The concept of coronary flow reserve (CFR) was first proposed more than 30 years ago.1 In patients with coronary artery disease (CAD), the extent of the reduction in CFR correlates directly with the severity of epicardial coronary artery stenosis. On the other hand, CFR is a marker of coronary microvascular dysfunction in persons with angiographically normal coronary arteries. Estimation of coronary perfusion has established the importance of coronary artery microcirculatory abnormalities in the pathogenesis of myocardial ischemia. Coronary microvascular dysfunction is under intense investigation at present, because of the growing awareness of its importance in many clinical conditions and its usefulness in predicting adverse clinical outcomes.2

In this issue of the Journal, Lee et al3 report their study in which they measured CFR noninvasively by transthoracic Doppler echocardiography in 354 subjects who presented with chest pain but did not have definitive CAD, and report its usefulness as an indicator of cardiovascular risk factors. Furthermore, CFR correlated significantly and inversely with the Framingham Risk Score (FRS). Among the components of the FRS, old age, low levels of high-density lipoprotein cholesterol, and cigarette smoking, were independently associated with low CFR. Although considerable therapeutic advances have been made over the past few decades, cardiovascular disease remains the leading cause of death worldwide, because of widespread under-recognition and under-treatment of individuals with risk factors for atherosclerosis and those with early-stage atherosclerosis. Today, several diagnostic modalities are available that can detect atherosclerotic vessels such as the carotid arteries, aorta, aortic valve, and arteries of the lower extremities as a surrogate for coronary atherosclerosis,4 or to directly visualize coronary plaques by multidetector-row computed tomography. However, these methods can only detect advanced-stage atherosclerosis. Once coronary atherosclerosis is at the advanced stage, the subsequent risk of cardiovascular events is already high, and it is difficult to induce marked regression of atherosclerosis even by intensive lipid-lowering therapy.5,6 Therefore, a method that can identify early-stage atherosclerosis is desirable. Coronary microvascular dysfunction assessed by CFR may represent the functional counterpart of traditional coronary risk factors, and thus be used as an early marker of arteriosclerosis in some of patients. At present, several measurements that can assess coronary circulation are available in clinical practice. Cardiac catheterization with Doppler flow wire is an established invasive method of evaluating coronary blood flow. Positron emission tomography and cardiovascular magnetic resonance imaging can be used for the quantification of myocardial blood flow. Positron emission tomography is a time-consuming and expensive method, and also associated with radiation exposure.
Cardiac magnetic resonance imaging is infrequently available for clinical use. More recently, transthoracic Doppler echocardiography was introduced for measurement of coronary blood flow, and it accurately reflects the invasive measurement by Doppler flow wire during cardiac catheterization. This method is noninvasive, repeatable, and requires less equipment and cost, though it requires skill with a significant learning curve. Despite additional limitations, including difficulty in measuring coronary flow in obese individuals and those with emphysema, the use of transthoracic Doppler echocardiography for the measurement of CFR might become widespread in the future for clinical evaluation of microvascular dysfunction.

Several pathogenic processes can lead to coronary microvascular dysfunction (Table). The coronary arterial system has 3 components with different functions: conductive arteries (diameter >500 μm), pre-arterioles (diameter 100–500 μm), and arterioles (diameter <100 μm). CFR is determined by measuring coronary blood flow at rest and at maximal hyperemia induced by adenosine or dipyridamole. The pre-arterioles are the most responsive to flow-dependent vasodilation. CFR is dependent on vascular resistance, extravascular myocardial resistance, and rheologic components. In the absence of stenosis in epicardial coronary arteries, CFR mainly represents the reactivity of the coronary microcirculation. Dipyridamole inhibits the reuptake of adenosine released by cardiac myocytes. Because adenosine increases intracellular cyclic adenosine monophosphate, which directly mediates smooth muscle relaxation, reduced CFR by adenosine or dipyridamole does not reflect endothelial dysfunction.

Accurate prediction of cardiovascular events by risk stratification with established cardiovascular risk factors such as the FRS is limited by the tendency to underestimate. Two important points should be considered when evaluating both the atherosclerosis status and the prevention of cardiovascular events. The first is the structural and anatomical vascular changes, which represent the burden of atherosclerosis. The second is atherosclerotic plaque vulnerability in association with active inflammation and possible endothelial dysfunction. CFR can detect microvessel arteriosclerosis before atherosclerotic plaque formation begins. Currently, the focus is widening to include microstructural changes for the early detection of atherosclerotic disease and the vulnerability of the atheroma, in order to provide comprehensive management of patients at high risk for cardiovascular events. It is argued that attenuation of CFR may not predict adverse clinical outcomes in patients presenting with chest pain and having normal angiograms, and in those with CAD, whereas endothelial dysfunction can predict cardiovascular events. Endothelial dysfunction, impaired CFR, and atherosclerotic plaque, although causally related to each other, are distinct problems and may exist separately. Recently, reactive hyperemia peripheral arterial tonometry was developed as a noninvasive, automatic, and quantitative clinical tool for evaluating peripheral endothelial function. This method predicts well coronary endothelial dysfunction and may be useful for risk stratification for cardiovascular events. Endothelial dysfunction is a reversible marker, even in patients with advanced atherosclerosis, and is most suitable for evaluating the efficacy of treatments, compared with CFR. Lee et al performed an acetylcholine provocation test during coronary angiography, suggesting that both coronary endothelial function and CFR can be evaluated in all subjects. If they can provide information regarding coronary endothelial function, their study should help to elucidate the associations among cardiovascular risk factors, endothelial-dependent vasoreactivity, and endothelial-independent vasoreactivity in subjects without definitive CAD.

Lately, cardiovascular mortality has decreased substantially, but this improvement in prognosis has been limited to men. Evolving knowledge regarding sex differences in ischemic heart disease is emerging. The prevalence of CAD is lower in women than in men, and women with symptomatic CAD have milder epicardial coronary atherosclerosis than men. Nevertheless, coronary microvascular dysfunction is more prevalent in women than in men, because of risk factor clustering and hormonal changes, causing paradoxically frequent (atypical) symptoms, evidence of ischemia, and adverse outcomes. Therefore, the association between CFR and the FRS in women remains to be elucidated.

Based on their study, Lee et al advocate the use of noninvasive CFR by transthoracic echocardiography to assess exposure to cardiovascular risk factors. Further studies are warranted to elucidate whether CFR provides additional prognostic value for cardiovascular events, and its suitability for evaluating the response to various therapeutic strategies in subclinical coronary atherosclerosis.

References