Conventional approaches to risk assessment in patients with coronary artery disease (CAD), including assessment of systolic left ventricular function, inducible myocardial perfusion defects, and angiographic appearance of epicardial stenoses, have been unable to account fully for risk of future cardiovascular events (1). Part of this unexplained risk may be attributable to low-grade systemic inflammation that contributes to lesion progression, vascular dysfunction, insufficiency, and plaque rupture (2). In clinical practice, biomarkers of inflammation such as high-sensitivity C-reactive protein (hsCRP), identify higher risk individuals, even in the apparent absence of other conventional risk factors (3). In a recent meta-analysis of 54 prospective cohort studies, the magnitude of independent risk associated with a 1 SD change in hsCRP was equal to or greater than that of a comparable 1 SD change in blood pressure or cholesterol (4). Nonetheless, the complex biology linking inflammation to atherothrombotic risk has not been fully elucidated.

Coronary flow reserve (CFR) is emerging as an additional noninvasive quantitative imaging marker of vascular age and clinical risk (5–7). Significant progress has been made in the development of dynamic positron emission tomography (PET) perfusion imaging to accurately quantify CFR as the ratio of absolute global myocardial blood flow (MBF) measured at peak stress (i.e., during vasodilator-induced hyperemia) over that at rest (which is corrected for rate-pressure product as an index of baseline cardiac work). From a pathophysiologic perspective, CFR provides a measure of the integrated effects of epicardial CAD, diffuse atherosclerosis, vessel remodeling, and microvascular dysfunction on myocardial tissue perfusion (1) (Fig. 1).

CFR quantified using vasodilator PET can predict cardiac death and myocardial infarction, even in the absence of overt obstructive disease, independently of perfusion score (5–7). These associations are especially evident among high, but heterogeneous, risk cohorts, including patients with diabetes (8) and chronic renal impairment (9). In diabetics, diffuse coronary vascular dysfunction precedes overt atherosclerosis (10), and absence of myocardial ischemia on noninvasive testing does not necessarily identify a lower risk cohort (11). Diabetic patients without known CAD with impaired CFR show a risk of cardiac death comparable to, and possibly higher than, that for nondiabetic patients with known CAD (8).

There is growing evidence that microvascular dysfunction is associated with increased systemic inflammation, and may precede or coexist with high-risk coronary atherosclerosis. In a previous work, Recio-Mayoral et al. (12) showed that, compared with a healthy control group, patients with systemic lupus...
erythematous or rheumatoid arthritis, who had no significant CAD on invasive angiography, demonstrated impaired CFR in a manner that was directly related to disease duration. Recently, in patients presenting with acute coronary syndrome who were found to have nonobstructive CAD by angiography, those demonstrating coronary microvascular dysfunction (as assessed by coronary flow velocity using invasive Doppler flow velocity monitoring) also showed higher frequency of thin-cap fibroatheroma, greater plaque burden, and higher levels of hsCRP, despite similar amounts of epicardial disease by luminal area and fractional flow reserve measurements (13).

In this issue of JACC, Recio-Mayoral et al. (14) extend this work, showing that in a cohort of patients with cardiac syndrome X (CSX), elevation in hsCRP correlates with reduced CFR (Spearman $r = -0.49$, $p = 0.02$). In brief, 21 nonsmokers who met a strict clinical definition for CSX, including exertional angina, ST-segment depression on exercise stress testing, and normal coronary angiography but without rest or Prinzmetal’s variant angina, diabetes mellitus, hypertension, obesity, or hyperlipidemia, underwent PET imaging following intravenous injection of adenosine and water labeled with oxygen-15. These 21 cases of CSX, none taking statins, were then compared with 21 well-matched asymptomatic controls. The cases differed, however, in 1 important risk factor. Eight of the 21 patients with CSX, but none of the control group, had elevated levels of hsCRP (>3 mg/l) at baseline. Only the 38% of CSX patients who had elevated baseline hsCRP demonstrated lower peak MBF and correspondingly,
decreased CFR. Of note, those patients with CSX who did not have elevated levels of hsCRP showed no difference in corrected CFR compared with the control group, despite an incidence of ST-segment depression during adenosine infusion that was not significantly different from that of high hsCRP CSX patients. These results thus reinforce previous observations (15–17) that inflammation is associated with impaired coronary vasoreactivity, and in the appropriate patient population, may be a better marker for poor outcomes associated with diffuse and/or microvascular CAD than conventional assessments for ischemia.

To date, no clinical trial has yet proven that directly reducing inflammation lowers cardiovascular event rates. However, 2 large-scale hard outcome trials have now been launched to address this issue. In the first, the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial, post-myocardial infarction patients with elevated CRP are being randomly allocated to placebo or to the interleukin (IL)-1β inhibitor canakinumab (18). In the second, the CIRT (Cardiovascular Inflammation Reduction Trial) study, funded by the National Heart, Lung, and Blood Institute, similar post-myocardial infarction patients with either diabetes or metabolic syndrome are being randomly allocated to placebo or to low-dose methotrexate (19). Both trials provide a unique opportunity to assess whether CFR might provide a simple noninvasive method to predict which patients best respond to targeted anti-inflammatory interventions. For example, with regard to IL-1β, previous work has suggested that the ability of statins to improve measures of coronary blood flow and endothelial dysfunction (20,21) is modified among carriers of a specific genetic polymorphism that reduces IL-1β expression (22). Further, short-term inhibition of IL-1 activity with the IL-1 receptor antagonist anakinra in rheumatoid arthritis patients without perfusion abnormalities has been shown to improve echocardiographic measures of left ventricular myocardial deformation (by speckle tracking) and CFR (by Doppler flow velocity in the left anterior descending artery [LAD]) (23). With regard to low-dose methotrexate, the use of this common systemic anti-inflammatory agent in early rheumatoid arthritis has been found to reduce clinical scores of disease severity and improve CFR (as measured by echo Doppler flow velocity in the LAD), without effect on common carotid intimal-medial thickness (24). As such, PET imaging substudies embedded in CANTOS and CIRT would provide not only an opportunity to investigate the clinical utility of CFR as a marker of subsequent vascular risk, but would also allow for a direct evaluation of 2 anti-inflammatory therapies on changes in coronary vascular function over time.

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