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EDITORIAL COMMENT

The Forgotten Vascular Layer in the Forgotten Coronary Disorder*

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Fundamental in medical school teaching are the 3 histological vascular layers (or tunica), the *intima* lined by the endothelium, the *media* containing vascular smooth muscle cells (VSMCs), and the *adventitia* with its connective tissue and adipose cells. Although under the microscope they appear to be innate structures that simply form the blood vessel wall, research over the past 40 years has demonstrated that they are dynamic structures that play a major role in coronary artery tone. The clinical disorder that most vividly manifests as a disturbance in coronary tone is vasospastic angina.

Vasospastic angina is the clinical manifestation of epicardial coronary artery spasm and encompasses conditions such as classic Prinzmetal variant angina (1). The diagnosis is made by clinically documenting a spontaneous episode (nitrate-responsive angina and ischemic electrocardiogram changes), or more often by provocative spasm testing. Whereas the diagnosis was considered and provocative spasm testing undertaken frequently in the 1980s, in more recent years it has fallen out of favor and become "the forgotten coronary disorder" (2). Exceptions to this practice are in Japan and Korea, where provocative spasm testing is performed regularly in patients whose chest pain cannot be explained by the angiographic findings. In part, this might be because of the increased prevalence of this disorder amongst these populations compared with Caucasians (3).

DYSFUNCTIONAL CORONARY MECHANISMS IN VASOSPASTIC ANGINA

TUNICA MEDIA DYSFUNCTION. Central to the pathogenesis of epicardial coronary artery spasm is a dysfunctional medial layer due to VSMC hyperreactivity. Classically, vasoconstriction occurs because of increased intracellular VSMC calcium (Ca^{++}) concentrations activating myosin light chain kinase via calmodulin and thereby promoting myosin phosphorylation and actin-myosin coupling. However, vasoconstriction can also arise with unchanged VSMC intracellular Ca^{++} concentrations because of increased Ca^{++} sensitivity. This increased Ca^{++} sensitivity arises from Rho kinase (RoK) inhibition of myosin light chain phosphatase, thereby inhibiting myosin dephosphorylation and prolonging the actin-myosin coupling. Both animal models and clinical data implicate the RoK pathway as a key determinant of VSMC hyper-reactivity in vasospastic angina, including the following: 1) increased blood RoK levels in patients with vasospastic angina that correlate with disease activity; 2) increased RoK messenger ribonucleic acid expression at vasospastic sites; 3) inhibition of inducible spasm by RoK inhibitors; and 4) relief of intractable spasm (resistant to nitrates and calcium channel blockers) by RoK inhibitors (4).

TUNICA INTIMA DYSFUNCTION. Since the discovery that the endothelium had a major influence on vascular reactivity more than 35 years ago (5), there has been an overwhelming body of research and publications concerning this vascular cell lining. Certainly, endothelial dysfunction plays a key role in the atherosclerotic process, but its role in the pathogenesis of coronary spasm is less clear. Although some initial studies suggested that the endothelium

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played an important role in coronary spasm, subsequent studies have implied the role might be minimal (3,4).

TUNICA ADVENTITIA DYSFUNCTION. Until recent times, the adventitial layer was merely considered as the "inert filler," consisting of connective tissue that provided a structural framework for the perivascular nerve fibers and vessels, that is, "the forgotten layer." However, the role of perivascular adipose tissue (PVAT) within this layer has ignited a plethora of research and interest in its exocrine and paracrine functions (6), especially as a source of inflammatory mediators (7). In this context, the PVAT has attracted particular attention in further understanding the pathogenesis of coronary artery spasm. Early evidence supporting a role for PVAT in coronary spasm includes an animal coronary vasospastic model based on the induction of adventitial perivascular inflammation (4) and an increased coronary PVAT volume in patients with vasospastic angina (8).

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This issue of the *Journal* provides compelling clinical evidence that PVAT-associated inflammation plays a role in epicardial coronary artery spasm by comprehensively assessing several inflammatory markers and relating these to vasospastic measures. In 27 patients with and 13 patients without vasospastic angina, Ohyama et al. (9) compared coronary "perivascular inflammatory markers," including positron emission tomography/computed tomography (CT) imaging of perivascular ^{18}F-fluorodeoxyglucose (FDG) uptake, coronary CT angiography–determined PVAT volume, and optical coherence tomography–assessed vasa vasorum formation, as well as coronary vasomotor reactivity evaluated by intracoronary acetylcholine provocation testing and by neutrophil RoK activity. They demonstrated that patients with vasospastic angina exhibited increased perivascular inflammation as documented by increases in FDG uptake, PVAT volume, and vasa vasorum density. Moreover, there was a significant correlation between the extent of coronary vasoreactivity (assessed by provocation testing and RoK activity) and each of these perivascular inflammatory markers. The vasospastic angina patients were also followed up for a median of 23 months (while receiving calcium channel blockers), and the authors reported an improvement in angina symptoms, FDG uptake, and RoK activity. Although interesting, these follow-up findings are difficult to interpret in the absence of control data and given the variable course of this condition.

CORONARY PVAT INFLAMMATION IN VASOSPASTIC ANGINA

These findings implicate coronary PVAT inflammation in the pathogenesis of coronary spasm. Accordingly, the vasospastic angina syndrome might arise from PVAT inflammation that induces VSMC hyperreactivity. This is consistent with the animal coronary spasm model, in which adventitial administered interleukin-1β beads up-regulated RoK activity, thereby producing VSMC hyper-reactivity (4). Furthermore, human studies have shown that inflammatory stimuli up-regulate RoK activity (10).

Coronary inflammation has long been proposed in the pathogenesis of vasospastic angina, with studies demonstrating increased levels of cytokine adhesion molecules (11) and high-sensitivity C-reactive protein (12), with the latter exhibiting a relationship to cigarette smoking (13) (the only established risk factor for vasospastic angina). The present study takes these observations to a new level because it supports the presence of inflammation within the coronary vessel wall, rather than only as an associated systemic phenomenon, as suggested by the systemic inflammatory markers. The relationship between systemic and local (PVAT) inflammatory responses requires further investigation. Interestingly, in patients with obstructive coronary artery disease undergoing elective coronary artery bypass grafting, epicardial PVAT demonstrated higher concentrations of inflammatory cytokines than subcutaneous PVAT from the same patients, confirming the regional nature of the inflammatory response (7). Whether this is applicable to vasospastic angina requires further investigation.

Ohyama et al. (9) also exemplify how advances in imaging contribute to our understanding of vascular wall pathogenesis. Several other reports have described associations between optical coherence tomography measurement of vasa vasorum density and both atherosclerotic and nonatherosclerotic coronary disease (14,15). Recently, the analysis of PVAT by coronary CT angiography was extended to include a new measure of PVAT inflammation, called the fat attenuation index, which shows promise in detecting early coronary atherosclerosis and vulnerable plaques (16). Together, these studies lend support to the paradigm that vasculopathies are mediated at least in part from their "outside-in" (17), by adventitial remodeling, vasa vasorum expansion, and perivascular inflammation, and this may yet have implications for future treatment directions.

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In conclusion, the forgotten vascular layer might have a pivotal role in the pathogenesis of vasospastic angina (the forgotten coronary disorder), and whether interventions targeting this inflammatory process will improve coronary spasm requires further consideration.

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