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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

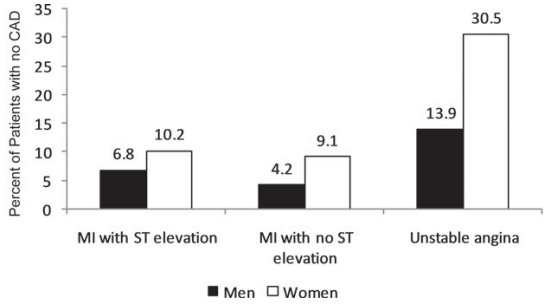

Figure 1 Percentage of Patients Who Had IHD But Not CAD

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).

the removal of coronary atherosclerotic obstructions is considered. Most reports agree that, on top of medical therapy, revascularization improves symptoms, but in many patients angina recurs after 2 to 3 years, and myocardial infarction and death are not prevented. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (N = 2,287), which evaluated percutaneous coronary intervention (PCI) on top of medical therapy, ~30% of patients were still symptomatic with angina 1 year after PCI (7). Interestingly, the incidence of angina was not significantly different from that in patients who did not undergo a revascularization procedure (Fig. 2). Moreover, no significant between-group differences were noted for the composite endpoint (death, myocardial infarction, and stroke), all-cause mortality, hospitalization for acute coronary syndrome, or myocardial infarction.

The pathophysiological relevance of obstructive lesions in the genesis of IHD was further elucidated in the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study, in which 1,005 patients who had multivessel CAD were randomly assigned to undergo PCI with implantation of drug-eluting stents guided by using angiography alone or guided by using fractional flow reserve (FFR) measurements in addition to angiography (24). Patients assigned to FFR-guided PCI underwent stenting of indicated lesions only if FFR was ≤0.80, whereas those assigned to angiography-guided PCI underwent stenting of all angiographically significant lesions. The 1-year event rate was 18.3% in the angiography group and 13.2% in the FFR group (p = 0.02). Importantly, 78% of patients in the angiography group were free of angina at 1 year, compared with 81% of patients in the FFR group (p = 0.20). These results further support the notion that not all obstructive atherosclerotic lesions produce ischemia, the key principle of the obstructive CAD-IHD paradigm.

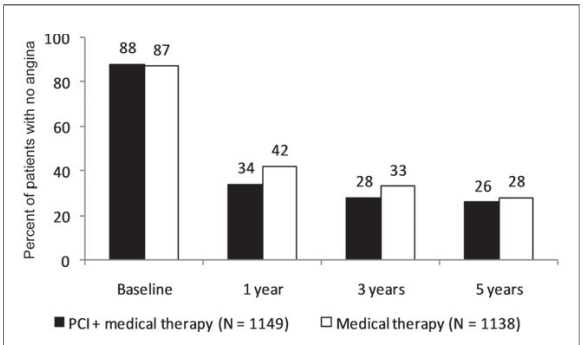

Figure 2 **Rate of Angina After PCI in the COURAGE Trial**

Compared with baseline, angina rates (median ± SEs) decreased in both groups. Significant differences between treatment groups were noted at the 1- and 3-year time points but not at baseline or at 5 years. PCI = percutaneous coronary intervention. COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation. Adapted, with permission, from Boden et al. (7).

In addition, a recent study (N = 1,212) found that even in patients who have obstructive CAD and heart failure, there was no significant difference in all-cause mortality between patients in the medical therapy group and those in the medical therapy plus coronary artery bypass grafting group (25). Such results are not groundbreaking: large clinical trials have consistently shown a lack of mortality benefit and a significant percentage of patients presenting with angina and positive stress test results after coronary revascularization (8–14).

These disappointing results for symptom control after coronary revascularization have been attributed to a number of factors, including incomplete revascularization, in-stent restenosis, and patient-related factors. However, in a highly selected cohort of 220 patients in whom all possible confounding factors had been excluded, one third of patients were symptomatic with angina and presented with a positive exercise stress test result 1 month after the index procedure (6). In the BARI (Bypass Angioplasty Revascularization Investigation) study (N = 407), 5 years after revascularization, jeopardized myocardium and angina recurrence occurred more often due to obstructive CAD progression in previously untreated arteries than to failed revascularization of the baseline hemodynamically significant lesions (10). Moreover, it has recently been reported that PCI, in the setting of acute coronary syndromes, does not prevent recurrence of ischemic events at the culprit lesion, as in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial (N = 697) (9). In that trial, 20.4% of patients had a recurrent major cardiovascular event within 3 years of a successful PCI. Roughly one half of these events were attributable to lesions that had been originally assessed as nonculprit lesions and were angiographically mild at baseline, whereas the other half occurred at the site of the previously stented culprit lesions.

These studies certainly do not deny the usefulness of revascularization in evidence-based situations such as STEMI, but they do raise questions about whether revascularization should continue to be regarded as the definitive treatment for IHD. The unchanged prognosis and the high recurrence rate clearly suggest that revascularization procedures remove the atherosclerotic obstructions but do not cure the underlying disease.

IHD as a Complex Pathophysiological Process

The pathophysiological events that occur at the coronary atherosclerotic plaque have been of great interest for the past few decades. As classically described in textbooks, fatty plaque progressively builds up to obstructive atherosclerotic plaque, causing myocardial ischemia and angina. At any stage of this progression, plaque rupture, fissure, or erosion may lead to thrombotic occlusion and precipitate acute coronary syndromes (26). However, obstructive plaque is only 1 of the manifestations of atherosclerotic disease.

Indeed, a number of alternative atherosclerotic mechanisms, including "spontaneous" thrombosis, coronary vasospasm, inflammation, microvascular dysfunction, endothelial dysfunction, and angiogenesis, have been shown to be capable of precipitating myocardial ischemia (27–29).

In a series of 132 autopsies of hearts from patients who died of noncardiac causes, coronary thrombi were shown to overlay the intima of a coronary vessel independently of plaque type and severity (27). Endothelial dysfunction, which has been shown to play an important role in the development of IHD through its regulation of vascular tone, platelet activity, leukocyte adhesion, and thrombosis, is a predictor of IHD in patients with and without obstructive CAD (30–32). In a study of 308 patients undergoing cardiac catheterization, acute cardiovascular events were independently predicted on the basis of epicardial and microvascular coronary endothelial dysfunction both in patients with angiographically normal coronary arteries and in patients with obstructive CAD (32). Inflammation is also a prominent part of the pathological process. Monocyte-derived macrophages and T lymphocytes produce and secrete mediator molecules, such as cytokines, chemokines, growth factors, enzymes, and disintegrins, which activate endothelial cells, increase vasoreactivity, and cause proliferation of smooth muscle cells and lesion progression (30). In particular, plasma C-reactive protein has been shown to be a risk factor for IHD in IHD-free middle-aged men and has been detected in patients with angina regardless of the presence of obstructive lesions (33,34). Lastly, vasomotor response, which has traditionally been considered to be a precursor of atherosclerosis, has now been shown to be an independent predictor of IHD in women with no or minimal epicardial stenosis and suspected ischemia (35).

Women represent a patient population in whom the attributes of IHD as a multifactorial disease are most clearly represented (28). In fact, while presenting with a lower coronary atherosclerotic burden, the morbidity and mortality of IHD in women are similar to those in men (36). The morbidity and mortality associated with the disease in this patient subset have been a driving force in the exploration of other causes of myocardial ischemia. In line with these considerations, microvascular coronary dysfunction in chronic angina is almost considered a disease of the female sex.

Thus, a large amount of evidence supports the concept that obstructive atherosclerosis is neither a sufficient nor a necessary cause for IHD but just 1 component of a complex pathophysiological process. Although these pathways are barely taken into consideration in clinical practice, several alternative causes of IHD are listed in the universal definition of myocardial infarction (37) as well as in a recent update of acute coronary syndrome guidelines (38).

Calling for a Copernican Revision

Given the inconsistencies associated with the obstructive "plaque-centric" approach, a shift in the paradigm that takes into consideration the multifactorial aspect of IHD seems warranted. Our attention should be focused on the microvasculature with resultant myocardial ischemia and on the myocardial cell. If we put the myocardial cell at the center of the model, all the potential pathological inputs that might drive progression to unstable angina, acute myocardial infarction, and sudden cardiac death can be considered, starting with obstructive atherosclerosis but also including inflammation, endothelial dysfunction, microvascular dysfunction, platelet dysfunction, thrombosis, and vasomotor dysfunction (Fig. 3).

Accordingly, we should adopt diagnostic and therapeutic strategies focused on myocardial ischemia rather than on obstructive coronary atherosclerosis. FFR is a valuable invasive tool for the assessment of the hemodynamic effects of epicardial vessel obstructions. Time to ST-segment depression during exercise, degree and extension of ST-segment depression, severity, and extension of perfusion defects at myocardial imaging may provide a noninvasive evaluation of myocardial ischemia that should not be denied in the absence of significant stenosis (i.e., "false-positive" results) or taken for granted in the presence of significant stenosis (i.e., "false-negative" results).

In daily practice, such a shift in focus could imply either identifying mechanisms responsible for ischemia and applying a specific treatment in each patient or developing strategies that can protect the cardiomyocytes from ischemic damage, regardless of the causative mechanism (39,40).

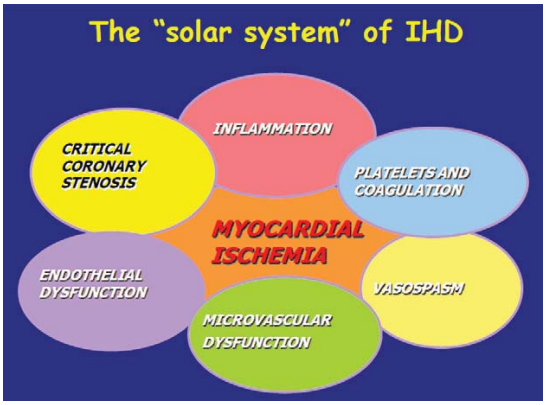

Figure 3 Proposed Paradigm Shift in IHD

The proposed shift in paradigm ("the solar system of ischemic heart disease [IHD]") puts myocardial ischemia at the center of our approach and critical coronary stenosis on the side as 1 of many contributors to myocardial ischemia.

Conclusions

A large body of evidence conclusively suggests that coronary artery obstruction is only 1 element in a complex multifactorial pathophysiological process that leads to IHD and that the presence of obstructive lesions in patients with IHD does not necessarily imply a causative role. A more comprehensive approach seems necessary to refocus preventive and therapeutic strategies and to decrease morbidity and mortality. To this effect, we propose a shift in approach to include the myocardial cell as well as the coronary vessel.

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