ORIGINAL ARTICLE

Cardiovascular outcomes of a positive nuclear stress test but negative coronary angiography in a multiethnic male predominant cohort

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ABSTRACT

Background: Patients presenting with chest pain and evidence of functional ischemia by myocardial perfusion imaging (MPI), but lacking commensurate angiographic disease pose a diagnostic and therapeutic dilemma. They are often dismissed as having 'false-positive MPI'. Moreover, a majority of the available long-term outcome data for it has been derived from homogenous female populations. In this study, we sought to evaluate the long-term outcomes of this presentation in a multiethnic male-predominant cohort. **Materials and Methods:** We retrospectively identified 47 patients who presented to our institution between 2002 and 2005 with chest pain and evidence of ischemia on MPI, but with no significant angiographic disease on subsequent cardiac catheterization (cases). The occurrence of adverse cardiovascular outcomes (chest pain, congestive heart failure, acute myocardial infarction and stroke) post-index coronary angiogram was tracked. Similar data was collected for 37 patients who also presented with chest pain, but normal MPI over the same period (controls). Overall average follow-up was over 22 months. **Results:** Fifty-three percent (26/47) of the cases had one or more of the adverse outcomes as compared with 22% (8/37) of controls ($P < 0.01$). Of these, 13 (50.0%) and 3 (37.5%) were males, respectively. **Conclusions:** Ischemia on MPI is predictive of long-term adverse cardiovascular outcomes despite normal ('false-negative') coronary angiography. This appears to be gender-neutral.

Key words: Cardiac syndrome X, multiethnic, male-predominant

INTRODUCTION

Cardiac stress testing is the basic screening tool for ischemic coronary artery disease (CAD). In the event of abnormal distribution of myocardial blood flow (or positive result indicative of functionally significant ischemia), coronary angiography is performed as the current gold standard in the diagnosis of ischemic CAD. This is particularly the case for patients presenting with suggestive chest pain and intermediate pre-test probability of significant CAD. Coronary angiography generally allows the clinician to draw definitive conclusions and guide management of ischemic coronary syndromes. Nevertheless, there are a significant number of patients who, despite suggestive clinical symptoms and myocardial perfusion imaging (MPI) evidence of ischemia, have angiographically normal coronary arteries. Data from the Women's Ischemic Syndrome Evaluation study indicate that, of the over 500,000 people who undergo left heart catheterization every year, approximately 48% of women and 17% of men have no intraluminal lesions or <50% narrowing of one or more coronary arteries.[1,2] A significant number of these individuals continue to present for evaluation of anginal-like chest pain. Also, there are significant subsets of these patients who present with recurrent classical angina and subsequently display MPI consistent with ischemia; however, they do not develop any significant angiographic diseases. These patients have traditionally been stratified to an ambiguous area of the coronary disease spectrum, known as cardiac syndrome x (CSX). Classified as having CSX (the current general consensus is that CSX patients have abnormal treadmill and/or abnormal MPI), these patients are left with little definitive long-term prognostic

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information.[3] They often continue to have classical anginal chest pain, without plausible (cardiac and noncardiac) causes to account for it following extensive workup.

Initial studies suggested that CSX conferred no significant increase in the risk of adverse cardiac events as compared to their counterparts with normal MPI.[4-12] However, recent data have shown that patients with CSX with endothelial dysfunction appear to have an increased risk for future adverse cardiac events.[13-16] Furthermore, much of the literature suggesting the syndrome as a benign condition rest largely on data from both observational and retrospective studies that have been underpowered to definitively reach this conclusion. Most of these investigations were performed prior to the era of advanced cardiac imaging modalities, including magnetic resonance imaging (MRI) and nuclear magnetic resonance (NMR) capable of assessing both endocardial and epicardial disease.[17,18] Also, little is known of the overall risk of adverse events when adjustments for age, sex and demographics are made.

Despite a number of unresolved questions, the available data suggest an overall increased prevalence of CSX in middle-aged Caucasian females as compared to all other populations. This, coupled with an increased association with features of the metabolic syndrome and migraine headache disease has led many to postulate the syndrome to be one of microvascular origin.[19] These patients tend to have other apparent associations including strong family history of CAD and prothrombotic states.[20] However, the long-term risk of adverse cardiac events in this population remains ill-defined at best and thus perpetuates the therapeutic dilemma for clinicians. Finally, because a majority of CSX data comes from homogenous samples, it is difficult to definitively extrapolate all results to a diverse population.

The purpose of this study was to assess long-term clinical outcomes of patients who presented to the Nashville Metropolitan General Hospital with the features of CSX. Further, employing the diverse patient population of our hospital, we sought to compare the outcomes seen in our institution to those from prior less diverse populations to compare clinical outcomes.

MATERIALS AND METHODS

The primary hypothesis was that patients with cardiac syndrome-X would have no significant differences in both the primary and secondary clinical endpoints as compared to individuals with negative nuclear stress tests and no subsequent angiography. Following institute's research board (IRB) approval, we identified 49 patients with typical chest pain and normal or near-normal coronary angiograms: 28 men and 21 women, who presented to the Nashville Metro General Hospital from 2002 to 2005. Inclusion criteria included established exertional angina, an abnormal nuclear stress test, suggesting ischemia (reversible perfusion defect on MPI) and normal or near-normal (less than 40% luminal narrowing) results on coronary angiography. The occurrence of adverse cardiovascular outcomes post the index coronary angiogram was evaluated. Similar data were collected for 37 randomly selected patients (controls) who had chest pain and negative (normal) nuclear perfusion stress tests in the same time period; 22 of these were men and 15 were women. The time for follow-up of clinical outcomes was an average of 24 months with a range of 15-36 months.

The exclusion criteria included a percutaneous transluminal coronary angioplasty (PTCA); coronary artery bypass grafting (CABG) or prior myocardial infarction; coronary spasm during the coronary angiography; severely uncontrolled hypertension (defined as blood pressure >200/110 mmHg); arrhythmias such as paroxysmal atrial fibrillation (PAF); and left bundle branch block (LBBB). Furthermore, patients having a history of cocaine use were also excluded. All exclusion criteria were applied to the time of the index coronary angiogram.

Our primary outcome was the combined endpoint of definite or suspected death from heart disease (including sudden cardiac death), non-fatal myocardial infarction and fatal or non-fatal stroke, assessed in the entire cohort (major adverse cardiovascular endpoints). Secondary outcomes included examination of the number of subsequent hospitalizations for chest pain, number of emergency room visits for chest pain, development of clinical heart failure and the number of individuals requiring repeat cardiac catheterization.

In addition, we assessed both the primary and secondary outcomes separately for men and women as well as for individual ethnic groups [Table 1]. Also, the outcomes were correlated with known cardiovascular disease risk factors. We also examined the magnitude of the relationship of clinical endpoints to the frequency of individual baseline risk factors (including smoking status, history of hypertension, diabetes, sex, cardiovascular medications, HDL and LDL cholesterol concentrations). The controls were screened randomly from a list of all patients undergoing nuclear stressing over the same 4-year period. Specifically, every 7th patient-chart was selected (contingent that they met none of the exclusion criteria) for the control group until a number needed for statistical power was reached. This approach allowed us to determine the outcome differences of those stratified to the syndrome-X population, while still preserving the randomized allocation.

Statistical analysis

All data are expressed as mean ± standard deviation (SD). A *P*-value <0.05 was considered statistically significant.

Table 1: Baseline demographics of the cases and controls

	CSX-like group (Cases)	Negative MPI (Control)
Male Gender	28	22
Female	21	15
Age, (years)	51.0±3.4	51.7±2.9
BMI kg/m^2	33.0±1.4	28.7±1.3
Tobacco use	28 (57.1%)	15 (40.5%)
Diabetes	18 (38.2%)	6 (16.7%)
HTN	42 (85.4%)	17 (47.2%)
Family Hx	23 (46.9%)	8 (21.6%)
Ethnicity		
Caucasian	11 (23.4%)	5 (13.5%)
Black or African American	34 (72.3%)	28 (75.7%)
Hispanic or Latino	2 (4.25%)	1 (2.7%)
Native American/Other	2 (4.25%)	3 (8.1%)

CSX – Cardiac syndrome-x; MPI – Myocardial perfusion imaging; BMI – Body mass index; HTN – Hypertension; Family Hx – Family history of cardiovascular disease in primary relative

Statistical analysis involved the comparison of primary and secondary outcomes between the abnormal stress test cohort and the control cohort, respectively, by use of the z-test of proportions test. Each patient's first angiogram was counted as the index procedure.

RESULTS

A total of 53 patients were found to have positive nuclear stress testing and negative coronary angiography. However, only 47 individuals were eligible for the study, and the mean duration of follow-up was 19.1 ± 8.4 months (range 9-47 months), which yielded a total of 898 patient-months of follow-up. More than 40% had at least 2 years of follow-up. The mean age of the study population was 51.0 ± 3.4 years (range 30-74 years) and the mean BMI was 33.0 ± 1.4 kg/m^2. In this cohort, 42 (85.7%) had hypertension, 28 (57.1%) were smokers and 18 (38.2%) had diabetes diagnosed prior to the index angiogram. The ethnicity of the study population is delineated in Table 1 along with various other baseline characteristics.

A total of 37 patients with negative nuclear stress testing and, thus, no subsequent coronary angiography were identified via the screening method described above. From the 37 individuals selected, the mean duration of follow-up was 29.3 ± 6.8 months (range 1-47 months), yielding 1,084 patient-months. More than 35% had at least 3 years of follow-up. The mean age of the study population was 51.7 ± 2.9 years (range 30-74 years) and the mean BMI was 28.7 ± 1.3 kg/m^2. In this cohort, 17 (47.2%) had hypertension, 15 (40.5%) were smokers and 6 (16.7%) had diabetes diagnosed prior to the index angiogram [Table 1].

The number of patients with adverse outcomes in the control group was 8 (21.6%). However, in the case group, the patients with adverse outcomes numbered 26 (53%). The difference between the two groups is statistically significant with a *P*-value of 0.0063. The number of males with adverse outcomes was 13 (27.7%) and 3 (8.1%) in the case and control groups, respectively. The overall number of adverse outcomes in the control and case cohorts was 11 and 45, respectively. Furthermore, the number of cardiac-related hospitalizations was 4 and 35 in the control and case groups, respectively [Figure 1].

Within the positive-nuclear stress (case) group, 22 (46.8%) patients had recurrent chest pain necessitating emergency room visitation as compared to only 9 (24.3%) patients from the normal nuclear stress group during the same follow-up period. However, only individuals (2 or 4.3%) from the positive stress cohort went on to undergo repeat cardiac catheterization for recurrent chest pain.

Incident CHF was seen in 9 (19.1%) patients of the case cohort and 2 (5.4%) of the control group (different patients from those with repeat catheterization) in the period of follow-up. When the study population is reviewed for the development of acute coronary syndrome(s) (ACS), only 2 (4.3%) patients required hospitalization for a documented ACS event. No patients from the control population went on to develop a documented ischemic event.

In the case population, 1 patient suffered from a cerebrovascular event and 3 individuals developed a cardiac arrhythmia, respectively.

DISCUSSION

Our results show that, in a male-predominant cohort of chest pain patients, ischemia on MPI despite subsequent negative coronary angiography is associated with a long-term higher risk of adverse cardiovascular events as compared with chest pain patients without ischemia on MPI. These results consistently hold true across all pre-defined markers of cardiovascular outcomes, except when sudden cardiac death is considered (no deaths). There is no significant deviation in this trend accounting for gender, race and ethnicity. However, it must be stated that this trend reaches statistical significance only when either the combined primary and secondary endpoints ($P = 0.005$) or the secondary endpoint alone are evaluated. A level of statistical significance is not reached when the major adverse cardiovascular outcomes (MACE) alone are examined. Nevertheless, the case cohort does continue to demonstrate the same trend of increased incidence when MACE alone is assessed (despite not reaching statistical significance).

The significant increase in cardiovascular morbidity demonstrated by the investigators appears to contradict a significant body of literature, indicating that the syndrome confers no additional additive risk of adverse

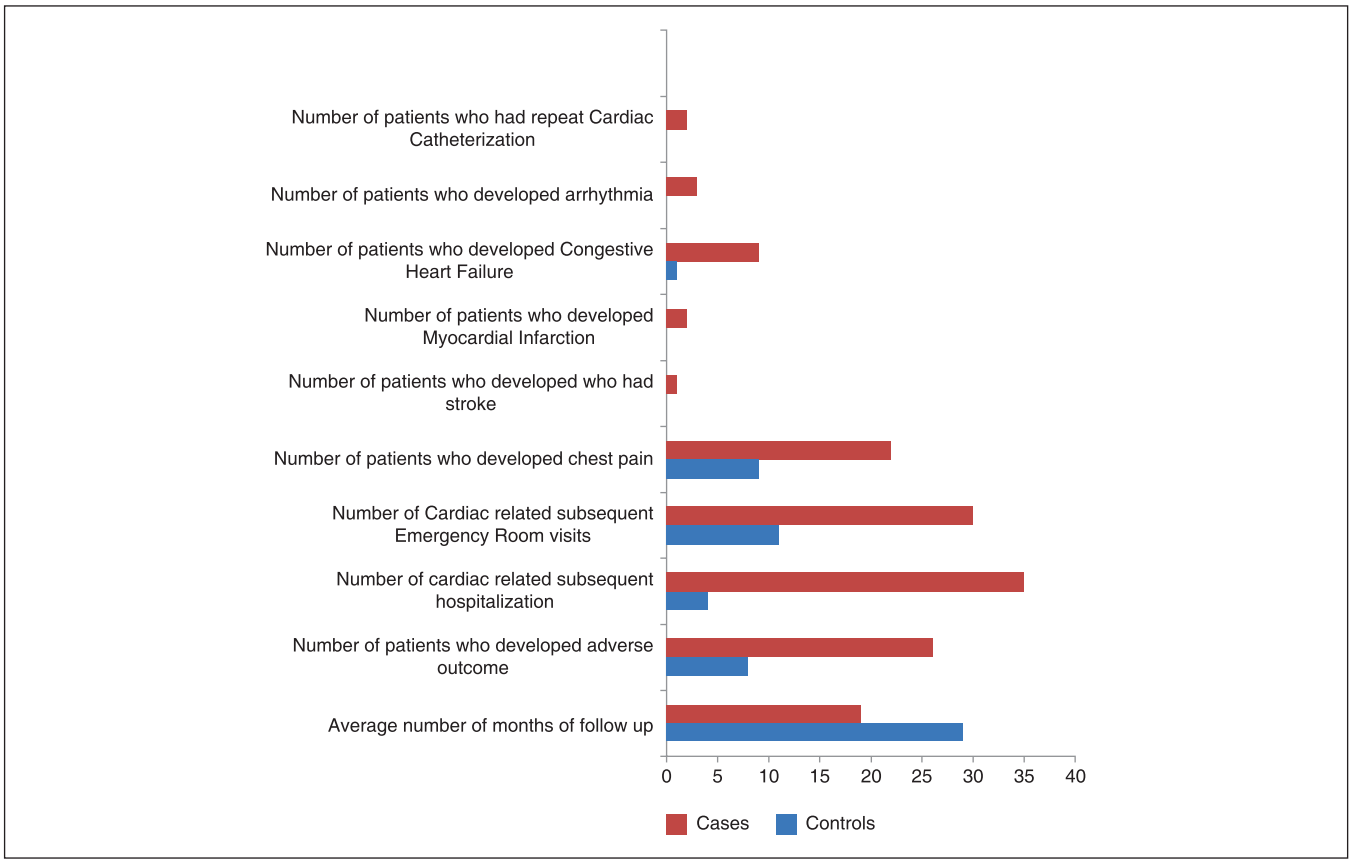

Figure 1: Clinical cardiovascular outcomes of both cohorts

cardiac events. But, as previously stated, the parameters considered in our population differs from the majority of previous populations studied. This includes the fact that a majority of prior studies have focused on outcome data in middle-aged Caucasian women.[21] We acknowledge that some of the additional risk seen in this population may be attributed to baseline cardiovascular risk factors, including the CAD equivalent diabetes, which may account for some of the differences shown. However, despite the increased prevalence of diabetes and hypertension in our patients with adverse outcomes, the number did not reach statistical significance. In fact, only tobacco was found to confer a statistically significant association with long-term outcomes on matching the cohorts.

Interestingly, other investigators have found results similar to ours.[22] Delcour *et al*., found that, in a retrospective analysis of 48 older male veterans undergoing coronary angiography, following abnormal stress testing, a statistically significant number of patients studied were at some level of increased risk for adverse cardiac outcomes.[23]

When estimating the ramifications of these findings, it is important to note that, individuals with chest pain and normal coronary arteriogram have been observed to represent 10-27% of those undergoing coronary arteriography after clinical suspicion of angina.[24,25] These figures represent a large number of individuals from the population in light of the prevalence of ischemic disease. In our institution, just over 8% were found to meet the inclusion described above (as well as meet no exclusion criteria), which was not without precedence, as other investigators have found population incidences as low as 3% (Most studies employed a combination of at least three inclusion criteria, namely (effort induced) angina pectoris, positive exercise test result and a normal coronary angiogram).[3]

Once individual CV outcomes are sub-analyzed, not surprisingly, a significant increase in the incidence of recurrent chest pain admissions is demonstrated. It is reasonable to argue that the higher volume of chest pain visits may be explained by the clinical history employed for qualification in this study in addition to the psychological impact of having a positive stress test. But, the increase in adverse outcomes post-index catheterization suggests that reasonable consideration should be given to future complaints of chest pain in this population.

As stated above, when matched for clinical outcomes, patients with baseline hypertension and diabetes mellitus

appeared to be at higher risk for future adverse events as compared to those free of these co-morbidities. A number of investigators opted to exclude this population for the CSX classification. However, the exclusion gives no explanation for the abnormal MPI. Furthermore, because diabetics are in constant state of increased systemic inflammation along with increased vascular endothelial dysfunction and diffuse small vessel disease, we argue that diabetics are predisposed to angiographically silent microvascular ischemia.[26,27] This postulation has been suggested by other investigators as well and our data also supports this. It is also important to note that the prevalence of tobacco (an agent known to increase both inflammation and endothelial dysfunction leading to a pro-atherogenic state) use was significantly higher in the study group. These findings led us to argue that the underlying pathogenesis of this syndrome involves subendocardial ischemia.

It is because of this subendocardial ischemia that we suggest the use of calcium channel-blockers coupled with the judicious use of anti-platelet therapy.[27,28] Treatments that improve endothelial function, such as angiotensin-converting enzyme inhibitors, estrogen, statins and lifestyle modifications, may be promising additions to treatment regimens for CSX. However, due to the largely unknown pathogenesis of this syndrome and the lack of quality outcome data, we suggest large, randomized prospective trials aimed at answering these therapeutic questions (with the additional use of MRI and NMR to help define the microvasculature circulation).

Although a number of investigators have argued that CSX is a disease limited almost exclusively to women, our findings imply otherwise. In fact, recent reviews suggest that over 43% of individuals proposed to meet criteria for syndrome x are male sex.[3] The Veterans Association (VA) study demonstrated an increase in adverse events among their all-male, predominantly, white cohort.[23] In our selection of patients, we found that over 50% of individuals meeting criteria for syndrome x-like disease were male. However, potentially more interesting is that the population studied was significantly more ethnically diverse and may better represent entire CSX cohort as a whole, an analysis called for by the VA investigators. Nevertheless, given the diverse nature of the patient population studied, it is reasonable to, at minimum, reject the hypothesis that male sex confers near immunity to the disease.

Aspirin is a standard therapy in patients considered to have underlying ischemia without significant contraindication (data currently suggests contraindication to its use in patients who are believed to have been ruled-out for ischemic disease over concern for its non-steroidal anti-inflammatory properties). However, even after anti-platelet use is considered, there is no significant correlation with outcomes. In fact, all anti-platelet, vasodilator, calcium-channel and neurohormonal-modulating agents were used equally or significantly more frequently in the case cohort, suggesting that the observed outcomes were not due to non-treatment with these medications. We could not routinely screen for medication compliance given the retrospective nature of this study. However, since the study cohorts were both gender- and age-matched (on review, there was a predominance of males who underwent stress testing at many institutions) after meeting inclusion criteria, this approach should still lead to an unbiased estimate of the effects of a clinical presentation consistent with CSX-like disease.

Our study has several limitations. First, the inherent limitations of a retrospective study must be acknowledged, including missing data and the inability to control for all confounders. Second, because of the limited size of the study population, statistical power could not be reached when evaluating several of the secondary endpoints, including arrhythmia and CHF admissions. However, as described above, the study did reach statistical power to sufficiently evaluate its primary endpoint. Finally, limitations in data collection hindered determination of the effect of medications such as calcium-channel blockers on disease outcome.

CONCLUSION

In summary, our study demonstrated that chest pain patients with a positive stress test and negative coronary angiograms are still at a higher risk of subsequent adverse cardiovascular events when compared to those with a negative stress test. These may be more appropriately labelled as 'false-negative' coronary angiograms rather than 'false-positive' stress tests. This appears to be gender-neutral and more likely to be seen in those patients with multiple cardiovascular disease risk factors, including tobacco use, hypertension and diabetes. Rather than dismissing these patients as having non-cardiac chest pain, aggressive preventive strategies might be useful in attenuating the morbidity and costs associated with this condition.

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REFERENCES

1. Pepine CJ, Balaban RS, Bonow RO, Diamond GA, Johnson BD, Johnson PA, *et al*. National Heart, Lung and Blood Institute, American College of Cardiology Foundation. Women's Ischemic Syndrome Evaluation: Current status and

future research directions: Report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002: Section 1: Diagnosis of stable ischemia and ischemic heart disease. Circulation 2004;109:e44-6.
2. Johnson DB. Clinical diagnosis of angina-the WISE experience. Women and Ischemia Syndrome Evaluation: Diagnosis and Pathophysiology of Ischemic Heart Disease Workshop; 2002.
3. Vermeltfoort IA, Raijmakers PG, Riphagen II, Odekerken DA, Kuijper AF, Zwijnenburg A, *et al*. Definitions and incidence of cardiac syndrome X: Review and analysis of clinical data. Clin Res Cardiol 2010;99:475-81.
4. Kemp HG Jr, Vokonas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary angiograms. Report of a six year experience. Am J Med 1973;54:735-42.
5. Pasternak RC, Thibault GE, Savoia M, DeSanctis RW, Hutter AM Jr. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. Am J Med 1980;68:813-7.
6. Dart AM, Davies HA, Dalal J, Ruttley M, Henderson AH. "Angina" and normal coronary arteriograms: A follow-up study. Eur Heart J 1980;1:97-100.
7. Wielgosz AT, Fletcher RH, McCants CB, McKinnis RA, Haney TL, Williams RB. Unimproved chest pain in patients with minimal or no coronary disease: A behavioral phenomenon. Am Heart J 1984;108:67-72.
8. Papanicolaou MN, Califf RM, Hlatky MA, McKinnis RA, Harrell FE Jr, Mark DB, *et al*. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986;58:1181-7.
9. Day LJ, Sowton E. Clinical features and follow-up of patients with angina and normal coronary arteries. Lancet 1976;2:334-7.
10. Ockene IS, Shay MJ, Alpert JS, Weiner BH, Dalen JE. Unexplained chest pain in patients with normal coronary arteriograms: A follow-up study of functional status. N Engl J Med 1980;303:1249-52.
11. Isner JM, Salem DN, Banas JS Jr, Levine HJ. Long-term clinical course of patients with normal coronary arteriography: Follow-up study of 121 patients with normal or nearly normal coronary arteriograms. Am Heart J 1981;102:645-53.
12. Hurst T, Olson TH, Olson LE, Appleton CP. Cardiac syndrome X and endothelial dysfunction: New concepts in prognosis and treatment. Am J Med 2006;119:560-6.
13. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101:1899-906.
14. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948-54.
15. Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, *et al*. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106:653-8.
16. von Mering GO, Arant CB, Wessel TR, McGorray SP, Bairey Merz CN, Sharaf BL, *et al*. National Heart, Lung, and Blood Institute. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: Results from the National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:722-5.
17. Kwong RY, Schussheim AE, Rekhraj S, Aletras AH, Geller N, Davis J, *et al*. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. Circulation 2003;107:531-7.
18. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, *et al*. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 2002;346:1948-53.
19. Wessel TR, Arant CB, McGorray SP, Sharaf BL, Reis SE, Kerensky RA, *et al*. NHLBI Women's Ischemia Syndrome Evaluation (WISE). Coronary microvascular reactivity is only partially predicted by atherosclerosis risk factors or coronary artery in women evaluated for suspected ischemia: Results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE). Clin Cardiol 2007;30:69-74.
20. Cannon RO 3rd. Microvascular angina and the continuing dilemma of chest pain with normal coronary angiograms. J Am Coll Cardiol 2009;54:877-85.
21. Kaski JC. Overview of gender aspects of cardiac syndrome X. Cardiovasc Res 2002;53:620-6.
22. Johnson BD, Shaw LJ, Buchthal SD, Bairey Merz CN, Kim HW, Scott KN, *et al*. National Institutes of Health-National Heart, Lung, and Blood Institute. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: Results from the National Institutes of Health-National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:2993-9.
23. Delcour KS, Khaja A, Chockalingam A, Kuppuswamy S, Dresser T. Outcomes in patients with abnormal myocardial perfusion imaging and normal coronary angiogram. Angiology 2009;60:318-21.
24. Verna E, Ceriani L, Giovanella L, Binaghi G, Garancini S. "False-positive" myocardial perfusion scintigraphy findings in patients with angiographically normal coronary arteries: Insights from intravascular sonography studies. J Nucl Med 2000;41:1935-40.
25. Libby P, Bonow RO, Mann DL, Zipes DP, editors. 2007. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 8th ed. Philadelphia: Elsevier Sanders; 2008:371-90.
26. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, *et al*. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities Study): A cohort study. Lancet 1999;353:1649-52.
27. Cannon RO 3rd, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. Am J Cardiol 1985;56:242-6.
28. Sorop O, Bakker EN, Pistea A, Spaan JA, VanBavel E. Calcium channel blockade prevents pressure-dependent inward remodeling in isolated subendocardial resistance vessels. Am J Physiol Heart Circ Physiol 2006;291:H1236-45.

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