Invited commentary

Microvascular ischemia and the stress of impaired relaxation

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Ischemic heart disease (IHD) remains the number one cause of death worldwide [1], though promising strides in both IHD diagnosis and management have improved this outlook in recent decades. In the United States alone age-adjusted IHD mortality rates have steadily declined since the 1960's, owing primarily to the treatment of atherosclerosis and its risk factors [2]. Consequently, current approaches to IHD diagnosis have largely shifted towards coronary atherosclerosis as a central etiology. Yet we now recognize that atherosclerosis alone is neither necessary nor sufficient to account for signs and symptoms of IHD in many patients. For example, 10–30% of patients with typical angina have no evidence of obstructive atherosclerosis at invasive angiography [3]. Conversely, obstructive atherosclerosis by anatomical testing has poor correlation with both the presence of functional ischemia and patient symptoms. Thus, the ischemic cascade can no longer be associated exclusively with obstructive coronary atherosclerosis, but may result from a number of mechanisms to include endothelial dysfunction and coronary vasospasm [4] (Fig. 1).

As shown in Fig. 1, myocardial ischemia results when there is an imbalance between myocardial demand for oxygen and its supply. Subsequently, transient or fixed electrocardiogram (ECG) changes, diastolic and/or systolic dysfunction may develop depending on multiple factors including the size/location, duration and extent of hypoperfusion (e.g., subendocardial vs transmural). Importantly, atherosclerosis is only one precipitant of ischemia and may co-exist with other IHD mechanisms. Not shown in Fig. 1, however, is the contribution of a 50–70% blood flow pressure drop across the high resistance small arteries, with an ability of small caliber arterioles to maintain constant capillary flow despite variations in arterial blood pressure. At this level, endothelial dysfunction resulting in abnormal smooth muscle tone and response to stretch (e.g., the Bayliss effect – most prominent in arterioles) has potential to impact myocardial perfusion both at rest and during periods of stress. This idea forms the basis for acetylcholine (ACh) testing, which results in vasodilation in normal vessels, but paradoxic vasoconstriction at sites of impaired endothelial dysfunction by impaired release of nitric oxide. This simplified model demonstrates what amounts to a complicated interplay of IHD pathophysiology with an ability to target disease-specific mechanisms.

In a recent issue of Atherosclerosis, Dr. Arrebola-Moreno and colleagues take a significant step in understanding IHD pathophysiology among patients with chronic stable angina in the absence of obstructive coronary artery plaque [5]. In this selected population, acetylcholine (ACh) testing was used to demonstrate associations between microvascular spasm, myocardial ischemia, and changes in left ventricular contractile function.

While several studies have documented decreased coronary blood flow in patients undergoing acetylcholine (ACh) testing, few have successfully linked functional impairment in blood supply to myocardial ischemia and associated diastolic dysfunction. Proposed reasons for this missed connection [6], with importance to findings by Dr. Arrebola-Morena et al., include:

(1) Acetylcholine dose

Previous protocols for ACh dosing typically use ≤ 100 µg [7], while the current study demonstrates a majority of patient responses at higher doses of ACh (n = 30/31 responded to 100–200 µg). Though high doses of ACh may be expected to limit test specificity, their findings challenge traditional ACh protocols, which would have “missed” 45% (n = 14/31) of vasospastic responses in this study. Importantly, as ACh can have nonspecific effects on endothelium-dependent vasodilatation and action as a direct vasoconstrictor, the exact mechanism accounting for these
findings remains unclear and further study is needed to explain variant angina at more physiologic Ach levels.

(2) Limitations of methods used to detect ischemia

Previous definition of an Ach response by Mohri et al. [8] and others relies on typical angina symptoms and ischemic ECG changes during Ach infusion (combined with angiographic findings) to detect epicardial and microvascular ischemia. As ECG changes provide limited sensitivity for this purpose, it seems fitting to expand our study of Ach response to include more sensitive markers of ischemia. This study adds echocardiographic changes in diastolic function (change in deceleration time, E/A, or E wave downstroke), or a 20% increase in ultrasensitive cardiac troponin (US-cTn) to define a positive Ach response. As expected, all diastolic echo parameters and US-cTn changes demonstrated higher sensitivity to predict a positive Ach test compared to ECG findings at the expense of variable specificity.

(3) Intermittent nature of microvascular disease

Coronary tone, patient symptoms and responses to Ach testing can vary markedly. Indeed, diurnal variations in endothelial function and the timing of ischemia have been demonstrated in patients with variant angina [9]. Additionally, risk factors for vasospasm (e.g., age, gender, myocardial bridging) may contribute to between-patient responses, and further study is needed to examine variations in response to Ach testing and changes resulting from patient management.

Of particular novelty in the current study is the observation that coronary vasospasm of the microvasculature may cause regional dysfunction, and is associated with an increase in US-cTn. Given that >10% of patients presenting to the emergency department with elevated US-cTn levels will have normal or non-obstructive CAD [10], it will be important to understand the actual prevalence of vasoconstriction across clinical settings as a potential cause of ischemia. Further, while the current analysis excluded patients with obstructive atherosclerosis, there is no reason to believe that plaque “protects” the distal vascular bed from endothelial or microvascular dysfunction and likely contributes to these mechanisms. To this end, the true prevalence of microvascular spasm remains unknown and further work is needed to build on the important contributions by Dr. Arrebola-Moreno and colleagues.

Disclosures

The authors have no relevant disclosures. The views expressed here are those of the authors only.

References