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Rethinking Stable Ischemic Heart Disease

Is This the Beginning of a New Era?

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Thomas Kuhn's landmark book, *The Structure of Scientific Revolutions*, postulated that scientific progress proceeds linearly until the accumulation of a sufficient weight of evidence that the current paradigm is unable to accommodate forces the reexamination of underlying assumptions, and a new paradigm must be established (1). Viewed through this framework, stunning advances of past decades in identification and quantification of obstructive coronary artery disease (CAD) stenosis represent the success of the traditional belief that this condition underlies essentially all stable ischemic heart disease (SIHD) syndromes. However, there are now many "loose ends" that challenge this preoccupation equating obstructive stenosis with SIHD, suggesting that it may be time to rethink this scientific paradigm.

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To this end, a timely opinion paper based on the proceedings of a recent international conference appears in this issue (2). The authors call for a revision of the widely held premise that SIHD is equivalent to an obstructive coronary artery stenosis caused by atherosclerosis (e.g., CAD). In this regard, the authors are to be congratulated for tackling an important clinical dilemma and identifying potential pathophysiological mechanisms underlying symptoms and signs of myocardial ischemia in the absence of an obstructive stenosis. This work brings at least 2 important topics into focus: 1) what causes SIHD; and 2) if this differs sufficiently from the current paradigm, how to best initiate the needed paradigm shift.

What Causes SIHD?

Decades of information from pathological studies have established that atherosclerosis underlies SIHD in the overwhelming majority of cases. However, this finding, reinforced by coronary angiographic data from large trials/registries, was assumed to mean a flow-limiting lesion in a major coronary artery (e.g., obstructive CAD). Indeed, in the absence of obstructive CAD, management of patients with angina and other findings of SIHD represents a considerable challenge for which there is virtually no reliable evidence base. The link between symptoms and an obstructive stenosis is so ingrained that many physicians doubt that a patient may have symptoms and/or signs of ischemia in the absence of such a stenosis. Such patients are often labeled "atypical" or having "false-positive results" at noninvasive evaluation. However, long-term follow-up studies document that such patients may have increased adverse event rates, poor quality of life, and consume considerable health care resources compared with those without evidence of ischemia (3–6). Several recent large studies have also documented increased mortality (3,4,7), underscoring the need for a better understanding of the pathophysiology of this entity to improve identification and treatment.

Evidence Against Flow-Limiting Stenosis as the Reference Standard for the Presence of SIHD

We agree with the authors (2) that evidence against flow-limiting stenosis as the sine qua non for IHD is accumulating. Briefly, the majority of patients with symptoms (e.g., chronic angina) and/or signs of ischemia undergoing angiography have no flow-limiting coronary stenosis (3,5,8). Even when an obstructive stenosis is documented, clinicians recognize that there is often wide variability in symptoms and effort tolerance, as well as variable ischemic responses to stress testing, making lack of concordance the rule (9). Furthermore, there is a high degree of scatter in the relationship between stenosis severity and flow (10,11). Conversely, reduced flow responses to a variety of stressors in myocardial regions perfused by nonstenotic vessels have been well documented (12). The highly variable clinical outcome after apparently successful intervention for stenosis relief is such that current meta-analyses fail to document differences in outcomes comparing medical therapy with percutaneous coronary intervention (13).

The "SIHD equals obstructive CAD" paradigm fails to recognize many other mechanisms that may alter determinants of myocardial oxygen supply-demand with the potential to result in ischemia (Table 1). For example, there is evidence for microparticle embolization and/or microvascu-

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Table 1 Proposed Classification for Stable Ischemic Heart Disease Syndromes

Type	Location of Defect	Potential Mechanisms
Vascular		
Coronary	Macrovessels	Flow-limiting stenosis (atherosclerosis) Endothelial dysfunction (e.g., athero RFs, some viruses) Spasm (e.g., mostly athero RFs, cocaine) Muscle bridge Inflammation (e.g., cardiac transplant, collagen diseases such as SLE or polyarthritis) Aberrant origin Dissection (e.g., pregnancy, chest trauma, Marfan syndrome)
	Microvessels	Microvascular dysfunction (some athero RFs) Endothelial dysfunction (e.g., mostly athero RFs) Spasm (athero RFs, others?) Inflammation (cardiac transplant, collagen diseases such as SLE or polyarthritis) Microemboli (e.g., athero RFs, AF) Capillary insufficiency (e.g., LVH) ?
Other vessels	Capacitance vessels	Increased stiffness (e.g., aging, calcification, hypertension, CRI) ?
Nonvascular		
Cardiomyocyte		
	Transcellular	Oxygen transport (reduced diffusion [e.g., infiltrate, amyloid]) Energy substrate (e.g., depleted FFA, glucose) ?
	Intracellular	Oxygen transport (e.g., defective myoglobin) Energy substrate (e.g., depleted FFA, glucose) ?
	Mitochondria	Mitochondrial dysfunction/adaptation (e.g., ischemic injury and protection, heart failure, diabetes, aging) ?
Adventitia	Adipocytes	?
Matrix	Mast cells	Spasm, others?
Miscellaneous	?	?

Aberrant origin = anomalous coronary artery origin (e.g., left coronary artery from the right sinus of Valsalva), coronary dissection associated with trauma, Marfan syndrome; AF = atrial fibrillation; athero RF = atherosclerosis risk condition (e.g., hypertension, dyslipidemia, dysglycemia, insulin resistance, smoking, chronic renal insufficiency [CRI]); FFA = free fatty acid; LVH = left ventricular hypertrophy; SLE = systemic lupus erythematosus; ? = unknown.

lar dysfunction that might impair flow without a macrovascular flow-limiting stenosis with long-term outcome consequences (14,15). Dynamic obstruction of larger (e.g., coronary artery spasm) and/or smaller (e.g., microvascular spasm) vessels, as a result of heightened smooth muscle activation and/or endothelial dysfunction, are increasingly documented to cause ischemia and lead to impaired outcomes (15,16). Stiffening conduit vessels may modify determinates of myocardial oxygen supply-demand to the same extent as a flow-limiting stenosis (17,18). Even with similar ischemic injury, there is differential expression of cardiac biomarkers (19). In addition, the cardiomyocyte and its metabolism, barriers to oxygen transport, the matrix, etc. may all be implicated either alone or in combination in the same or different (e.g., hypertension, heart failure, diabetes) patient subgroups.

However, we disagree with the authors' attempt to debunk the "direct" relationship between obstructive CAD and IHD (2), rather than recognizing that there is, in fact, a direct relationship, but that this relationship is not the only pathway to myocardial ischemia. Thus, a more enlightened position would be that obstruction does not always imply presence of ischemia and absence of obstruction does not always imply absence of ischemia. We agree there is clearly a need to shift to a multifactorial model highlighting causes and mechanisms in pathoanatomy involved in the pathogenesis of myocardial ischemia (Table 1). Otherwise, we risk being like the drunken man, searching for his lost keys under the streetlight, simply because the light is better. A new multifactorial model could open novel pathways to the development of diagnostic and therapeutic approaches well beyond the current focus on revascularization. This is the essence of Kuhn's scientific revolution: adoption of different ways of thinking that promise new, better solutions in the future.

Initiating Paradigm Shift Regarding the Cause of SIHD

The first step is to recognize the growing evidence against the unitary theory of flow-limiting stenosis as the prerequisite for SIHD and to accept the need to readjust the prevailing wisdom of myocardial ischemia. The conference summary helped to raise the profile of this question and, in doing so, call for a revision using "the Copernican" revolution metaphor. But in our opinion, that paradigm shift is best initiated by gradual or stepwise call for change, beginning with development of a new terminology (Table 1). The focus of Marzilli et al. (2) on the cardiomyocyte is important but does not further advance the field by suggesting a taxonomy that would provide a platform for future research. Whether we need to abandon the term IHD remains to be seen, but we do need a lexicon that better encompasses the breadth of causes for the mismatch between substrate delivery and cellular requirements that result in myocardial ischemia. We also need to eliminate the inevitable confusion possible if the term IHD continues to be used in both the "conventional" way (i.e., as meaning obstructive CAD), as well as with a new definition.

What Are the Implications of a Paradigm Shift for SIHD?

Clearly, the clinical and research implications need to be better developed. Once freed from the constraints of equating an "obstructive stenosis" with SIHD and vice versa, scientists and clinicians will be better able to recognize novel processes. Unfortunately, all of the processes proposed by

the opinion paper (e.g., inflammation, microvascular and macrovascular dysfunction [either at the smooth muscle or endothelial level or both], thrombosis, angiogenesis) are well documented as part of the atherosclerosis (or atherothrombosis) disease process. Therefore, when dealing with a vascular basis for SIHD, atherosclerosis (or its risk conditions) remains the likely mechanism. Scientists and clinicians will also be better able to explore the novel role of nonatherosclerotic mechanisms (Table 1). Taking the view that atherosclerotic CAD means a flow-limiting stenosis ignores other factors and unnecessarily, severely restricting our inquiry. It also no longer fits the evidence.

Conclusions

Clearly, dyshomeostasis, particularly at the coronary vascular level, plays a critically important role in the occurrence of symptoms and signs of ischemia (chronic angina and test abnormalities). But in addition to flow-limiting stenosis, many other mechanisms likely contribute to this very complex syndrome. Recognizing that stable ischemic syndromes do not necessarily require a flow-limiting stenosis in a large coronary artery, and severe stenosis does not necessarily cause all ischemic syndromes, advances our understanding of the disease process(es) underlying these syndromes and ultimately will lead to improved diagnostic approaches and therapies. The conference summary in this issue (2) should be viewed as a start in the right direction and perhaps a new era in IHD.

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