Angina and Coronary Ischemia Are the Result of Coronary Regional Blood Flow Differences

R. M. Fleming, MD, FACA

Background—The current definition of angina is cardiac pain caused by decreased blood flow, presumably through a narrowed coronary artery, resulting in inadequate coronary blood flow for the needs of the heart at the time of chest pain. If angina is truly due to an "anatomic" narrowing only, then 100% of angina patients would be expected to have some degree of coronary stenosis versus the observed 15-30% currently reported. It is known that coronary artery disease resulting from narrowing of coronary arteries, intimal plaque deposition (vulnerable plaque), and/or endothelial dysfunction decreases coronary flow reserve (CFR). A diseased coronary artery with decreased CFR has by definition "physiologic" narrowing regardless of anatomic findings. If angina is not limited to anatomically reduced blood flow but is instead due to physiological differences in coronary regional blood flow, then these differences, should be associated with anginal symptoms with or without anatomically detectable coronary stenosis.
Methods—To test this hypothesis, coronary angiography and MPI were performed on 72 individuals (39 men, 33 women) with anginal symptoms.
Results—Patients served as their own controls for expected changes in blood flow. Results were compared with angiographic data, which revealed detectable narrowings in 18 of 72 (25%) patients. When the cumulative ischemic burden (CIB) was analyzed, there was a statistical increase (ranging from $p<0.05$ to <0.001) in regional ischemic burden (RIB) as the number of diseased vascular beds increased, regardless of the presence or absence of angiographically detectable narrowings.
Conclusions—These angiographically identified narrowings (coronary lumen disease/CLD) did not account for the incidence of anginal symptoms reported in this or recent studies. Individuals with reduced CFR have clearly been shown to have reduced vasodilatory response with subsequent differences in coronary regional blood flow, despite showing an absolute increase in coronary blood flow following high-dose dipyridamole (HDD). Such differences demonstrate "physiologic" narrowings, due to "anatomic" narrowings (CLD), intimal (vulnerable) plaque identified by intravascular ultrasound (IVUS), endothelial dysfunction, small- and medium-sized artery disease or other causes not yet elucidated, which match anginal symptoms. As CIB and RIB differences increased, so did the number of anginal symptoms, and MPI documented diseased coronary arterial beds. These results support the hypothesis that angina is due to differences between regional coronary blood flow, which represents a "physiologic" narrowing that may or may not have an anatomically detectable component.

Key Words: Angina • Nuclear Cardiology • Coronary Reserve

Background

Coronary artery disease (CAD) remains the number 1 cause of death worldwide with nearly 1 million Americans (1 every 10 seconds) dying from heart disease yearly, and since 1995, more

From the Department of Radiation Oncology, University of Nebraska Medical Center, Omaha; and The Camelot Foundation, Omaha, Nebraska
Journal of the American College of Angiology may be contacted at http://www.collegeofangiology.org

women have died from heart disease than men. Diagnostic evaluation of CAD has focused on several approaches, including coronary angiography (catheterization), which utilizes contrast media injections to detect coronary narrowings (percent diameter stenosis/%DS), previously thought to be present in all individuals with CAD. By tradition, angina has been defined as the symptoms produced as a consequence of decreased blood flow proceeding through a stenosed coronary artery. However, recently it has been demonstrated[1-3] that most myocardial events (70%) occur in arteries with little or no detectable %DS and that only a small fraction (15-30%) of patients with angina have truly detectable abnormalities[4-7] by angiography. Other diagnostic studies,[8-10] including intravascular ultrasound (IVUS), endothelial function studies, and myocardial perfusion imaging (MPI), have revealed CAD in these individuals, supporting the hypothesis[11] that angina is not strictly due to anatomic narrowings within the lumen of coronary arteries.

The question remains, however, if significant %DS exists in only 15-30% of those individuals with angina, but angina is presumed to be due to decreased flow through a narrowed coronary artery, then why do the remaining individuals have angina? Furthermore, it is well known that individuals undergoing diagnostic testing with myocardial perfusion imaging (MPI) using either single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging can have anginal symptoms[12,13] following the "stress" part of the study. When "stress" was performed with use of exercise treadmill, and both heart rate and blood pressure increased, the idea of decreased blood flow through a narrowed coronary artery with increased oxygen demand continued to appear to be valid. However, with the use of pharmacologic agents like dipyridamole and adenosine, which affect coronary blood flow through vasodilation without changing the oxygen demand of the heart, there should be no angina, since vasodilation would carry more, and not less, blood through the coronary arteries. In work published in 1995, the use of high-dose dipyridamole (HDD) was associated not only with increased blood flow through coronary arteries but also with an increase in reported anginal symptoms[14-17] in people with true coronary artery lumen disease as documented by both visual and quantitative coronary angiography (QCA).

This suggests that the cause of angina is due not solely to an "anatomic" narrowing as previously suspected, but rather to a "physiologic" narrowing that results from more than just anatomic lumen narrowing alone. In the presence of diseased coronary arteries caused by "anatomic" narrowing, endothelial dysfunction, vulnerable plaque, and/or other causes,[16,18] there is a reduction in the arteries' ability to increase (vasodilate) coronary flow (coronary flow reserve/CFR) upon demand,[19-22] regardless of whether that demand to increase blood flow is due to exercise or pharmacologic stimuli. It is this difference in CFR that is truly being tested via MPI, since CFR is the comparison of maximal coronary blood flow to resting flow. The ability to detect CAD by MPI is made possible by detection of differences in coronary blood flow as demonstrated by differences in tracer activity between resting and "stressed" conditions. Most nuclear laboratories do not determine absolute radioactive tracer counts, which represent coronary blood flow, but rather depend on differences in images in either gray-scale or color images to make their diagnostic decisions. Nonetheless, the quantitation of flow[23-29] is part and parcel of every study whether applied directly or not.

Given the idea that diseased coronary arteries dilate less than nondiseased arteries, then one would expect differences in coronary blood flow from dipyridamole to be due to differences