majority of these patients have diffuse coronary atherosclerosis[47], and therefore, use of anti-platelet agents such as aspirin in patients with evidence of ischemia and no obstructive CAD can be appropriate.

Anti-ischemic Therapy

Nitrates—There are no clinical trials exploring the role of nitrates specifically in patients with MCD. Observationally from experience, it appears that the effects of nitrates on angina frequency and duration can be unpredictable in patients with MCD, though for many patients, they can provide relief.

ACE Inhibitors and ARBs—Angiotensin-converting enzyme (ACE) inhibitors as well as angiotensin-renin blockers (ARBs)[98] and has shown to improve endothelium-dependent relaxation of coronary resistance arteries by increasing the availability of NO.[99]

Beta-blockers—Beta-blockers are effective in relieving anginal symptoms in up to two thirds of CSX patients; although responses vary.[5] Beta-blockers, particularly atenolol reduce the number and severity of anginal episodes and improve functional capacity in patients with MCD.[100] Newer generation beta blockers with alpha-blocking properties (carvedilol) may offer additional benefit as beta-blockers alone can worsen symptoms in the minority of patients with coronary spasm.[101]

L-arginine—L-arginine is a precursor of nitric oxide, and its use (2 g, 3 times daily) over 4 weeks led to improved endothelial function and angina symptoms in patients with no obstructive CAD[102]; caution should be exercised as this therapy worsened outcomes in post-myocardial infarction patients in a clinical trial.[103]

Calcium Channel Blockers (CCBs)—CCBs are first line therapy for vasospastic (Prinzemetal's) angina. The use of CCBs for management of MCD is not yet supported by evidence. Lanza et al compared amlodipine, atenolol, and nitrate in randomized controlled trial and demonstrated that only atenolol was more effective in treating MCD patients.[100]

Ranolazine—Ranolazine is an anti-anginal agent acts by reducing calcium overload in the ischemic myocyte through inhibition of the late sodium current.[104] A recent pilot randomized trial in MCD patients demonstrated efficacy for angina.[105]

Xanthine Derivatives (aminophylline) [106], nitrate-potassium channel agonist (nicorandil)[107], rho kinase inhibitor (fasudil)[108] etc. has some beneficial effects in MCD.

Bernard J. Gersh: There are reports of a benefit from aminophylline, which is an adenosine-receptor antagonist. (Elliott PM, Karzyzowska-Dickenson K, Calveno R, et al. Effect of oral aminophylline in patients with angina and normal coronary arteriograms (cardiac syndrome X). Heart. 1997; 77:523–526)

Enhanced External Counterpulsation (EECP)—A recent study by Kronhaus and colleagues showed that (EECP) improves angina in 87% of 30 patients with CSX at 11.9 months follow-up.

Abnormal Cardiac Nociception Therapy—Low dose tri-cyclic medication (imipramine, amitryptaline)[109] improves symptoms in patients with abnormal cardiac nociception by its effect on modulation of norepinephrine uptake. Non-pharmacologic approaches, including cognitive behavioral therapy[110], transcendental meditation[111], transcutaneous electrical nerve stimulation,[112] and spinal cord stimulation[113] have been shown to have varying degree of benefits in this patient population.

Bernard J. Gersh: Although hormone replacement therapy has been shown to reduce the frequency of anginal episodes on one study, its use needs to be weighed against the overall negative effect of such therapy and cardiovascular outcomes. (Rosano GM, Peters NS, Lefroy D. Lindsay DC, Sarrel PM, Collins P, Poole-Wilson PA. 17-beta-Estradiol therapy lessens angina in postmenopausal women with syndrome X. J Am Coll Cardiol. 1996; 28(6):1500–1505)

Conclusions

MCD is prevalent in women with signs and symptoms of ischemia and no obstructive CAD. Long-term prognosis is not benign as previously thought; new findings demonstrate that these patients are at increased risk for major adverse cardiac events. Despite this, MCD has received relatively limited attention with the resultant diagnostic and therapeutic challenges. Currently, understanding of MCD pathophysiology can be used to guide diagnosis and therapy. Continued research in MCD is needed to further advance our understanding.

Bernard J. Gersh: There is a strong predominance of women among patients with exertional chest pain and no angiographic evidence of obstructive disease. We now recognize that microvascular coronary dysfunction, which previously masqueraded under the sobriquet of syndrome X is a definite syndrome with a complex pathophysiology, significant morbidity, and an adverse prognosis in regard to cardiovascular events. Doctors Kothawade and Bariery Merz have provided us with a timely and authoritative monograph which illustrates the complexity of this disease entity and which highlights what as recently been learned but also what remains unknown. We need new approaches to therapy, but I believe we have learned the

benefits of aggressive risk factor reduction in regard to the primary prevention in this disease and its role in secondary prevention is logical. In order to comprehensively prevent and treat disease, we need to understand its etiology, and in this respect the WISE study under the principle investigatorship of Dr. Bairey Merz, in addition to other studies from centers with a longstanding interest in this condition, have taught us a great deal. This is an interesting and evolving area, and I suspect that if this monograph is re-written in 5 years' time there will be much in it that is new.

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Abbreviations

CRT	coronary reactivity testing
MCD	microvascular coronary dysfunction
CAD	coronary artery disease
CFR	coronary flow reserve
CED	coronary endothelial dysfunction
CMRI	cardiac magnetic resonance imaging
CBF	coronary blood flow
CSX	cardiac syndrome X

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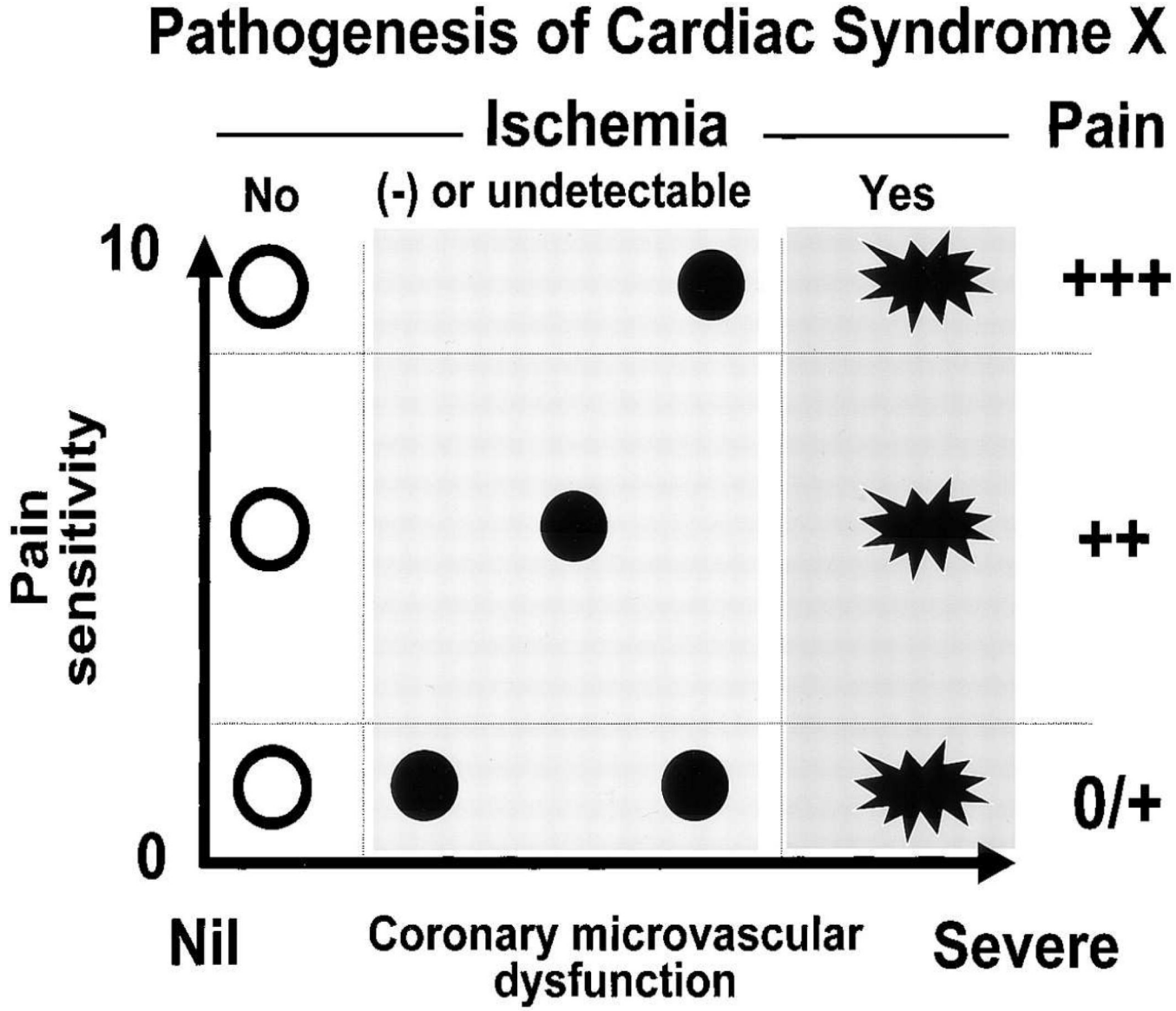


Figure 1.

Interrelations between chest pain and microvascular dysfunction are important in the pathogenesis of CSX and are likely to determine the patient's clinical presentation. A given patient with markedly increased pain sensitivity (y axis, arbitrary severity scale 1 to 10) may develop chest pain in response to algogenic cardiac (and probably also non-cardiac) stimuli even in the absence of major coronary microvascular dysfunction or myocardial ischemia. Adenosine and potassium release have been suggested to cause chest pain and ECG changes in CSX patients. Endothelin-1 and the autonomic nervous system modulate pain threshold. Patients with both marked microvascular dysfunction (x axis) and reduced pain threshold will be highly symptomatic and are also likely to have objective evidence of myocardial ischemia. Patients with intermediate degrees of chest pain sensitivity and microvascular dysfunction may have no ischemia or this may be undetectable; the latter depending on the sensitivity of the diagnostic tools employed for investigation and the severity and location of ischemia. Variable interactions between pain threshold and microvascular dysfunction can explain the heterogeneous pathogenesis of CSX. Both pain threshold and microvascular

dysfunction have ample gradation spectra regarding severity and are also modulated by factors such as endothelial dysfunction, inflammation, autonomic influences, and psychological mechanisms, among others. Reprinted with permission from Kaski JC. Pathophysiology and Management of Patients With Chest Pain and Normal Coronary Arteriograms (Cardiac Syndrome X). Circulation 2004;109(5):568–572.

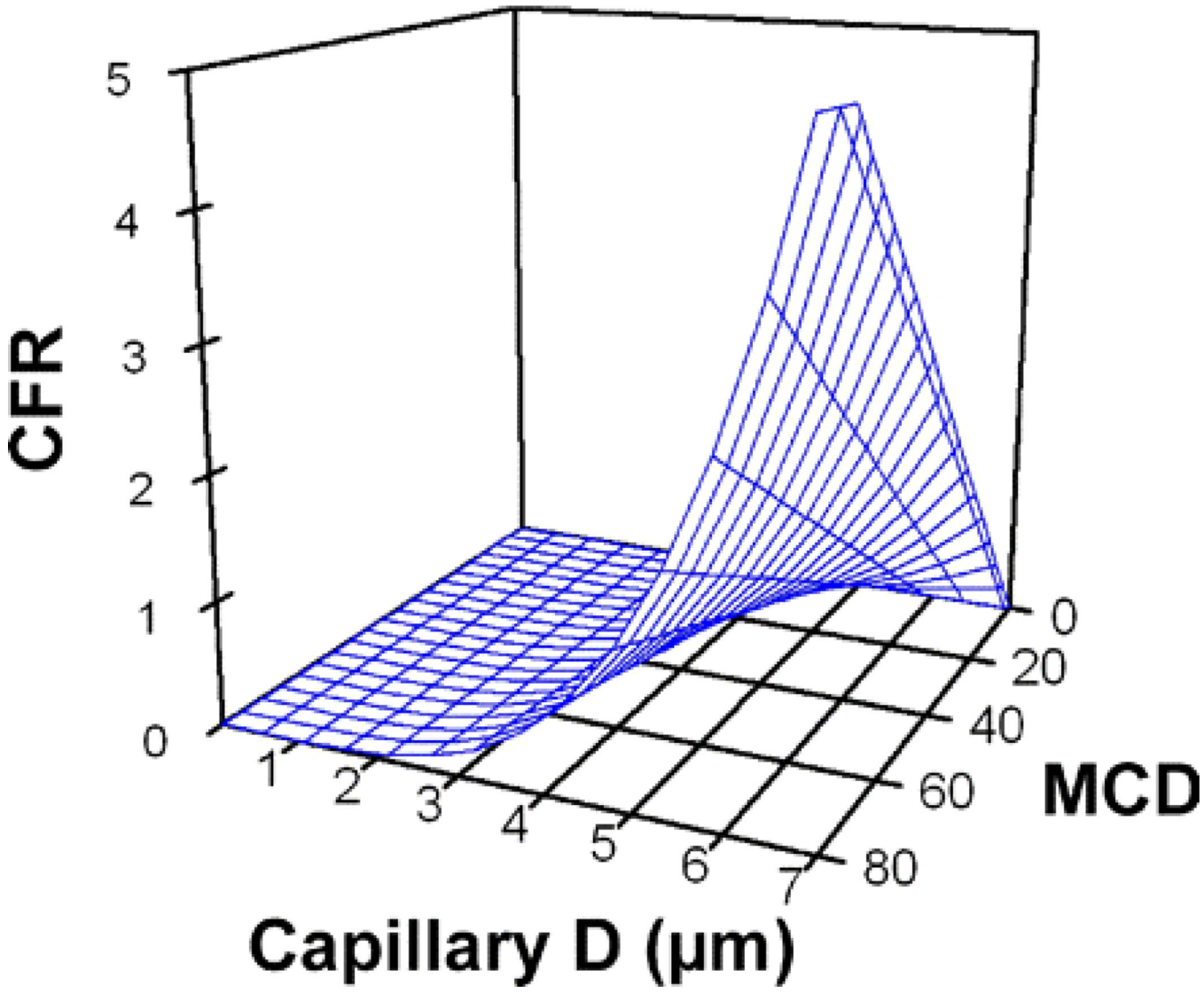
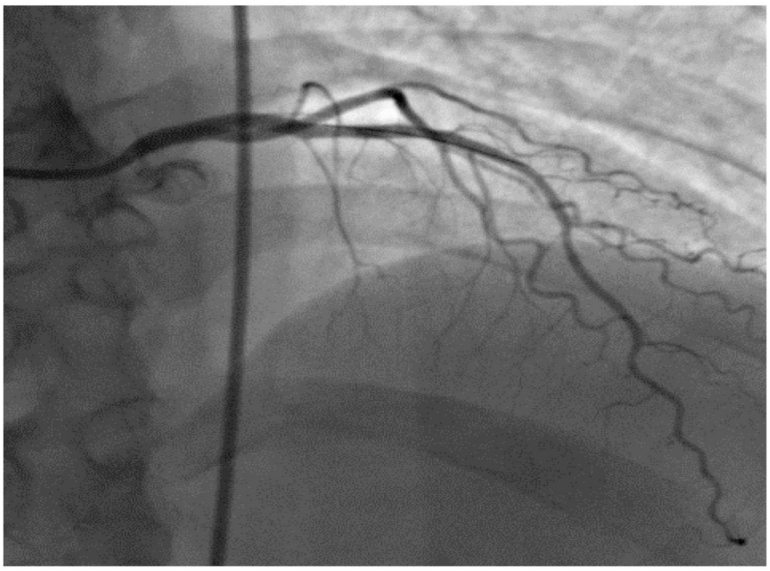


Figure 2.
Model-Derived Relation Between Capillary Diameter (X-Axis), Myocardial Capillary Density (Z-Axis), and CFR (Y-Axis). Please note that MCD in this diagram stands for Myocardial Capillary Density Reprinted with permission from Kaul S, Jayaweera AR. Myocardial Capillaries and Coronary Flow Reserve. J Am Coll Cardiol 2008;52(17):1399–1401.

3A



3B

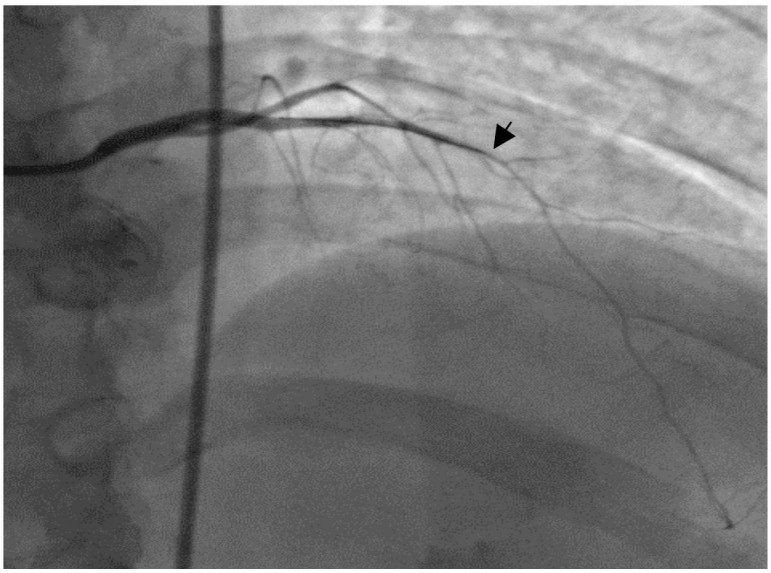
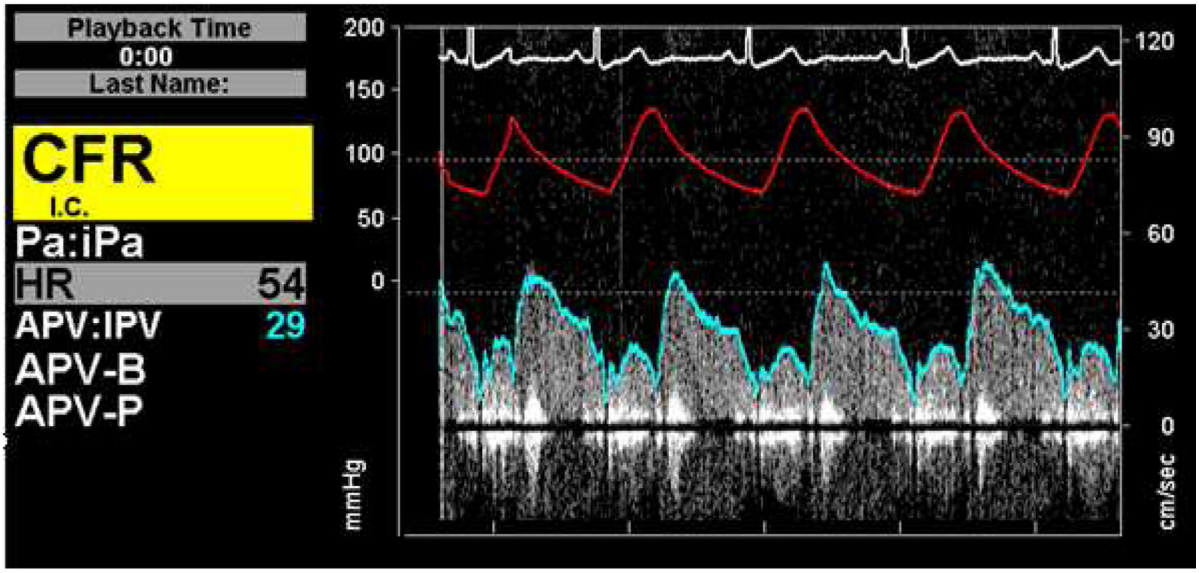


Figure 3.

Doppler flow wire in coronary artery measures changes in coronary blood flow and peak velocity in response to Acetylcholine (A: Baseline, B: following injection of 10^{-4} Ach injection demonstrating constriction of the coronary arteries). Arrow indicates tip of the Doppler flow wire positioned at mid-left anterior descending artery.

4A



4B

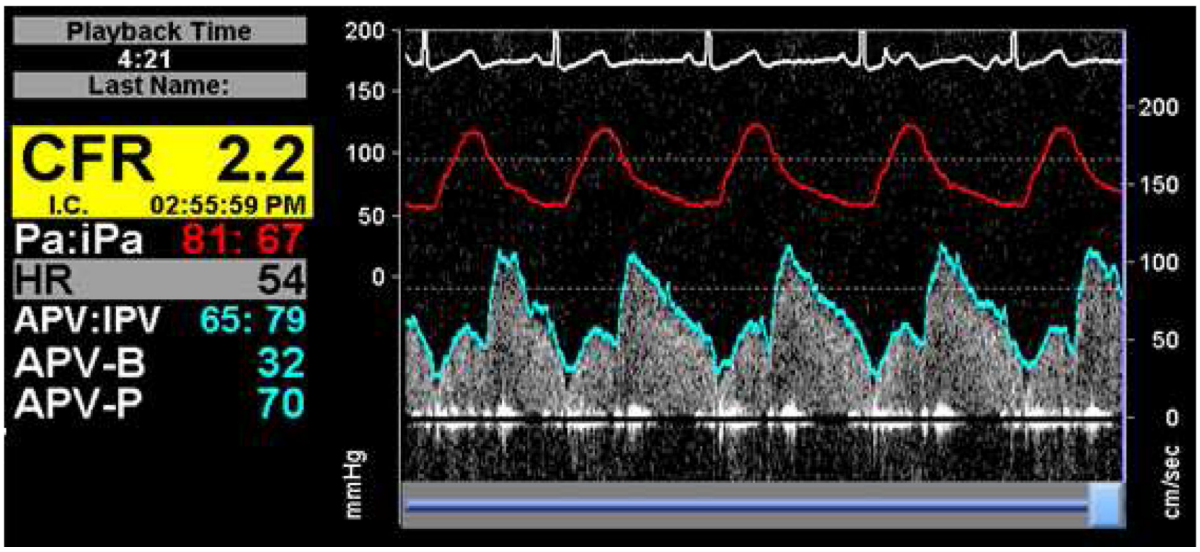


Figure 4.

Intracoronary Doppler blood flow velocity waveforms before intracoronary adenosine (A), and after intracoronary adenosine infusion (B). CFR is the ratio of average peak velocities before and after adenosine.

Table 1

Coronary Reactivity Testing Mechanistic Pathways of MCD

	Adenosine	Acetylcholine	Nitroglycerine
Microvascular	Non-Endothelial Dependent	Endothelial Dependent	×
Epicardial	×	Endothelial Dependent	Non-Endothelial Dependent

Table 2

Pathogenetic Mechanisms of MCD

Alterations	Causes
Structural	
Luminal obstruction	Microembolization in acute coronary yndromes or after recanalization
Vascular-wall infiltration	Infiltrative Heart disease (e.g., Anderson—Fabry cardiomyopathy)
Vascular remodeling	Hypertroph c cardiomyopathy, arterial hypertension
Vascular rarefaction	Aortic stencsis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
Dysfunction of smooth-muscle cell	Hypertroph C cardiomyopathy, arterial hypertension
Autonomic dysfunction	Coronary recanalization
Extravascular	
Extramural compression	Aortic stencsis, hypertrophic cardiomyopathy, arterial hypertension
Reduction in diastolic perfusion time	Aortic stencsis

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Table 3

Clinical Techniques Frequently Utilized to Evaluate Functional Abnormalities in the Human Coronary Microvasculature.

Assessment of myocardial ischemia
Electrocardiograph (stress ECG test)
Positron emission tomography (metabolic tracers)
Magnetic resonance spectroscopy
Transmyocardial metabolic studies
Myocardial perfusion techniques
Myocardial scintigraphy
Positron emission tomography (blood flow tracers)
Magnetic resonance imaging
Contrast echocardiography
Angiographic myocardial blush
Coronary blood flow techniques
Coronary sinus thermodilution
Intracoronary Doppler flowire
Angiographic frame count
Doppler echocardiography

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Table 4

Treatment of Subjects with Angina, Evidence of Myocardial Ischemia, and No Obstructive CAD*

Microvascular Coronary Dysfunction (MCD)
Abnormal Endothelial Function
Angiotensin Converting Enzyme Inhibitors (ACE-I)
HMG CoA Reductase Inhibitors (Statins)
L-arginine supplementation
Aerobic Exercise
Enhanced External Counterpulsation (ECP)
Abnormal Non-endothelial Function
Beta-blockers/alpha-beta blockers
Nitrates
Anti-Anginal -Anti-Ischemic
Ranolazine
Xanthine derivatives
Abnormal Smooth Muscle Function (Prinzmetal's Angina)
Calcium Channel Blockers
Nitrates
Abnormal Cardiac Nociception
Low Dose Tricyclic Medication
Spinal Cord Stimulation
Cognitive Behavioral Therapy

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