Angina With “Normal” Coronary Arteries
A Changing Philosophy

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EACH 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. 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-
Acute coronary syndrome MI without ST-segment elevation 2 41/450 (9.1) 55/1299 (4.2) .001

States alone.

coronary disease annually in the United

dial infarction with nonobstructive

tive coronary disease, while half

disease and no myocardial ischemia.13

test results. This view is sup-

contextual of such patients depends

to myocardial ischemia likely related to ath-

termed between 1976 and 1986 with this

ney with “normal” coronary arteries on angiog-

“normal” coronary arteries may be true

atherosclerotic disease, and not false-

nter related to chest pain, but prognosis and optimal thera-

Nonobstructive Coronary Arteries

Obstructive Coronary Artery Disease

478 JAMA, January 26, 2005—Vol 293, No. 4 (Reprinted) ©2005 American Medical Association. All rights reserved.

Table. Prevalence of “Normal” and Nonobstructive Coronary Arteries in Women Compared With Men

<table>
<thead>
<tr>
<th></th>
<th>No./Total (%)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Acute coronary syndrome GUSTO²</td>
<td>343/1768 (19.4)</td>
<td>95/555 (17)</td>
</tr>
<tr>
<td>TIMI II²</td>
<td>394/4638 (8.4)</td>
<td>99/1099 (9)</td>
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<tr>
<td>Unstable angina²</td>
<td>252/826 (30.5)</td>
<td>220/1580 (13.9)</td>
</tr>
<tr>
<td>TIMI III²</td>
<td>30/113 (26.5)</td>
<td>27/278 (8.3)</td>
</tr>
<tr>
<td>MI without ST-segment elevation²</td>
<td>41/450 (9.1)</td>
<td>55/1299 (4.2)</td>
</tr>
<tr>
<td>MI with ST-segment elevation²</td>
<td>50/492 (10.2)</td>
<td>119/1759 (6.8)</td>
</tr>
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</table>

Abbreviations: GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MI, myocardial

Coronary Artery Spasm

Myocardial infarction, cardiac arrest, and sudden death can occur, although infre-

the signs and symptoms of ischemia are not as be-

ted patients with unstable angina and non-

stic coronary artery disease includes a 2% risk of death or myocardial

Angina With “Normal” Coronary Arteries

Mature death, myocardial infarction and

many disease (luminal irregularities <50% judged visually) at coronary an-

Coronary Artery Spasm

Obstructive Coronary Artery Disease

Obstructive coronary artery disease in-

obstructive coronary disease and evi-

bution of study populations. Character-

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ported by the documentation of abnormal coronary blood flow responses to vasoactive stimuli, production of sensitive markers of ischemia, including increased transmural myocardial lipoperoxide activity, and abnormalities in myocardial phosphorus metabolism consistent with stress-induced myocardial ischemia. 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 during angina and ST-segment depression, which generated doubts on the ischemic origin of pain in a part of these patients.

**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. 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. Of note, even in women with obstructive coronary artery disease, pain perception is often increased for reasons that remain poorly understood.

**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. Although there is little empirical support for a different symptom profile or vocabulary, the results of a recent study 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. 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. 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; radiation of the discomfort to the submammary areas; and features associated with pain, such as mental arousal, or palpitation. 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.

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 myocardial oxygen demand. Coronary flow reserve is the increase in blood flow in response to metabolic or pharmacologic stimulations. Maximal or near-maximal coronary vasodilatation can be induced by various interventions, the most clinically relevant being intravenous administration of dipyridamole or adenosine. A normal coronary flow reserve is an increase of 2.5- to 3-fold. An impaired coronary flow reserve is an indication that ischemia can be precipitated during periods of increased myocardial oxygen demand.

Opherk et al 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. More recent studies addressed this issue calculating myocardial perfusion by magnetic resonance imaging. Approximately 25% of the population of patients with angina and “normal” or near-normal angiograms had an abnormally reduced flow reserve using this technique; 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, and positron emission tomography can also detect abnormal flow reserve patterns. The prevalence of vascular dysfunction by coronary flow assessment, single-photon emission computed tomography, or positron emission tomography 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, neurohumoral substances, and myocardial metabolism. 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.

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, but it also increases intracellular cyclic adenosine monophosphate, which directly mediates smooth muscle relaxation.

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, idopathic dilated cardiomyopathy, and systemic collagen diseases. 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.

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. Conversely, when impaired coronary flow reserve is accompanied by coronary endothelial dysfunction, as assessed by acetylcholine testing, it predicts an unfavorable outcome.

Outcomes, therefore, can be quite different in an apparently homogeneous population of women found to have chest pain related to abnormalities in impaired coro-
Confirmation.

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. 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. A recent investigation 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. 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).

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, and acetylcholine during brachial artery ultrasound can be used for determining peripheral endothelial function. Many clinical research studies extrapulate 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 line is regarded as a sign of early stage vascular injury and atherosclerosis. 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. Endothelial dysfunction has been related to oxidative stress that may result from atherosclerotic risk factors, inflammation, and genetic conditions still poorly understood. 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. 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, 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. There does not appear to be a correlation between plaque burden and endothelial and nonendothelial coronary blood flow response. 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.

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. Others may show underlying atherosclerotic plaques and normal coronary flow reserve. Thus, endothelial dysfunction may not simply be a marker of atherosclerosis. Conversely, hyperlipidemia causes endothelial dysfunction and early reversible atherogenetic processes even before there are angiographically visible plaques. 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.

Accordingly, women previously found to have “normal” coronary angiograms but abnormal response to acetylcholine 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. Other work has documented that calcium antagonists fail to ameliorate the diminished coronary blood flow reserve of these patients. Nitrate 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.

β-Blockers have been shown to be highly effective for reduction of chest pain episodes during daily life.
are several potential mechanisms by which β-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. β-Blockers are endothelium-dependent vasodilators as well. The proven benefit of exercise training in this population suggests that mechanism of adrenergic modulation plays a role.

Imipramine improves the symptoms of patients with abnormal cardiac pain perception and “normal” coronary angiograms, possibly through a visceral analgesic effect. Imipramine also has anticholinergic and α-antagonist effects, which have been demonstrated in the coronary as well as peripheral circulation 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. 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. Statins and angiotensin-converting enzyme inhibitors improve endothelial dysfunction, may counteract oxidative stress, and may be of benefit in patients with “normal” angiograms. The beneficial effects of statins on coronary microcirculation have been documented in other clinical studies. Combination of drugs, specifically statins and angiotensin-converting enzyme inhibitors, may largely amplify these benefits. 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.

CONCLUSIONS
Patients with “normal” or nonobstructive coronary angiography have historically 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. 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, β-adrenergic blockers may reduce myocardial oxygen consumption and symptoms. Exercise training has also been demonstrated to be beneficial. 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.

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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(Reprinted) JAMA, January 26, 2005—Vol 293, No. 4 483


