

# 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.

JAMA. 2005;293:477-484

[www.jama.com](http://www.jama.com)

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Gamble, Novartis, AstraZeneca, Bristol-Myers Squibb Medical Imaging, Boston Scientific, IVAX (generic drugs), Eli Lilly, Medtronic, Johnson & Johnson, SCIE Insurance, ATS Medical (heart valve), and Biosite.

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**Clinical Review Section Editor:** Michael S. Lauer, MD. We encourage authors to submit papers for consideration as a "Clinical Review." Please contact Michael S. Lauer, MD, at [lauer@mccf.org](mailto:lauer@mccf.org).

**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>			
Unstable angina <sup>2</sup>	252/826 (30.5)	220/1580 (13.9)	
TIMI III <sup>4</sup>	30/113 (26.5)	27/278 (8.3)	
MI without ST-segment elevation <sup>2</sup>	41/450 (9.1)	55/1299 (4.2)	
MI with ST-segment elevation <sup>2</sup>	50/492 (10.2)	119/1759 (6.8)	

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).

Opher 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>

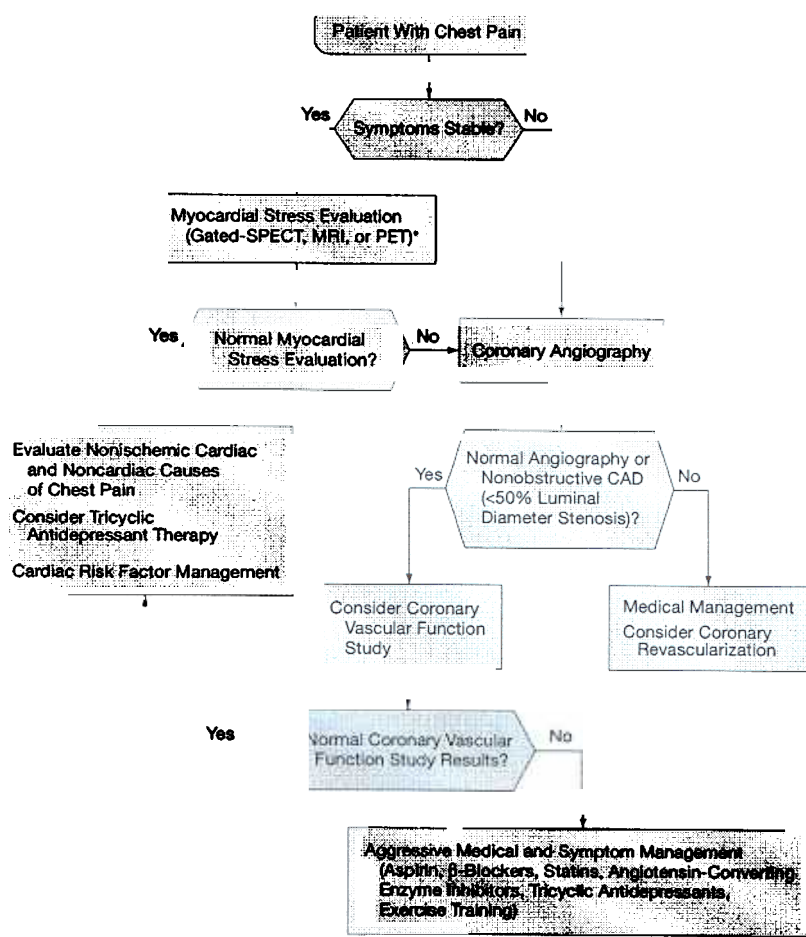
Coronary flow reserve is directly measured using adenosine and dipyridamole and indirectly using acetylcholine. Dipyridamole induces vasodilatation by inhibition of the reuptake of adenosine

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>

**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-

**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]).

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>30-33</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>30</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 atherosclerosis,

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>

**Author Contributions:** Drs Bugiardini and Bairey Merz had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**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.

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

—Margaret Fuller (1810-1850)