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STATE-OF-THE-ART REVIEW AND COMMENTARY

Obstructive Coronary Atherosclerosis and Ischemic Heart Disease: An Elusive Link!

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In the current pathophysiological model of chronic ischemic heart disease (IHD), myocardial ischemia and exertional angina are caused by obstructive atherosclerotic plaque, and the clinical management of IHD is centered on the identification and removal of the stenosis. Although this approach has been in place for years, several lines of evidence, including poor prognostic impact, suggest that this direct relationship may present an oversimplified view of IHD. Indeed, a large number of studies have found that IHD can occur in the presence or absence of obstructive coronary artery disease and that atherosclerosis is just 1 element in a complex multifactorial pathophysiological process that includes inflammation, microvascular coronary dysfunction, endothelial dysfunction, thrombosis, and angiogenesis. Furthermore, the high recurrence rates underscore the fact that removing stenosis in patients with stable IHD does not address the underlying pathological mechanisms that lead to the progression of nonculprit lesions. The model proposed herein shifts the focus away from obstructive epicardial coronary atherosclerosis and centers it on the microvasculature and myocardial cell where the ischemia is taking place. If the myocardial cell is placed at the center of the model, all the potential pathological inputs can be considered, and strategies that protect the cardiomyocytes from ischemic damage, regardless of the causative mechanism, can be developed. (J Am Coll Cardiol 2012;60:951–6) © 2012 by the American College of Cardiology Foundation

In 1974, Gould and Lipscomb (1) described the effects of progressive coronary artery narrowing on resting and maximal coronary blood flow. A reduction in coronary artery diameter of ≥50% limited maximal coronary vasodilative capacity and a reduction of ≥85% limited resting coronary blood flow. These laboratory findings were soon transposed into the clinical setting, in which obstructive atherosclerosis ≥50% was defined as hemodynamically significant coronary stenosis and ≥85% as critical coronary stenosis (2). The concept of "critical coronary stenosis" was then further transmuted into "ischemia-causing stenosis." On the basis of this chain of postulates, coronary stenosis, and therefore atherosclerotic obstructions, gained increasing recognition as a consistent cause of ischemic heart disease (IHD). Thus, when a relatively simple percutaneous technique that could reduce the atherosclerotic obstruction was introduced (3), the cardiology community reacted with great enthusiasm and promptly endorsed the method.

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However, after the performance of hundreds of thousands of these procedures worldwide, outcome analysis does not support the initial enthusiasm, except for opening of acutely occluded arteries in patients with ST-segment elevation myocardial infarction (STEMI). Several lines of evidence suggest that the direct relationship between chronic obstructive coronary atherosclerosis and IHD has been taken for granted and may represent an overly simplified view of IHD. Many patients with evidence of myocardial ischemia

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Abbreviations and Acronyms

CAD = coronary artery disease

FFR = fractional flow reserve

IHD = ischemic heart disease

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

do not have visible coronary atherosclerosis at angiography, and conversely, some patients with severe coronary atherosclerotic obstructions neither experience chest pain nor present with any evidence of myocardial ischemia (4,5). Furthermore, in a large fraction of patients having undergone coronary revascularization, myocardial ischemia persists or reoccurs after a short time interval, and overall elective reduction or bypass of the stenosis has little impact on prognosis (6–14). These inconsistencies between theory and clinical reality should strongly encourage us to question carefully the assumption that there is a 1-to-1 relationship between severity of atherosclerotic obstruction and IHD and to review the data supporting the idea that IHD is a complex multifactorial condition.

Despite Current Practices, Coronary Artery Disease and IHD Are Not Consistently Associated

In clinical practice, the perception that there is a 1-to-1 causal relationship between obstructive coronary artery disease (CAD) and IHD has led to IHD and CAD becoming essentially synonymous. The diagnosis of IHD in a patient who has angina and myocardial ischemia is only accepted if significant coronary atherosclerotic obstruction can be identified at coronary angiography. A similar patient with comparable evidence of ischemia, but no atherosclerotic obstruction at coronary angiography, is generally regarded with suspicion or dismissed. Similarly, sensitivity and specificity of provocative tests are established based on the presence or absence of coronary atherosclerosis and, hence, not on the evidence of myocardial ischemia. As a result, diagnosis, prevention, and treatment of IHD are centered on the presence and severity of coronary atherosclerotic obstructions (15).

However, the concept of coronary atherosclerotic stenoses being necessary and sufficient to cause myocardial ischemia does not hold up to scrutiny. In fact, extensive data have failed to show that all patients who have atherosclerotic obstructions have IHD or, conversely, that all patients who have IHD present with obstructive coronary atherosclerosis. In a cohort of 163 symptomatic patients, Lin et al. (16) found that 39 patients presented with obstructive CAD and 105 with nonobstructive lesions. Of note, 15 of the 39 patients with flow-limiting lesions presented with normal stress test results for ischemia.

Although the atherosclerotic process often progresses toward flow-limiting stenosis, most patients die of an acute coronary syndrome, commonly attributed to ruptured plaques, rather than progressive stenosis (17).

To further complicate the subject, in an autopsy study of young adults who died as a result of accidents, homicides, and suicides, 60% of men had American Heart Association grade 2 or higher left anterior descending plaques but had never experienced IHD (18). Because the incidence of angina pectoris is estimated to remain <30% in older (>65 years of age) Western populations, it is likely that a large number of these young men would never have developed IHD (19,20). Another pathology series showed that although critical coronary stenosis was present in >90% of patients with acute and chronic IHD, it also reached 50% in control subjects with no history of IHD (21). Thrombosis, which was the principal characteristic of acute unstable ischemic syndromes, was also found in 12% of patients with stable angina, 14% of patients with ischemic cardiomyopathy, and 4% of control subjects. In a 1980 study of 212 consecutive patients with acute coronary syndrome, coronary angiographic and electrocardiographic data showed that 30.6% of patients had normal or near-normal vessels (22). Similarly, in the large GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb) study of patients with acute coronary syndromes (N = 12,142), 30.5% of women with unstable angina and 10.2% of women with STEMI had normal coronary angiographies (Fig. 1) (23).

These data thus underscore the fact that the 1-to-1 assumption which cardiologists have become accustomed to is too narrow, as IHD may be present with or without obstructive CAD. Thus, the presence or absence of coronary atherosclerotic obstructions is of limited relevance to the diagnosis and treatment of IHD.

Removing Stenoses Does Not Consistently Treat IHD

The "plaque-centric" hypothesis can also be called into question when the impact of therapeutic strategies based on

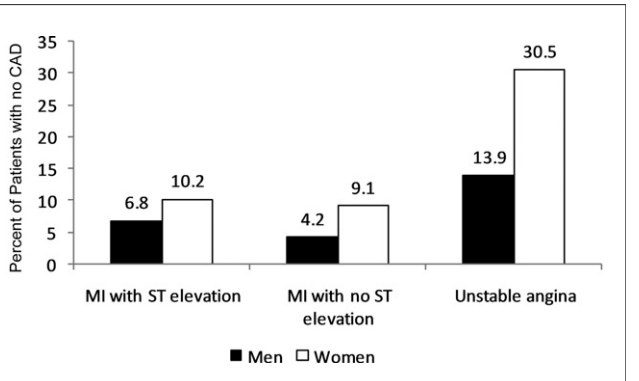

Figure 1 Percentage of Patients Who Had IHD But Not CAD

The percentage of patients who had ischemic heart disease (IHD) but no coronary artery disease (CAD) varied from 4% to 30% depending on clinical presentation (myocardial infarction [MI] with ST-segment elevation, MI with no ST-segment elevation, and unstable angina) and sex. Total number of patients was 6,406. Adapted, with permission, from Hochman et al. (23).