

STATE-OF-THE-ART PAPER

Microvascular Angina and the Continuing Dilemma of Chest Pain With Normal Coronary Angiograms

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Since initial reports over 4 decades ago, cases of patients with angina-like chest pain whose coronary angiograms show no evidence of obstructive coronary artery disease and who have no structural heart disease continue to be a common occurrence for cardiologists. Many features of this patient population have remained constant with successive reports over time: a female predominance, onset of symptoms commonly between 40 and 50 years of age, pain that is severe and disabling, and inconsistent responses to conventional anti-ischemic therapy. Because patients may have had abnormal noninvasive testing that led to performance of coronary angiography, investigators have sought to show an association of this syndrome with myocardial ischemia. Abnormalities in coronary flow and metabolic responses to stress have been reported by several groups, findings consistent with a microvascular etiology for ischemia and symptoms, but others have questioned the presence of ischemia, even in patients selected for abnormal noninvasive testing. Despite considerable efforts by many groups over 4 decades, the syndrome remains controversial with regard to pathophysiology, diagnosis, and management. (J Am Coll Cardiol 2009;54:877-85) © 2009 by the American College of Cardiology Foundation

As coronary angiography became more widely practiced in the 1960s, it was soon apparent that not all patients with clinical suspicion of coronary artery disease (CAD) had obstruction of epicardial coronary arteries. Several published series, including the National Heart, Lung, and Blood Institute-sponsored CASS (Coronary Artery Surgery Study) and the WISE (Women's Ischemia Syndrome Evaluation) study, have reported that up to one-half of patients undergoing coronary angiography are found to have normal or nonobstructed epicardial coronary arteries (1-3). In 1967, Likoff et al. (4) reported on 15 women ranging in age from 30 to 53 years with chest pain despite normal coronary angiograms (CPNCA), but with electrocardiographic (ECG) abnormalities at rest (ST-segment depression or T-wave inversion) that were accentuated by exercise. Despite the ECG changes during exercise, the hemodynamic response—as assessed by pulmonary artery pressure, cardiac output, and oxygen consumption—was reported as normal in the 8 patients in whom these measurements were made. The authors of this article stated that “usual therapy of CAD was

ineffective and unwarranted” in this setting (4). That same year, Kemp et al. (5) reported on a series of 50 patients (62% women) with CPNCA, commenting that as a group, “these patients may frequently have the most severe pain syndromes, often proving refractory to conventional forms of therapy.” Of the 41 patients who underwent metabolic study during isoproterenol stress, 11 showed myocardial lactate production supportive of myocardial ischemia. Of these 11 patients, 4 had ischemic-appearing ECGs during exercise stress; however, 5 additional patients with ischemic-appearing ECGs during exercise stress did not show myocardial lactate production during isoproterenol infusion. In a 1973 editorial, Kemp (6) noted that the heterogeneity of patients included in studies of patients with CPNCA makes it difficult to derive clinical or mechanistic insights about this syndrome. The term “syndrome X” was used in this editorial (based on group X in the article under discussion) to denote the uncertainty of chest pain etiology in these patients, a term subsequently used by other investigators, but often with different criteria for its definition.

Twenty-six years ago, our group considered whether impaired coronary microcirculatory dilator responsiveness could limit blood flow response to stress, producing myocardial ischemia and angina, and published our initial findings during the inaugural year of the *Journal* (7). Epstein and I subsequently proposed microvascular angina as a suitable descriptor for this syndrome (8). Abnormalities in coronary flow and metabolic responses to stress were reported over the years by several groups, findings consistent

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Abbreviations and Acronyms

CAD	= coronary artery disease
CPNCA	= chest pain despite normal coronary angiograms
ECG	= electrocardiographic
L-NMMA	= N ^G -monomethyl-L-arginine
MRI	= magnetic resonance imaging
NMR	= nuclear magnetic resonance
NO	= nitric oxide

with a microvascular etiology (by default, based on normal coronary angiograms) for ischemia and symptoms. Others, however, have questioned an ischemic cause for symptoms, even in patients selected for abnormal non-invasive testing such as ischemic appearance of stress ECG, designated by some groups as having syndrome X. In 1992, Camici, Epstein, and I wrote a review article entitled *Pathophysiological Dilemma of Syndrome X* (9). Despite considerable efforts by many groups since that time, the syndrome remains controversial with

regard to pathophysiology, diagnosis, and management.

Despite differences of opinion regarding cardiac versus noncardiac mechanisms of chest pain in this population, most groups have reported that patients with CPNCA and structurally normal hearts have a better prognosis with regard to serious cardiac events (myocardial infarction, cardiovascular death) compared with CAD patients (10–14). Although reassurance helps many patients, most continue to have chest pain resulting in emergency room evaluations, hospitalizations, and repeat cardiac catheterizations, with adverse effects on quality of life, employment, and health care costs (15–18).

Focus on the Coronary Microcirculation

In response to surrounding myocardial metabolic conditions, arterioles dilate or constrict to match flow appropriate to myocardial oxygen demands. Micropuncture measurements of pressure in small subepicardial arteries of the beating cat heart, however, showed that 40% to 50% of the total coronary resistance is imposed by pre-arteriolar arteries between 100 and 300 μm in diameter (19,20). The discovery of endothelium-derived relaxing factors (21)—nitric oxide (NO) in particular (22)—led to numerous studies of the role of the endothelium in coronary physiology, including levels of the circulation distal to epicardial arteries. In this regard, inhibition of NO synthesis with the L-arginine antagonist N^G-monomethyl-L-arginine (L-NMMA) increased basal coronary vascular resistance and blunted the vasodilator response to the endothelium-dependent agonist acetylcholine in isolated perfused hearts (23). Small arteries (100- to 300- μm diameter) and arterioles from cholesterol-fed animals contracted in response to doses of acetylcholine that produced relaxation in similar-sized small arteries from control animals, despite equivalent relaxation to an NO donor in the 2 groups (24–26). Microscopic examination of the vascular segments from these studies showed the endothelium to be structurally intact and free of atherosclerosis,

although small lipid deposits or vacuoles were commonly seen within endothelial cells.

Bioavailability of NO may be diminished in experimental settings by a combination of reduced synthesis (which may be selective for specific signal transduction pathways) and accelerated degradation, resulting in impaired endothelium-dependent vascular relaxation and dilation. In this regard, accumulation of methylated arginines such as asymmetric dimethylarginine may compete with L-arginine for the substrate binding site on NO synthase (27). Also, NO may be degraded to biologically inactive nitrogen oxide compounds by the action of superoxide anions, which may be increased in hypercholesterolemia (28).

The Coronary Microcirculation in Humans

Several groups have reported evidence for dysfunction of the coronary circulation at a level too small to be assessed visually by measurement of coronary flow responses to endothelium-dependent and endothelium-independent vasodilators in patients undergoing cardiac catheterization, generally for chest pain evaluation (29–31). Quyyumi et al. (31) investigated the contribution of NO to coronary circulatory dynamics by infusing L-NMMA into the coronary arteries of 31 patients (17 women) with CPNCA, although most had 1 or more risk factors for atherosclerosis. Inhibition of NO synthesis caused a 10% to 15% constriction of epicardial arteries and a 15% to 20% reduction in coronary blood flow in patients who had no risk factors for atherosclerosis (Fig. 1). In contrast, patients with risk factors had less of a constrictor effect on the coronary circulation, consistent with reduced NO bioactivity. Further, co-infusion of L-NMMA with acetylcholine caused greater attenuation of the dilator effects of this agonist in patients without risk factors than in those with risk factors, indicating that the effect of acetylcholine on normal arteries, regardless of size, is largely mediated through enhanced NO release (Fig. 2). Coronary microvascular dysfunction in some cases, however, may be independent of the endothelium. Thus, Reis et al. (32) of the WISE study group reported that of 159 women undergoing invasive study, 74 (47%) had what they defined as subnormal coronary flow responses (<2.5 ratio increase from baseline) to intracoronary adenosine. Age and the number of years post-menopause correlated inversely with reduced coronary flow reserve, but not lipid and hormone levels, blood pressure, or left ventricular ejection fraction. A subsequent report from the WISE study group with 210 women undergoing this testing indicated that conventional atherosclerosis risk factors accounted for <20% of the observed variability in the coronary flow response to adenosine, suggesting the role of other yet-unidentified factors responsible for microvascular dysfunction (33).

The investigators of these studies concluded that microvascular dysfunction may exist in patients with CPNCA, and may limit coronary flow during stress. The clinical

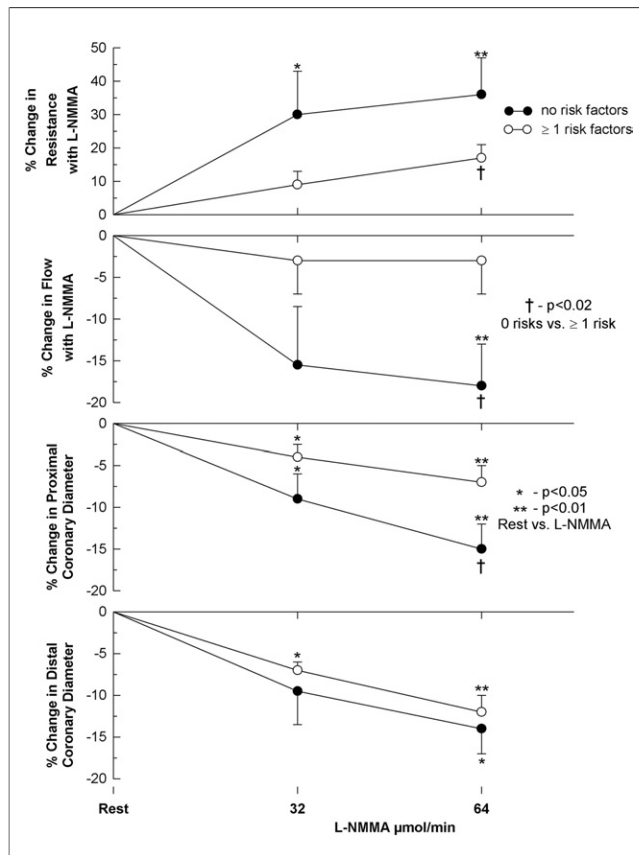


Figure 1 Contribution of NO to Epicardial and Microvascular Coronary Tone

The effect of risk factors for coronary atherosclerosis on the change in resting coronary vascular tone with N^G -monomethyl-L-arginine (L-NMMA), an antagonist of nitric oxide (NO) synthesis. The percent change in the coronary vascular resistance, flow, and proximal and distal epicardial diameters with L-NMMA are compared in patients with ≥ 1 risk factor (open circles) and in patients without risk factors (solid circles). Results expressed as mean $\pm$ SEM. $\dagger p < 0.02$ denotes differences in the response to L-NMMA by repeat-measures analysis of variance between patients with and patients without risk factors. $*p < 0.05$ and $**p < 0.01$ denote differences between rest and post-L-NMMA measurements in each group. Reprinted, with permission, from Quyyumi et al. (31).

implications of these findings, however, are uncertain: similar abnormalities of coronary microvascular function may exist in asymptomatic subjects who have no indication for cardiac catheterization and invasive study of coronary dynamics.

The Case for Myocardial Ischemia

Several conditions have been proposed to account for coronary microvascular dysfunction, including altered autonomic tone (34,35), insulin resistance (36–38), enhanced ion transport across cell membranes (39), increased endothelin-1 release (40,41), estrogen deficiency (42), and endothelial dysfunction (43–45). In many cases, patients were selected for invasive study based on an abnormal test result, such as from treadmill stress ECG or nuclear perfusion imaging, consistent with inducible ischemia. Such test results, however, could be not only false positive for

epicardial CAD (by selection), but also false positive for ischemia, whatever the etiology. Accordingly, metabolic evidence for ischemia might support claims of coronary microvascular dysfunction sufficient to limit appropriate blood to myocardium during stress. Thus, Buffon et al. (46) investigated metabolic evidence of ischemia during stress by measuring lipid hydroperoxides and conjugated dienes—molecules generated on reoxygenation of ischemic tissue—as metabolic markers of ischemia in arterial and great cardiac vein blood. Samples were drawn before and after rapid atrial pacing in 9 patients (4 women) with CPNCA, 7 of whom had ischemic-appearing ST-segment depression during exercise stress and 5 of whom had reversible nuclear perfusion defects.

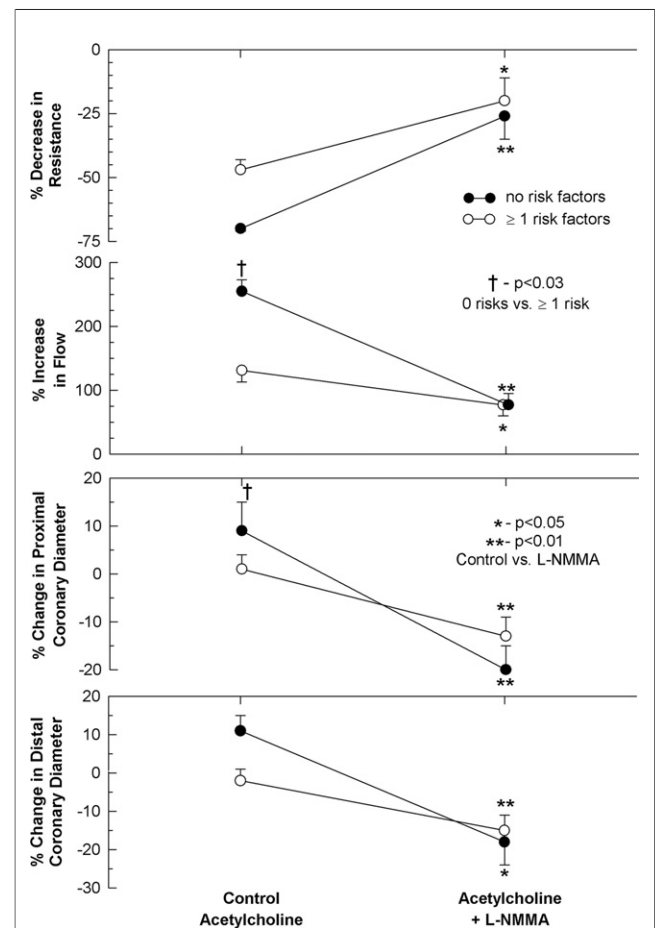


Figure 2 Atherosclerosis Risk Factors and Coronary Tone During Endothelial Stimulation

The impact of risk factors for coronary atherosclerosis on the vascular effects of acetylcholine before and after inhibition of nitric oxide synthesis with N^G -monomethyl-L-arginine (L-NMMA). The percent change in the coronary vascular resistance, flow, and proximal and distal epicardial diameters with acetylcholine are compared in patients with ≥ 1 risk factor (open circles) and in patients without risk factors (solid circles) for atherosclerosis. Responses to the peak dose of acetylcholine are compared before and after L-NMMA in the 2 groups. Results expressed as mean $\pm$ SEM. $\dagger p < 0.03$ denotes differences in the response to acetylcholine between patients with and patients without risk factors. $*p < 0.05$ and $**p < 0.01$ denote differences between control and post-L-NMMA measurements in each group. Reprinted, with permission, from Quyyumi et al. (31).

These measurements were compared with those of 5 patients with mitral valve disease who underwent this study and served as control subjects. Curiously, levels of these molecules were higher in great cardiac vein blood than arterial blood before pacing in patients, whereas the reverse was true in control subjects. In patients, but not control subjects, great cardiac venous levels of these molecules increased after pacing (160 beats/min or heart rate at development of ST-segment depression for 3 min) that induced ST-segment depression and chest pain in all but 1 patient.

Buchthal et al. (47) from the WISE study group reported that 7 of 35 women with CPNCA who underwent nuclear magnetic resonance (NMR) spectroscopy had findings compatible with myocardial ischemia during repetitive hand-grip exercise. This conclusion was based on a reduction in spectral signals from the phosphate of phosphocreatine relative to the phosphates of adenosine triphosphate that was similar to the decline in the ratio of these high-energy phosphate spectra recorded in patients with CAD. The frequency of exercise-induced nuclear perfusion defects and abnormal brachial artery endothelial testing, however, was similar for the 7 women with reduction in the ratio of high-energy phosphate spectra and the 28 women with lesser reduction (or actual increases) in these spectra. No coronary flow dynamic data were reported to ascertain relevance to invasive measures of microvascular function.

Magnetic Resonance Imaging (MRI) and Subendocardial Ischemia

Invasive measures of coronary microvascular dynamics and performance of NMR spectroscopy are unavailable to most cardiologists. Further, widely accepted values for normal versus abnormal responses to these tests are lacking. Cardiac MRI is being used with increasing frequency to show ischemia in patients with suspected CAD, including the emergency department setting for patients presenting with chest pain, with sufficient resolution to show subendocardial ischemia or infarction (48). Panting et al. (49) performed cardiac MRI in 20 patients (16 women) with CPNCA and ischemic-appearing ECG responses to exercise stress and in 10 age- and sex-matched control subjects. Fourteen of the patients had undergone nuclear perfusion imaging studies. None showed reversible perfusion abnormalities after stress to suggest inducible myocardial ischemia. Images were obtained at baseline and during adenosine infusion to dilate the coronary microcirculation and maximally increase coronary blood flow. In control subjects, adenosine similarly increased perfusion in the endocardium and the epicardium by analysis of short-axis slices of the left ventricle. In contrast, patients showed less increase in endocardial perfusion but preserved increase in epicardial perfusion in response to adenosine. During the adenosine infusion, 19 of 20 patients experienced chest pain that was often intense in severity, whereas 4 of 10 control subjects experienced chest pain that was generally mild in severity. The investigators

concluded that coronary microvascular dysfunction may limit appropriate increases in endocardial blood flow. Left unexplained is why ischemic chest pain should have occurred when endocardial perfusion was not actually reduced by adenosine in this study.

On the other hand, Vermeltfoort et al. (50) performed adenosine-stress cardiac MRI in 20 patients (15 women) with CPNCA—all of whom had ischemic-appearing ECGs and/or reversible nuclear perfusion defects during exercise stress—and reported comparable increases in subendocardial and subepicardial signal intensity after adenosine infusion. As highlighted by Camici (51) in an accompanying editorial, transient reductions in subendocardial signal intensity, commonly noted in this study, are likely an artifact of the first-pass sequence, unlike the sustained signal loss in the subendocardium seen in patients with CAD, which is generally believed to represent subendocardial ischemia.

The Case Against Myocardial Ischemia

Although many of the studies cited previously support the paradigm that coronary microvascular dysfunction in the absence of structural heart disease may precipitate myocardial ischemia, other studies—beginning with the report from the Montreal Heart Institute (52) that prompted the 1973 Kemp editorial (6)—have questioned the existence of myocardial ischemia in patients with CPNCA who have structurally normal hearts, including those with ischemic-appearing stress ECGs or other noninvasive testing suggestive of inducible ischemia. Such studies have included analysis of coronary sinus metabolites of carbohydrates and fatty acids (53) and pH monitoring of coronary sinus blood before and during rapid atrial pacing (54), concluding that most patients with CPNCA do not show metabolic evidence of myocardial ischemia despite chest pain with stress.

Other groups have evaluated cardiac function during stress to determine whether ischemic appearance of the ECG during stress is associated with diminished regional or global wall motion consistent with inducible myocardial ischemia, as recognized in CAD. Thus, Nihoyannopoulos et al. (55) reported normal left ventricular systolic function by echocardiography immediately after exercise and during rapid atrial pacing in 18 patients with CPNCA despite experiencing chest pain with ischemic-appearing ST-segment depression during these stresses. We evaluated 70 consecutive patients (44 women) with CPNCA, of whom 22 had ischemic-appearing ECG responses during treadmill exercise and 13 had reversible perfusion defects, albeit without correlation between these 2 noninvasive tests (56). The results of exercise testing and dobutamine stress echocardiography from these 70 patients were compared with those of 26 healthy subjects. The transesophageal route for imaging was used to maximize the number of ventricular segments visualized and the quality of images for assessment of contractility. Dobutamine infused in stepwise increments to 40 $\mu\text{g/kg/min}$ induced chest pain in 59 patients but in

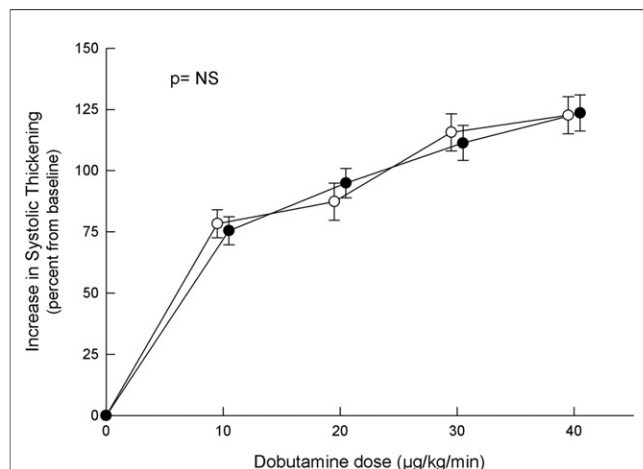


Figure 3 Left Ventricular Functional Responses to Stress

Comparison of the quantitative myocardial response to the infusion of incremental doses of dobutamine in healthy control subjects (open circles) and in patients with chest pain and normal coronary angiograms (solid circles). Results expressed as mean $\pm$ SEM. The p value corresponds to comparison of the different responses by repeat-measures analysis of variance. Reprinted, with permission, from Panza et al. (56). NS = not significant.

none of the control subjects. Ischemic-appearing ST-segment depression developed in 22 patients and in 2 control subjects. Wall motion abnormalities occurred in none of the patients or control subjects, and no differences were observed in transmural contractile response to dobutamine between patients and control subjects (Fig. 3). Indeed, of the 70 patients, the quantitative myocardial contractile response to dobutamine was virtually identical in the 22 patients with ST-segment depression and the 48 patients without this ECG response during infusion.

Thus, despite the frequent provocation of characteristic chest pain, including those with ischemic-appearing ST-segment depression, patients with CPNCA do not show concomitant regional wall motion abnormalities, but instead show a quantitatively normal myocardial contractile response to stress that argues against inducible ischemia. In rebuttal to this conclusion, however, Maseri et al. (57) proposed that patchy microvascular constriction (or absence of appropriate vasodilation) may produce myocardial ischemia during stress that does not affect myocardial contractility because of compensatory vasodilation of adjacent arterioles.

Prognostic Implications of Coronary Endothelial Dysfunction

Although reports from large cohorts of patients with CPNCA suggest a benign prognosis (10–18), at least for life-threatening cardiac events, studies incorporating assessment of endothelial function indicate that subsets of patients may be at higher risk of serious cardiovascular events (58–61). These studies support the prognostic significance of coronary endothelial dysfunction at the epicardial or

microvascular level. The relevance to patients with CPNCA, however, is unclear. Similar demonstration of endothelial dysfunction in a population of comparable age and risk factor profile, but free of chest pain symptoms, might have identified similar cardiovascular risk.

Investigators from the WISE study group reported the prognostic implications of NMR spectroscopy testing in women with CPNCA, extending findings from their previous publication (62). This series included 74 women with no obstructive plaques on coronary angiograms, of whom 60 had no reduction in the ratio of phosphocreatine-to-adenosine triphosphate signals during hand-grip stress and 14 showed reduction in this ratio. At 3 years, 87% of the group with a normal ratio of high-energy phosphate signals were free of cardiovascular events, versus 57% in the abnormal spectral signal ratio group. The difference in events, however, was primarily attributable to the increased frequency of repeat hospitalizations for chest pain and repeat coronary angiography, and not to myocardial infarction or cardiovascular death.

Abnormal Cardiac Pain Perception: The Sensitive Heart

The observation that patients with CPNCA commonly experience their characteristic chest pain during the performance of diagnostic cardiac catheterization has led several groups to consider abnormal cardiac pain perception as a fundamental abnormality in this patient population, initially shown by simple catheter movement or saline injections within the heart (63–67). We found that in 36 patients (21 women) with CPNCA, characteristic chest pain could be provoked in 86% by electrical stimulation (right ventricular

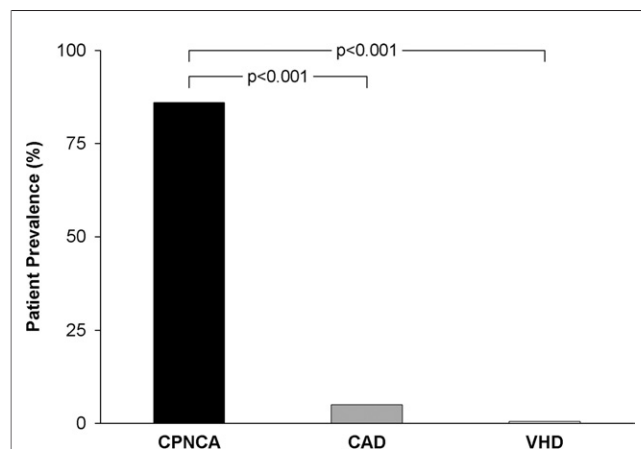


Figure 4 Chest Pain During Cardiac Catheterization: The Sensitive Heart

Prevalence of typical chest pain experienced during cardiac catheterization in 36 patients with chest pain and normal coronary angiograms (CPNCA), 44 patients with coronary artery disease (CAD), and 10 patients with valvular heart disease (VHD) provoked by pacing from apex of right ventricle at 5 beats over resting heart rate and/or injection of contrast media into the left coronary artery. Adapted and reprinted with permission from Cannon et al. (64).

pacing) at a heart rate 5 beats faster than their resting heart rate, with the pain worsened by increasing the stimulus intensity (64). In over one-half of these patients, pain could also be provoked by simply injecting contrast media into the left coronary artery (Fig. 4). In contrast, pain responses to these maneuvers were rarely encountered in patients with CAD or valvular heart disease. Other potent stimuli for pain provocation in CPNCA patients are dipyridamole and adenosine infusion (64,65). Exaggerated pain sensitivity has also been shown within the esophagus of patients with CPNCA (68), lending speculation that the mechanism of exaggerated visceral pain sensitivity may be neurophysiologically linked to whatever is responsible for anxiety and panic disorders commonly noted in patients with CPNCA (67,69–71).

Rosen et al. (72) measured regional cerebral blood flow by positron emission tomography as an index of neuronal activity at rest and during dobutamine stress in 8 patients (6 women) with CPNCA and ischemic-appearing ECG responses to exercise stress and in 8 control subjects. Dobutamine precipitated severe chest pain and ST-segment depression in all patients, although echocardiography showed increased left ventricular contractility. Patients and control subjects showed similar increases in blood flow in the hypothalamus, thalamus, right orbitofrontal cortex, and anterior temporal lobes. In patients, but not in control subjects, increased blood flow was also noted in the right anterior insula/frontal operculum junction. In a previous study of identical design but with CAD patients, dobutamine infusion provoked chest pain and echocardiographic evidence of myocardial ischemia. No increased blood flow in the right insula was noted in these patients (73). Thus, patients with this syndrome may have an altered pattern of cortical activation by visceral afferent signals, which could

contribute to abnormal pain perception during cardiac stress even in the absence of ischemia.

Treatment Trials and Management Approaches

Perhaps the most frustrating aspect of the syndrome of CPNCA is the management of chest pain symptoms, as was recognized in the earliest reports in the literature. Numerous therapies have been reported to be successful in clinical trials generally including small numbers of patients, including nitrates (74), beta-blockers (75,76), calcium-channel blockers (77), angiotensin-converting enzyme inhibitors (78), tricyclic antidepressants (79), aminophylline (80), estrogen replacement therapy (81) and L-arginine (82). The WISE study group is currently conducting randomized clinical trials with quinapril (NCT00150826) and ranolazine (NCT00570089). The clinical experience, however, has generally been that pain relief with medical therapy is not sustained over time, and patients are commonly prescribed a large number of drugs. Another management consideration is gastroesophageal testing, which may reveal acid reflux disease or esophageal motility disorders (68). Other groups have proposed nonpharmacologic approaches to pain symptoms in this patient population, including exercise training (83), transcendental meditation (84), cognitive behavioral therapy (85), and transcutaneous electrical nerve stimulation or spinal cord stimulation (86–88).

Absence of a widely accepted understanding of pathophysiology and approach to diagnosis and treatment should not preclude a sympathetic appreciation of symptoms, which can be debilitating for some patients. My management approach is to perform vasodilator stress cardiac MRI: if convincing evidence of subendocardial ischemia is present, then anti-ischemic therapy seems appropriate. If no ischemia is evident, I use a combination of beta-blocker and

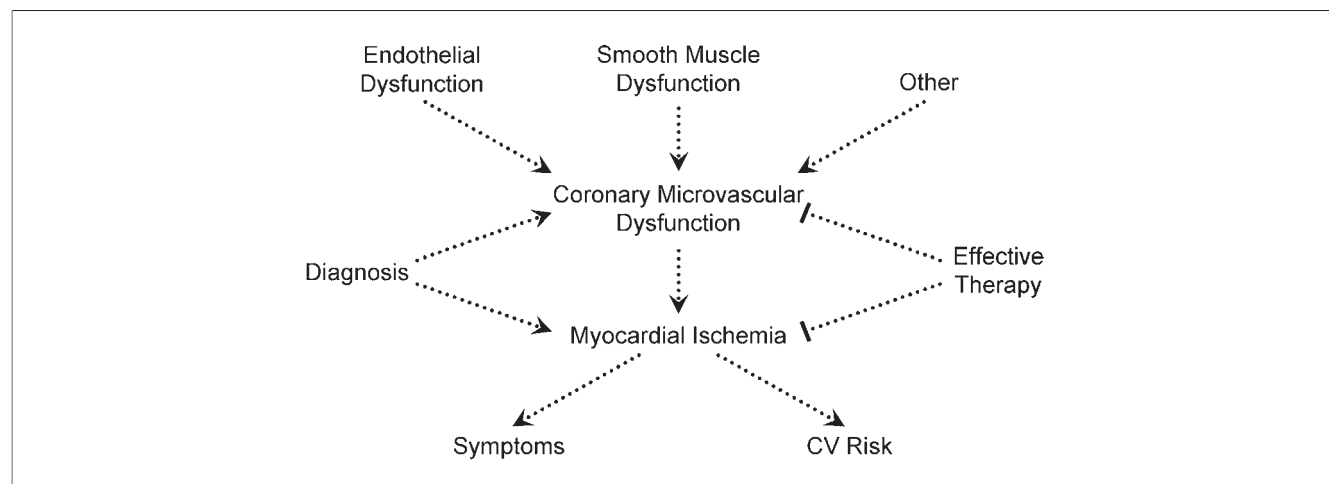


Figure 5 Microvascular Angina: Connecting the Dots

Future research should establish a coherent pathophysiology that links coronary microvascular dysfunction with myocardial ischemia. For the diagnosis to be clinically relevant, testing that separates those patients whose symptoms are caused by myocardial ischemia from those whose pain is nonischemic should be validated by multiple groups, and strategies for effective management must be supported by randomized clinical trials. CV = cardiovascular.

imipramine, and encourage enrollment in an aerobic exercise program. This approach is supported by several of the randomized clinical trials mentioned previously (75,76,79,83), but the combination has not been validated by a proper clinical trial design.

Future Research Directions

The studies cited in this review have generally focused on selected aspects of the syndrome of CPNCA in the absence of structural heart disease. Necessary to resolve the continuing debate and legitimize a specific diagnosis (e.g., microvascular angina) is to “connect the dots” by defining a coherent pathophysiology that links coronary microvascular dysfunction by some mechanism—and localized to that level of the circulation by exclusion of epicardial disease, perhaps using computerized tomographic coronary angiography—with evidence of myocardial ischemia (Fig. 5). For the diagnosis to be clinically relevant, testing that separates those patients whose symptoms are caused by myocardial ischemia from those whose pain is nonischemic should be validated by multiple groups, and strategies for effective management must be supported by randomized clinical trials. This last point is critical because patients suffer from pain that is susceptible to a placebo effect, without lasting benefit. If conventional noninvasive stress testing cannot reliably identify patients with inducible ischemia as a cause of chest pain, then testing that is not widely available (such as NMR spectroscopy) must be validated by several centers to support referral of patients for specialized testing. Greater experience with cardiac MRI, which is more widely available, may support use of this testing, but validation of findings from multiple centers is necessary. To be clinically useful, results of such testing must translate into effective treatment and improved quality of life for patients.

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