

# Angina With "Normal" Coronary Arteries

## A Changing Philosophy

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**E**ACH YEAR, MANY WOMEN ARE told that they have no significant heart disease following demonstration of "normal" or near-normal coronary arteries after coronary angiography and are offered no treatment beyond reassurance.<sup>1</sup> New data suggest that this approach may no longer be appropriate. Specifically, patients with chest pain and normal or near-normal coronary angiograms are a group in which the prognosis is not as benign as previously thought.

### METHODS

We searched English-language studies on MEDLINE and the Cochrane Database of Systematic Reviews from the database start dates to June 2004. Among the specific key words and phrases we used were *pathophysiology, diagnosis and therapy of angina with normal angiography; angina with normal coronary arteries; cardiac syndrome X, nonobstructive coronary disease and variant angina; etiology of chest pain of non-cardiac origin; and endothelial dysfunction and prognosis*. We also consulted reference lists of published articles and data from meeting presentations. Evidence synthesis was based on cohort studies, registry data, and trial data.

### RESULTS

#### Prevalence

*Normal*, defined as no visible disease, or nonobstructive atherosclerotic coro-

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**Context** Many women with angina are told that they have no significant heart disease following demonstration of normal or near-normal coronary arteries and are offered no specific treatment beyond reassurance.

**Evidence Acquisition** MEDLINE and the Cochrane Database of Systematic Reviews were searched from their start dates until June 2004 for analysis using specific key words including *diagnosis and therapy of angina with normal angiography* and *angina with normal coronary arteries*. Reference lists of published articles and data of meeting presentations were also consulted.

**Evidence Synthesis** Normal or nonobstructive coronary disease at angiography is not uncommon and occurs in 10% of women presenting with ST-segment elevation myocardial infarction compared with 6% in men. Patients with evidence of myocardial ischemia or myocardial infarction and nonobstructive atherosclerotic disease of the coronary arteries are more likely to be women and nonwhite. Symptoms are often indistinguishable from those with obstructive coronary artery disease. The prognosis of patients with unstable angina and nonobstructive atherosclerotic coronary artery disease is not benign and includes a 2% risk of death or myocardial infarction at 30 days of follow-up. Recent work has shown that at least 20% of women with normal or nonobstructive angiography have myocardial ischemia, likely due to atherosclerosis-related endothelial dysfunction, which itself is associated with an increased risk of later adverse cardiac events and development of frank future obstructive disease. Randomized placebo-controlled studies have demonstrated that tricyclic antidepressants,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, L-arginine, statins, and exercise may relieve symptoms, vascular dysfunction, or both; however, longer-term studies evaluating cardiac event rates need to be performed.

**Conclusions** Patients with chest pain and normal or nonobstructive coronary angiograms are predominantly women, and many have a prognosis that is not as benign as commonly thought. Assessment of endothelial function may help identify patients at risk for future cardiac events. Therapy should be directed at symptom relief with tricyclic agents and  $\beta$ -blockers, and aggressive antiatherosclerotic therapy with statins, angiotensin-converting enzyme inhibitors, or both should be applied when risk factors are present or prognostic risk is high. Large-scale randomized trials need to be conducted to determine optimal ways of preventing clinical events.

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**Table.** Prevalence of "Normal" and Nonobstructive Coronary Arteries in Women Compared With Men

	No./Total (%)		P Value
	Women	Men	
Acute coronary syndrome GUSTO <sup>2</sup>	343/1768 (19.4)	394/4638 (8.4)	<.001
TIMI 18 <sup>3</sup>	95/555 (17)	99/1091 (9)	<.001
Unstable angina <sup>2</sup>	252/826 (30.5)	220/1580 (13.9)	<.001
TIMI IIIa <sup>6</sup>	30/113 (26.5)	27/278 (8.3)	<.001
MI without ST-segment elevation <sup>2</sup>	41/450 (9.1)	55/1299 (4.2)	.001
MI with ST-segment elevation <sup>2</sup>	50/492 (10.2)	119/1759 (6.8)	.02

Abbreviations: GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

nary disease (luminal irregularities <50% judged visually) at coronary angiography is present in 10% to 25% of women presenting with acute coronary syndrome and ST-segment elevation myocardial infarction compared with 6% to 10% in men, suggesting that this is more common in women<sup>2-5</sup> (TABLE). Patients with evidence of myocardial ischemia or myocardial infarction and nonobstructive coronary arteries are more likely to be women.<sup>6</sup> Among these patients, approximately half have nonobstructive coronary disease, while half demonstrate no angiographically visually detectable disease at coronary angiography.<sup>6</sup> In some patients, pathologically important atherosclerotic coronary disease may be present even in the absence of angiographically observed stenoses because atherosclerosis may occur in a diffuse manner and lead to remodeling of the arterial wall, where the wall thickens and expands outward without encroaching on the lumen.<sup>7,8</sup>

There are an estimated 1.4 million patients discharged from US hospitals following an acute coronary syndrome annually, and among these 600 000 are women.<sup>9</sup> Among those women for whom angiographic data are available, this 10% to 25% "normal" coronary angiography rate<sup>1</sup> translates into 60 000 to 150 000 women with acute coronary syndrome or myocardial infarction with nonobstructive coronary disease annually in the United States alone.

### Prognosis

The prognosis of "normal" coronary arteries in the setting of signs and symptoms of myocardial ischemia is not as benign as reported by preliminary cohort studies,<sup>10-12</sup> and as commonly assumed by physicians. Short-term prognosis of patients with unstable angina and nonobstructive coronary artery disease includes a 2% risk of death or myocardial infarction at 30 days of follow-up.<sup>6</sup> Most recently, outcome data from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study documents that women with nonobstructive coronary disease and evidence of myocardial ischemia have a relatively poor prognosis compared with women with nonobstructive coronary disease and no myocardial ischemia.<sup>13</sup> More than 40% of these patients are rehospitalized for chest pain more than once, and 30% undergo repeat coronary angiography over 1- to 5-year follow-up periods despite demonstration of "normal" coronary arteries on angiography during a prior hospitalization.<sup>14</sup> In addition, compared with the baseline population, these patients are at increased risk for traditionally defined major cardiovascular events including premature death, myocardial infarction and stroke.<sup>15</sup>

### Causes of Angina With Normal Angiograms

The pathophysiology of women with angina and "normal" angiograms is not homogeneous: some patients have chest

pain of noncardiac origin, others have chest pain of cardiac but nonischemic origin, and others have chest pain due to myocardial ischemia related to atherosclerotic coronary vascular abnormalities, presumably related to diffuse disease without focal obstructions. All groups may have disability due to chest pain, but prognosis and optimal therapeutic management may be different.

Not only is angina with "normal" or nonobstructive coronary angiography a heterogeneous disorder, differences between different reported studies are likely also related to differences in constitution of study populations. Characterization of such patients depends on the extent to which they are investigated, usually with special testing not routinely used.

### Coronary Artery Spasm

Myocardial infarction, cardiac arrest, and sudden death can occur, although infrequently, with variant angina in the absence of obstructive coronary stenosis.<sup>16,17</sup> A number of studies have reported a low incidence of coronary artery vasospasm in predominantly white populations presenting with signs and symptoms of ischemia. Overall, only 2% to 3% of patients with chest pain undergoing coronary angiography appear to have variant angina.<sup>18</sup> Among 217 patients hospitalized at the Montreal Heart Institute between 1976 and 1986 with this diagnosis, 86 (40%) were found to have normal or near-normal angiograms.<sup>19</sup> Thus, while coronary artery spasm can account for the signs and symptoms of ischemia, it does not appear to play a major role in patients with angina in the absence of obstructive coronary disease.

### Myocardial Ischemia With Nonobstructive Coronary Arteries

Recent data suggest that the ST-segment changes and abnormalities in myocardial reversible perfusion defects frequently observed in patients with anginalike chest pain and "normal" coronary arteries may be true myocardial ischemia likely related to atherosclerotic disease, and not false-positive test results. This view is sup-

ported by the documentation of abnormal coronary blood flow responses to vasoactive stimuli,<sup>20</sup> production of sensitive markers of ischemia, including increased transmyocardial lipoperoxide activity,<sup>21</sup> and abnormalities in myocardial phosphorus metabolism consistent with stress-induced myocardial ischemia.<sup>22</sup> These data shed light on prior studies that failed to show myocardial lactate production, albeit an insensitive marker of myocardial ischemia, or impaired left ventricular dysfunction<sup>23,24</sup> during angina and ST-segment depression, which generated doubts on the ischemic origin of pain in a part of these patients.<sup>25</sup>

### Chest Pain of Noncardiac and Cardiac but Nonischemic Origin

Recurrent chest pain of noncardiac origin is a frequent clinical problem. Gastroesophageal reflux and psychiatric disorders are the most common causes of such pain.<sup>26,27</sup> A number of women with chest pain and normal coronary angiograms, including those with ischemic-appearing exercise electrocardiograms, may have exaggerated or abnormal cardiac pain perception that is unrelated to psychological disorders.<sup>28,29</sup> Of note, even in women with obstructive coronary artery disease, pain perception is often increased for reasons that remain poorly understood.<sup>30</sup>

### DIAGNOSIS AND ASSESSMENT

A variety of questions are relevant to assessment and therapeutic clinical decision making in the setting of angina and "normal" coronary arteries. These include: Are symptom patterns helpful in distinguishing etiology? How can vascular dysfunction be tested? and Is vascular dysfunction in the absence of obstructive coronary disease a treatment target? The goals of testing are to identify patients with nonobstructive coronary vascular dysfunction, as well as to risk stratify those patients at risk for future adverse cardiovascular events.

#### Symptoms

Chest pain presentation is often reported by clinicians to be more atypical

in women with so-called "normal" angiograms.<sup>31</sup> Although there is little empirical support for a different symptom profile or vocabulary, the results of a recent study<sup>32</sup> suggest that differences may indeed exist in angina pain location in a minority of these patients. The chest discomfort in angina with "normal" angiograms is often similar in quality to that of classic angina although it is usually more intense. Patients usually describe it as "constricting pain," rather than as an "oppressive feeling," and the pain may persist 30 minutes or more.<sup>32</sup> Data from the WISE study indicate that typical vs atypical angina does not discriminate between obstructive and nonobstructive coronary disease in a population of women undergoing coronary angiography.<sup>33</sup> Women with angina and normal angiograms may present with symptoms of both stable and unstable angina. The majority of patients seem to be between these 2 extremes, with a variable prevalence of the 2 types of symptoms.

Several clues in a patient's history may suggest the presence of angina despite "normal" angiograms; these include an extremely variable threshold of physical activity that provokes angina<sup>31</sup>; radiation of the discomfort to the submammary areas<sup>32</sup>; and features associated with pain, such as mental arousal, or palpitation.<sup>34</sup> A recent study demonstrated that chest pain that persists for many years after angiography in women with apparently "normal" coronaries is associated with future development of coronary atherosclerosis.<sup>32</sup>

In summary, patients with angina and nonobstructive coronary arteries are often indistinguishable from those with angina and obstructive coronary artery disease. Although clinical presentation and outcome of chest pain may provide some insights, it is too subjective to help with individual patient diagnosis and risk stratification.

#### Diagnosis of Vascular Dysfunction

Coronary arteriolar vessels continuously adjust vasomotor tone and therefore blood supply to changes in myo-

cardial oxygen demand. Coronary flow reserve is the increase in blood flow in response to metabolic or pharmacological stimulations.<sup>35</sup> Maximal or near-maximal coronary vasodilatation can be induced by various interventions, the most clinically relevant being intravenous administration of dipyridamole or adenosine.<sup>36,37</sup> A normal coronary flow reserve is an increase of 2.5- to 5-fold.<sup>35,38,39</sup> An impaired coronary flow reserve is an indication that ischemia can be precipitated during periods of increased myocardial oxygen demand (FIGURE 30).

Opherk et al<sup>40</sup> first reported the finding of reduced coronary flow reserve in patients with angina and "normal" angiograms using the argon washout method. Several investigators using different techniques, such as coronary sinus thermodilution, positron emission tomography, and intracoronary Doppler velocity, have subsequently confirmed this finding.<sup>20,23,38,39</sup> More recent studies addressed this issue calculating myocardial perfusion by magnetic resonance imaging.<sup>36,37</sup> Approximately 25% of the population of patients with angina and "normal" or near-normal angiograms had an abnormally reduced flow reserve using this technique<sup>37</sup>; however, this may underestimate the prevalence due to issues of providing an adequate stress in the magnetic resonance imaging magnet. Gated single-photon emission computed tomography,<sup>37</sup> and positron emission tomography<sup>38</sup> can also detect abnormal flow reserve patterns. The prevalence of vascular dysfunction by coronary flow assessment,<sup>39</sup> single-photon emission computed tomography,<sup>37</sup> or positron emission tomography<sup>38</sup> consistently demonstrate abnormalities in 50% to 60% of women with "normal" or near-normal angiograms, suggesting that vascular dysfunction is common in this population.

In summary, perfusion-imaging studies may provide evidence that patients with chest pain actually have vascular dysfunction measured by reduced coronary blood flow reserve in the absence of obstructive flow-limiting coronary stenoses.

**Assessing the Causes of Reduced Coronary Flow Reserve**

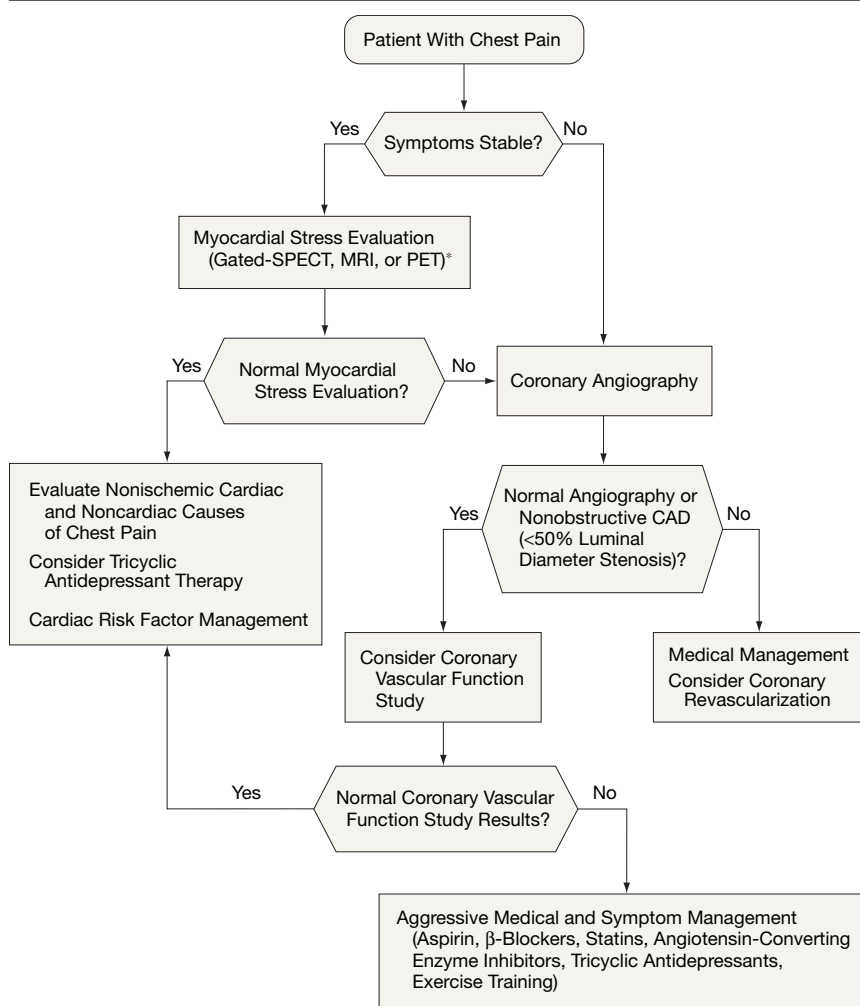
There are a number of likely causes for impairment of coronary flow reserve in patients with nonobstructive coronary angiograms. Coronary flow is regulated by several endothelium-dependent and independent factors influencing macrovascular and microvascular tone. Endothelium-independent factors include aortic pressure, myocardial compressive forces, neuro-

humoral substances, and myocardial metabolism.<sup>41</sup> The endothelium regulates vasomotor tone by stimulating release of vasoactive factors. A major vasodilator substance is nitric oxide, originally identified as an endothelium-derived relaxing factor.<sup>42</sup>

Coronary flow reserve is directly measured using adenosine and dipyridamole and indirectly using acetylcholine. Dipyridamole induces vasodilatation by inhibition of the reuptake of adenosine

released by cardiac myocytes. The vasodilator response to adenosine is the result of endothelium-dependent and endothelium-independent factors. Adenosine stimulates  $\alpha$  receptors on endothelial cells with subsequent opening of sensitive potassium channels and stimulation of endothelial release of nitric oxide,<sup>43</sup> but it also increases intracellular cyclic adenosine monophosphate, which directly mediates smooth muscle relaxation.<sup>44</sup> Acetylcholine specifically tests the endothelial-dependent aspect of vascular dysfunction. Patients with decreased endothelium-dependent vasodilation responses, by definition, have decreased coronary flow reserve. Conversely, impaired coronary flow reserve does not necessarily mean endothelial vascular dysfunction because the abnormality could reside in the endothelium-independent response. Functional derangements of the microvascular arteries with no or minor endothelial dysfunction have been widely reported in several clinical conditions, such as hypertrophic cardiomyopathy,<sup>45</sup> idiopathic dilated cardiomyopathy,<sup>46</sup> and systemic collagen diseases.<sup>47</sup> Nonobstructive arteriolar narrowing may be a marker of microvascular damage from aging, hypertension, inflammation, and other processes. A prior study suggests that it reflects coronary artery intimal thickening and medial hyperplasia, hyalinization, and sclerosis.<sup>48</sup>

**Figure.** Practical Algorithm for Management of Patients With Symptoms and Nonobstructive Coronary Artery Disease



MRI indicates magnetic resonance imaging; PET, positron emission tomography; CAD, coronary artery disease. Vascular function studies include coronary flow reserve and coronary acetylcholine testing. All patients should have cardiac risk factor management, as appropriate, according to the American Heart Association/American College of Cardiology guidelines.<sup>76,77</sup>

\*Which specific test to obtain depends on patient and institutional circumstances. In some cases serial tests may be needed (eg, first a stress electrocardiogram or echocardiogram followed by gated single-photon emission computed tomography [SPECT]).

**Prognostic Value of Coronary Flow Reserve**

Abnormalities in coronary microvascular responses to adenosine do not appear to be predictive of adverse outcomes in patients with chest pain and normal angiograms and in those with coronary artery disease.<sup>15,49-51</sup> Conversely, when impaired coronary flow reserve is accompanied by coronary endothelial dysfunction, as assessed by acetylcholine testing, it predicts an unfavorable outcome.<sup>15,32,49-51</sup> Outcomes, therefore, can be quite different in an apparently homogeneous population of women found to have chest pain related to abnormalities in impaired coro-

nary flow reserve as assessed by magnetic resonance imaging or single-photon emission computed tomography.<sup>13,32</sup>

Coronary endothelial dysfunction in patients with obstructive coronary artery disease provides prognostic value independent of that given by assessment of the traditional cardiovascular risk factors.<sup>50-53</sup> A number of studies have also addressed the long-term prognostic value of endothelial function testing in patients with nonobstructive coronary artery disease and demonstrate that endothelial dysfunction is significantly associated with more adverse cardiovascular events over a 2-, 4-, and 7-year follow-up.<sup>15,50,51</sup> A recent investigation<sup>30</sup> of 42 women demonstrated that 30% of those women with chest pain, "normal" angiograms, and severe endothelial dysfunction developed coronary disease during a 10-year follow-up.<sup>32</sup> An additional study in 163 patients with "normal" coronary angiography and abnormal endothelial function showed an overall event rate of 14% at 48 months. Outcome data included increased rates of cardiovascular death (10% of adverse events); acute myocardial infarction, congestive heart failure, or stroke (21% of adverse events); and angina, revascularization, or other vascular events (69% of adverse events).<sup>50</sup>

### Acetylcholine Testing and Endothelial Dysfunction

Techniques to detect coronary artery endothelial dysfunction are not widely used in the clinical setting. Intracoronary acetylcholine testing is considered the gold standard for detection of coronary endothelial function,<sup>52</sup> and acetylcholine during brachial artery ultrasound can be used for determining peripheral endothelial function.<sup>54</sup> Many clinical research studies extrapolate data obtained by peripheral testing to coronary circulation given the diffuse nature of atherosclerosis. However, the assumption that endothelial dysfunction in the brachial artery directly reflects coronary endothelial dysfunction needs confirmation.

Loss of endothelium-dependent vasodilatation in response to acetylcholine is regarded as a sign of early stage vascular injury and atherosclerosis.<sup>55</sup> An impaired ability of the endothelium to release vasoactive substances can facilitate inflammation, platelet aggregation, coronary vasoconstriction, leukocyte adhesion, and oxidative modification of low-density lipoprotein cholesterol.<sup>56</sup> Endothelial dysfunction has been related to oxidative stress that may result from atherosclerotic risk factors, inflammation, and genetic conditions still poorly understood.<sup>57,58</sup> All these factors may facilitate development of atherosclerosis in the vessel wall and predispose to vascular events by prothrombotic mechanisms, which may account for the prognostic value of acetylcholine testing.

## CONTROVERSIES

### Relation Between Angiographically Nonvisible Atherosclerosis and Endothelial Dysfunction

Many women presenting with chest pain and "normal" coronary arteries actually have coronary atherosclerosis not detected by coronary angiography but identifiable by intravascular ultrasound.<sup>59</sup> It is currently unknown what correlation there may be between plaque burden by intravascular ultrasound and the presence and severity of coronary vascular dysfunction.

Although intravascular ultrasound indices of plaque burden correlate with traditional atherosclerosis risk factors,<sup>60</sup> many other issues currently discourage the clinical use of intravascular ultrasound for characterization of coronary arteries in normal angiograms. Intravascular ultrasound may not be helpful in predicting adverse cardiac events.<sup>51</sup> There does not appear to be a correlation between plaque burden and endothelial and nonendothelial coronary blood flow response.<sup>51,60</sup> Atherosclerosis is a complex chronic disease, which is initiated early in life and is likely a common finding, irrespective of the presence of visible structural changes.<sup>55,61</sup>

Endothelial dysfunction, impaired coronary flow reserve, and atheroscle-

rosis, although causally related in many patients, are distinct problems and may exist separately. Many patients have mild atherosclerosis but normal endothelial function.<sup>15,51</sup> Others may show underlying atherosclerotic plaques and normal coronary flow reserve.<sup>60</sup> Thus, endothelial dysfunction may not simply be a marker of atherosclerosis. Conversely, hyperlipidemia causes endothelial dysfunction and early reversible atherogenic processes even before there are angiographically visible plaques.<sup>62</sup> Mild and moderate plaques are the most common cause of acute coronary syndrome, which may provide a link between seemingly "normal" coronary arteries and increased risk of future cardiac events.<sup>63</sup>

Accordingly, women previously found to have "normal" coronary angiograms but abnormal response to acetylcholine<sup>32</sup> may have an accelerated atherosclerotic process. Specifically, the development of obstructive coronary artery disease may reflect progression of endothelial dysfunction and atherosclerotic disease that was already present.

### Therapeutic Strategies

No randomized trials comparing therapies for the reduction of adverse cardiac events in patients with angina and "normal" coronary arteries have been conducted, and available adverse outcome data are limited to cohort studies. Observational evidence does not support the widespread use of calcium antagonists in patients with "normal" angiograms because they seem to do little to prevent chest pain during daily life in these patients.<sup>34,64-66</sup> Other work has documented that calcium antagonists fail to ameliorate the diminished coronary blood flow reserve of these patients.<sup>67</sup> Nitrates are referred to be of help anecdotally in some patients but not in others. No cohort studies have reported the effects of nitrates during daily life, and the placebo effect of nitrates cannot be ruled out.

$\beta$ -Blockers have been shown to be highly effective for reduction of chest pain episodes during daily life.<sup>34,65</sup> There

are several potential mechanisms by which  $\beta$ -blockers may act in reducing chest pain recurrences. They may counteract the proischemic effects of increased adrenergic tone or may simply reduce myocardial oxygen demand.  $\beta$ -Blockers are endothelium-dependent vasodilators as well.<sup>68</sup> The proven benefit of exercise training in this population suggests that mechanism of adrenergic modulation plays a role.<sup>69</sup>

Imipramine improves the symptoms of patients with abnormal cardiac pain perception and "normal" coronary angiograms, possibly through a visceral analgesic effect.<sup>13</sup> Imipramine also has anticholinergic and  $\alpha$ -antagonist effects, which have been demonstrated in the coronary as well as peripheral circulation<sup>70</sup> and which may be relevant in the modulation of the coronary microcirculation.

More recently, oxidative stress has been shown to be a potential mechanism of disease in women with normal or near-normal angiography and endothelial dysfunction.<sup>64</sup> Accordingly, long-term, 6-month supplementation of L-arginine, the precursor of nitric oxide, improved endothelial function and symptoms in patients with nonobstructive coronary artery disease.<sup>71</sup> Statins and angiotensin-converting enzyme inhibitors improve endothelial dysfunction,<sup>64,72</sup> may counteract oxidative stress, and may be of benefit in patients with "normal" angiograms.<sup>64,72,73</sup> The beneficial effects of statins on coronary microcirculation have been documented in other clinical studies.<sup>74</sup> Combination of drugs, specifically statins and angiotensin-converting enzyme inhibitors, may largely amplify these benefits.<sup>64</sup> Menopausal hormone therapy may improve emotional well-being in postmenopausal women with angina and "normal" angiograms; however, there is no significant treatment effect on chest pain occurrence and its threshold when these patients exercise.<sup>75</sup>

## CONCLUSIONS

Patients with "normal" or nonobstructive coronary angiography have his-

torically been reassured that they do not have heart disease. New findings demonstrate that many of these patients, who are predominantly women, frequently have persistence of symptoms, are rehospitalized, and have relatively high rates of progression to obstructive coronary artery disease and adverse cardiac events. Uncertainty about the mechanism of the symptoms and treatment efficacy can potentially lead to perpetuation of symptoms, difficulties in management, and neglect of atherosclerotic cardiac risk factor treatment.

## Recommendations

Perfusion testing with magnetic resonance imaging or gated single-photon emission computed tomography can be a first step toward identifying patients with chest pain and "normal" or nonobstructive coronary angiograms who are at risk of subsequent cardiac events. Additional invasive testing aimed at determining coronary endothelial dysfunction may be helpful to assess the etiological mechanisms of impaired coronary flow reserve and further risk stratification of future adverse cardiac events (Figure).

Lifestyle changes and risk factor management should be considered essential components of any therapeutic approach for patients with traditional cardiac risk factors, evidence of atherosclerosis, or both.<sup>76,77</sup> For patients without evidence of a cardiac etiology for their chest pain, referral for evaluation of noncardiac causes of chest pain is appropriate. For patients with apparent cardiac chest pain but without evidence of myocardial ischemia, vascular dysfunction, or both, analgesic intervention with imipramine may be an appropriate symptomatic treatment. For patients with cardiac chest pain and evidence of ischemia by perfusion testing,  $\beta$ -adrenergic blockers may reduce myocardial oxygen consumption and symptoms. Exercise training has also been demonstrated to be beneficial.<sup>69</sup> Aggressive therapy with statins and angiotensin-converting enzyme inhibitors should be used for patients who

qualify for this treatment by the presence of cardiac risk factors and have evidence of atherosclerosis or evidence of endothelial dysfunction. Persistence or deterioration of symptoms despite aggressive medical therapy in women with endothelial dysfunction may be indicative of coronary disease progression and repeat coronary angiography can be appropriate (Figure).

## Future Directions

Knowledge of the mechanisms and pathophysiology of vascular dysfunction in patients with angina and "normal" or nonobstructive coronary disease is still rudimentary. Although experimental, clinical, and epidemiological studies show associations and potential links between oxidative stress, endothelial dysfunction, and early reversible atherogenic processes, there is a substantial need for further work.

Large-scale collaborative randomized clinical trials are needed to determine the effectiveness of symptomatic treatment, as well as treatment of coronary endothelial dysfunction, and to test whether change in endothelial function relates to changes in outcomes. Future study should also be directed at determining the value of less invasive methods of endothelial dysfunction and an early coronary atherosclerotic burden evaluation.<sup>78</sup>

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**Study concept and design:** Bugiardini, Bairey Merz.

**Acquisition of data:** Bugiardini, Bairey Merz.

**Analysis and interpretation of data:** Bugiardini, Bairey Merz.

**Drafting of the manuscript:** Bugiardini, Bairey Merz. **Critical revision of the manuscript for important intellectual content:** Bugiardini, Bairey Merz.

**Administrative, technical, or material support:** Bugiardini, Bairey Merz.

**Study supervision:** Bugiardini, Bairey Merz.

## REFERENCES

1. Panza JA. Myocardial ischemia and the pains of the heart. *N Engl J Med*. 2002;346:1934-1935.
2. Hochman JS, Tamis JE, Thompson TD, et al; Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *N Engl J Med*. 1999;341:226-232.
3. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women

- with acute coronary syndromes. *JAMA*. 2002;288:3124-3129.
4. Hochman JS, McCabe CH, Stone PH, et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. *J Am Coll Cardiol*. 1997;30:141-148.
  5. Krumholz HM, Douglas PS, Lauer MS, Pasternak RC. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? *Ann Intern Med*. 1992;116:785-790.
  6. Diver DJ, Bier JD, Ferreira PE, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-III Trial). *Am J Cardiol*. 1994;74:531-537.
  7. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Koletis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316:1371-1375.
  8. Schoenhagen P, Nissen SE, Tuzcu EM. Coronary arterial remodeling: from bench to bedside. *Curr Athroscle Rep*. 2003;5:150-154.
  9. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, Tex: American Heart Association; 2003.
  10. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol*. 1986;7:479-483.
  11. Lichten PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol*. 1995;25:1013-1018.
  12. Kaski JC, Rosano GM, Collins P, et al. Cardiac syndrome X: clinical characteristics and left ventricular function: long-term follow-up study. *J Am Coll Cardiol*. 1995;25:807-814.
  13. Johnson BD, Shaw LJ, Buchthal SD, et al. 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;109:2993-2999.
  14. Cannon RO III, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med*. 1994;330:1411-1417.
  15. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation*. 2002;106:653-658.
  16. MacAlpin RN. Cardiac arrest and sudden unexpected death in variant angina: complications of coronary spasm that can occur in the absence of severe organic coronary stenosis. *Am Heart J*. 1993;125:1011-1017.
  17. Bertrand ME, LaBlanche JM, Tilmant PY, et al. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation*. 1982;65:1299-1306.
  18. Mark DB, Califf RM, Morris KG, et al. Clinical characteristics and long-term survival of patients with variant angina. *Circulation*. 1984;69:880-888.
  19. Walling A, Waters DD, Miller DD, Roy D, Pelletier GB, Theroux P. Long-term prognosis of patients with variant angina. *Circulation*. 1987;76:990-997.
  20. Bugiardini R, Pozzati A, Ottani F, Morgagni GL, Puddu P. Vasotonic angina: a spectrum of ischemic syndromes involving functional abnormalities of the epicardial and microvascular coronary circulation. *J Am Coll Cardiol*. 1993;22:417-425.
  21. Buffon A, Rigattieri S, Santini SA, et al. Myocardial ischemia-reperfusion damage after pacing-induced tachycardia in patients with cardiac syndrome X. *Am J Physiol Heart Circ Physiol*. 2000;279:H2627-H2633.
  22. Buchthal SD, den Hollander JA, Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med*. 2000;342:829-835.
  23. Camici PG, Marraccini P, Lorenzoni R, et al. Coronary hemodynamics and myocardial metabolism in patients with syndrome X: response to pacing stress. *J Am Coll Cardiol*. 1991;17:1461-1470.
  24. Panza JA, Laurienzo JM, Curiel RV, et al. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol*. 1997;29:293-301.
  25. Cannon RO III, Balaban RS. Chest pain in women with normal coronary angiograms. *N Engl J Med*. 2000;342:885-887.
  26. Ho KY, Kang JY, Yeo B, Ng WL. Non-cardiac, non-oesophageal chest pain: the relevance of psychological factors. *Gut*. 1998;43:105-110.
  27. Mayou RA, Bass CM, Bryant BM. Management of non-cardiac chest pain: from research to clinical practice. *Heart*. 1999;81:387-392.
  28. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. *Heart*. 2002;87:513-519.
  29. Cannon RO III, Quyyumi AA, Schenke WH, et al. Abnormal cardiac sensitivity in patients with chest pain and normal coronary arteries. *J Am Coll Cardiol*. 1990;16:1359-1366.
  30. Sheps DS, Kaufmann PG, Sheffield D, et al. Sex differences in chest pain in patients with documented coronary artery disease and exercise-induced ischemia: results from the PIMI study. *Am Heart J*. 2001;142:864-871.
  31. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol*. 1991;17:499-506.
  32. Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study on women with chest pain and normal angiograms. *Circulation*. 2004;109:2518-2523.
  33. Johnson BD, Kelsey SF, Bairey Merz CN. Clinical risk assessment in women: chest discomfort: report from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. In: Shaw LJ, Redberg RF, eds. *Coronary Disease in Women: Evidence-Based Diagnosis and Treatment*. Totowa, NJ: Humana Press; 2003:129-142.
  34. Bugiardini R, Borghi A, Biagetti L, Puddu P. Comparison of verapamil versus propranolol therapy in syndrome X. *Am J Cardiol*. 1989;63:286-290.
  35. Berne RM. Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow. *Am J Physiol*. 1963;204:317-322.
  36. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med*. 2002;346:1948-1953.
  37. Doyle M, Fuisz A, Kortright E, et al. The impact of myocardial flow reserve on the detection of coronary artery disease by perfusion imaging methods: an NHLBI WISE study. *J Cardiovasc Magn Reson*. 2003;5:475-485.
  38. Reis SE, Holubkov R, Conrad Smith AJ, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J*. 2001;141:735-741.
  39. Reis SE, Holubkov R, Lee JS, et al. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease: results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol*. 1999;33:1469-1475.
  40. Opherk D, Mall G, Zebe H, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. *Circulation*. 1984;69:1-7.
  41. Tune JD, Gorman MW, Feigl EO. Matching coronary blood flow to myocardial oxygen consumption. *J Appl Physiol*. 2004;97:404-415.
  42. Drexler H. Factors involved in the maintenance of endothelial function. *Am J Cardiol*. 1998;82:3S-4S.
  43. Hein TW, Kuo L. cAMP-independent dilation of coronary arterioles to adenosine: role of nitric oxide, G proteins, and K(ATP) channels. *Circ Res*. 1999;85:634-642.
  44. Abebe W, Makujina SR, Mustafa SJ. Adenosine receptors-mediated relaxation of porcine coronary artery in presence and absence of endothelium. *Am J Physiol*. 1994;266:H2018-H2025.
  45. Cannon RO III, Dilisizian V, O'Gara PT, et al. Myocardial metabolic, hemodynamic, and electrocardiographic significance of reversible thallium-201 abnormalities in hypertrophic cardiomyopathy. *Circulation*. 1991;83:1660-1667.
  46. Stolen KQ, Kempainen J, Kalliokoski KK, et al. Myocardial perfusion reserve and peripheral endothelial function in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2004;93:64-68.
  47. Strauer BE, Brune I, Schenk H, Knoll D, Perings E. Lupus cardiomyopathy: cardiac mechanics, hemodynamics, and coronary blood flow in uncomplicated systemic lupus erythematosus. *Am Heart J*. 1976;92:715-722.
  48. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. *Ophthalmology*. 2003;110:933-940.
  49. Targonski PV, Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr, Lerman A. Coronary endothelial dysfunction is associated with an increased risk of cerebrovascular events. *Circulation*. 2003;107:2805-2809.
  50. von Mering GO, Arant CB, Wessel TR, et al. 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;109:722-725.
  51. 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;101:948-954.
  52. Quyyumi AA, Cannon RO III, Panza JA, Diodati JG, Epstein SE. Endothelial dysfunction in patients with chest pain and normal coronary arteries. *Circulation*. 1992;86:1864-1871.
  53. Schachinger V, Britten M, Zeiher A. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*. 2000;101:1899-1906.
  54. Kuvin JT, Karas RH. Clinical utility of endothelial function testing: ready for prime time? *Circulation*. 2003;107:3243-3247.
  55. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med*. 1990;323:27-36.
  56. Diodati JG, Dakak N, Gilligan DM, Quyyumi AA. Effect of atherosclerosis on endothelium-dependent inhibition of platelet activation in humans. *Circulation*. 1998;98:17-24.
  57. Dhamrait SS, Stephens JW, Cooper JA, et al. Cardiovascular risk in healthy men and markers of oxidative stress in diabetic men are associated with common variation in the gene for uncoupling protein 2. *Eur Heart J*. 2004;25:468-475.
  58. Le NA. Inflammation, oxidative stress, and atherosclerosis. *Curr Opin Lipidol*. 2004;15:227-229.
  59. Erbel R, Ge J, Bockisch A, et al. Value of intracoronary ultrasound and Doppler in the differentiation of angiographically normal coronary arteries: a prospective study in patients with angina pectoris. *Eur Heart J*. 1996;17:880-889.

60. Newby DE, McLeod AL, Uren NG, et al. Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking: direct link between endothelial dysfunction and atherothrombosis. *Circulation*. 2001;103:1936-1941.
61. Tuzcu EM, Kapadia SR, Tutar E, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. *Circulation*. 2001;103:2705-2710.
62. Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *J Am Coll Cardiol*. 1994;24:1468-1474.
63. Haft JJ, Haik BJ, Goldstein JE, et al. Development of significant coronary artery lesions in areas of minimal disease: a common mechanism for coronary disease progression. *Chest*. 1988;94:731-736.
64. Pizzi C, Manfredi O, Fontana F, Bugiardini R. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac syndrome X: role of superoxide dismutase activity. *Circulation*. 2004;109:53-58.
65. Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. *Am J Cardiol*. 1999;84:854-856.
66. Masumoto A, Mohri M, Takeshita A. Three-year follow-up of the Japanese patients with microvascular angina attributable to coronary microvascular spasm. *Int J Cardiol*. 2001;81:151-156.
67. Sutsch G, Oechslin E, Mayer I, Hess OM. Effect of diltiazem on coronary flow reserve in patients with microvascular angina. *Int J Cardiol*. 1995;52:135-143.
68. Kalinowski L, Dobrucki LW, Szczepanska-Konkel M, et al. Third-generation beta-blockers stimulate nitric oxide release from endothelial cells through ATP efflux: a novel mechanism for antihypertensive action. *Circulation*. 2003;107:2747-2752.
69. Eriksson BE, Tyni-Lenne R, Svedenhag J, et al. Physical training in Syndrome X: physical training counteracts deconditioning and pain in Syndrome X. *J Am Coll Cardiol*. 2000;36:1619-1625.
70. Kelley BM, Porter JH. The role of muscarinic cholinergic receptors in the discriminative stimulus properties of clozapine in rats. *Pharmacol Biochem Behav*. 1997;57:707-719.
71. Lerman A, Burnett JC Jr, Higano ST, McKinley LJ, Holmes DR Jr. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation*. 1998;97:2123-2128.
72. Kayikcioglu M, Payzin S, Yavuzgil O, Kultursay H, Can LH, Soydan I. Benefits of statin treatment in cardiac syndrome-X1. *Eur Heart J*. 2003;24:1999-2005.
73. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. *Am J Cardiol*. 2002;90:974-982.
74. Manfredi O, Pizzi C, Morgagni GL, Fontana F, Bugiardini R. Effects of pravastatin on myocardial perfusion after percutaneous transluminal coronary angioplasty. *Am J Cardiol*. 2004;93:1391-1393.
75. Adamson DL, Webb CM, Collins P. Esterified estrogens combined with methyltestosterone improve emotional well-being in postmenopausal women with chest pain and normal coronary angiograms. *Menopause*. 2001;8:233-238.
76. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*. 2004;109:672-693.
77. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. *Circulation*. 2002;106:388-391.
78. de Feyter PJ, Nieman K. Noninvasive multi-slice computed tomography coronary angiography: an emerging clinical modality. *J Am Coll Cardiol*. 2004;44:1238-1240.

If you have knowledge, let others light  
their candles in it.

—Margaret Fuller (1810-1850)