Novel Functional Risk Factors for the Prediction of Cardiovascular Events in Vulnerable Patients Following Acute Coronary Syndrome

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Over the years there has been considerable improvement in the clinical outcomes of patients treated for acute coronary syndrome (ACS). Despite a significant reduction in acute mortality, a large percentage of patients post ACS continue to experience adverse cardiovascular (CV) events, with high long-term mortality rates and overall suboptimal medical management. Long-term risk prediction tools rely on traditional CV risk factors and are developed and validated in specific populations. Established CV risk factors, however, only explain half or fewer of CV events. These risk models may thus not be optimal in determining individual risk for long-term adverse outcomes or in helping to identify individual patients who do not respond to therapy. Identifying the specific plaque characteristics associated with increased likelihood for thrombotic complications and rapid progression has led to the concept of the vulnerable plaque. Recently, “vulnerable myocardium” (ie, myocardium that is prone to myocardial ischemia and fatal arrhythmia) has been shown to play an important role in outcome. Both vulnerable plaque and vulnerable myocardium are associated with functional vascular abnormalities, such as endothelial dysfunction, which are considered a key event in the initiation, progression and complications of coronary artery disease. Endothelial dysfunction may serve as an underlying unifying mechanism that would independently predict long-term outcome in patients with ACS undergoing revascularization. (Circ J 2012; 76: 778–783)

Key Words: Acute coronary syndrome; Endothelial dysfunction; Endothelium; Therapeutic endpoint; Vascular health

Global Magnitude of Heart Disease

Globally, cardiovascular disease (CVD) is the number 1 cause of death and is projected to remain so. An estimated 17.5 million people died from CVD in 2005, representing 30% of all global deaths. Of these deaths, 7.6 million were from acute coronary syndrome (ACS) and about 80% of these deaths occurred in low- and middle-income countries. CVD accounted for 34% of all deaths in the US in 2006 and is the leading cause of death in women, with a higher annual mortality than all cancers and pulmonary disease combined.

Over the years there has been considerable improvement in the clinical outcomes of patients treated for ACS which has largely been attributed to improvements in percutaneous coronary intervention (PCI), including stent designs and advances in medical treatment for secondary prevention. Despite the high rates of angiographic success with low incidence of complications and significant reduction in acute mortality, a large percentage of patients post ACS continue to experience cardiac events with high long-term mortality rates and overall suboptimal medical management. A recent multicenter trial of more than 4,000 patients hospitalized for ACS showed a 22.4% rate of the composite endpoint of adverse events at 2 years, despite an intensive lipid-lowering statin regimen and optimized medical therapy. Several other cohort studies have reported similar results. Despite temporal increases in the combined use of evidence-based pharmacologic therapies, which is associated with improved outcome, medical management of ACS remains suboptimal. Quality improvement strategies are needed to enhance the appropriate use of effective therapies, targeting specifically the high-risk but under-treated patients who may derive the greatest therapeutic benefit.

Mechanism of Atherosclerosis

Traditional Risk Factors

Traditional risk factors established in the Framingham study are used in clinical guidelines for primary and secondary prevention of coronary artery disease (CAD) and to recommend risk management guidelines. Patients presenting with ACS,
however, continue to have high event rates despite optimized therapy per guidelines. Indeed, patients with myocardial infarction (MI) have a 5% mortality rate at 6 months after initial presentation and up to 20% at 2 years. In patients with ACS, the traditional risk factors poorly predict increased risk of adverse events. Paradoxically in a large cohort of patients hospitalized with incident MI, the in-hospital mortality was inversely related to the number of traditional coronary heart disease risk factors. Similar results have been observed in smaller cohorts. Also, the performance of the Framingham risk score, when applied to different populations, has inconsistent results. Indeed, traditional risk factors overall are thought to account for only 50% of CHD events.

These studies underscore the complex interplay among cardiovascular (CV) risk factors, genetic predisposition, and other individual atheroprotective factors in the prediction of CV events. It would be desirable, to have a tool depicting the individual’s risk burden at a given moment. Endothelial dysfunction the functional expression of the overall CV risk burden and the sum of all vasculoprotective factors in any given individual, may provide a better prognostic indicator for patients post ACS.

Endothelial Dysfunction
The endothelium is an active monolayer of cells lining the lumen of the vessels, separating the vascular wall from the circulating blood. The vascular endothelium has been recognized as an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and maintenance of vascular homeostasis. It maintains vascular tone and remodeling by releasing endothelial-derived factors, which regulate local and systemic inflammation and oxidative stress. Recent insights into the basic mechanisms involved in atherogenesis indicate that deleterious alterations of endothelial physiology and biology, also referred to as endothelial dysfunction, may represent a key early step in the development of atherosclerosis and may also signal lesion progression and the occurrence of its complications. This hypothesis is underscored by the observation that, similar to atherosclerosis, endothelial dysfunction is a systemic inflammatory disease affecting arteries in different vascular beds in a segmental manner.

Functional vascular abnormalities such as endothelial dysfunction are considered a key event in the initiation, progression, and complications of CAD. Endothelial dysfunction is a systemic disorder affecting multiple vascular beds and can be regarded as the integrated index of both the overall CV risk factor burden and the sum of genetic risk factors and environmental factors. It can be regarded as being the ultimate risk of the risk factors, indicating the existence of a specific atherosclerotic vascular milieu. Therefore endothelial dysfunction may serve as an underlying unifying mechanism that will independently predict long-term outcome in patients with ACS undergoing revascularization.

Vulnerable Plaque, Vulnerable Myocardium and Endothelial Dysfunction
Atherosclerosis is a diffuse inflammatory disease of the vascular wall, with focal complications such as plaque development, rupture, erosion, and calcification. Plaques with a necrotic core and a thin fibrous cap (thin-cap fibroatheroma) are prone to rupture and thus are associated with adverse CV events. These vulnerable plaques are characterized by an inflammatory, procoagulatory and prothrombotic state. We have previously shown that segments of the coronary epicardial arteries with endothelial dysfunction are associated with plaque characteristics that are typical of vulnerable plaque. Thus, endothelial dysfunction may play an important role in the development of a vulnerable plaque.

Coronary microcirculatory dysfunction has also been associated with ACS as both a cause and as a consequence of the primary epicardial event. In one construct, the myocardial microcirculation dysfunction is thought to be secondary to either a mechanical or functional obstruction of the microcirculation after MI. This mechanism, however, fails to explain the difference in degree of acuity of presentation (unstable angina vs. ST-elevation MI vs. sudden cardiac death) in patients with similar coronary pathoanatomy. A different concept considers microvascular dysfunction as one of the causes of ACS presentation (vulnerable myocardium) rather than a consequence of MI. This theory is supported by studies showing that the extent of microcirculatory dysfunction in non-STEMI is less severe than that observed in STEMI patients. Hence, the presence not only of vulnerable plaque but also of vulnerable myocardium may determine the clinical presentation of ACS or adverse events in patients after ACS.

Endothelial Dysfunction and CV Prognosis
Several studies have implicated endothelial dysfunction (both in the coronary and systemic circulations) as a marker of atherosclerotic risk and prognosis. We have reported the long-term follow-up of patients without obstructive coronary atherosclerosis who had undergone invasive coronary endothelial function testing. When these patients were stratified by their coronary microvascular endothelial function status, cardiac events occurred only in those with coronary endothelial dysfunction during follow-up. These findings were extended to the epicardial coronary arteries by Schächinger et al who demonstrated that patients who experienced CV events affecting the coronary or systemic circulation had significantly impaired endothelium-dependent epicardial coronary vasoreactivity at the initial examination. Moreover, multivariable analysis, which included traditional CV risk factors and angiographic evidence for atherosclerosis, identified the presence of coronary endothelial dysfunction as an independent predictor of future CV events.

Peripheral endothelial dysfunction has also been shown to predict adverse outcomes. In a cohort of hypertensive patients, severe peripheral endothelial dysfunction was shown to be an independent predictor of adverse events. This was also shown in a cohort of patients with documented CAD. More recently, endothelial function measured by brachial flow-mediated dilatation was shown to improve the classification of subjects as having low, intermediate and high CVD compared with the Framingham risk score alone.

Taken together, these studies indicate an association between coronary and peripheral endothelial dysfunction and CV events, underscoring the systemic nature of endothelial dysfunction. The prognostic impact of endothelial dysfunction in peripheral, easily accessible arteries suggests that assessment of peripheral endothelial function may afford an additional means of risk stratification in patients with ACS at risk for CV events.

Endothelial Function and Mental Stress
The relationship between exposure to mental stress and the CV system, particularly endothelial function, in the mechanism of ACS and CAD, continues to emerge. Thus, identification of novel risk factors and specifically their interaction and effect on endothelial function may have important implications. Moreover, acute and chronic mental stressors are important independent risk factors, as each contributes to morbidity and mortality in CAD.

Mental stress can precipitate transient endothelial dysfunction particularly in individuals who have hypertension or high cholesterol. A growing body of evidence suggests that mental stress, a known trigger for increased myocardial oxy-
Enlarged demand and significant changes in systemic hemodynamics, can cause myocardial ischemia, acute MI and acute heart failure in patients with CVD. The significance of this acute hemodynamic response to mental stress is underscored by previous reports of increased incidence of CV events following traumatic events such as wars, earthquakes and major sporting events. More recently, it has been shown that mental stress can trigger a transient, but measurable impairment in endothelial function, as measured by using high-resolution ultrasound of the radial artery, as well as in overall left ventricular function.

We have shown that treatment of OSA is associated with a reduction in cardiac deaths in ACS patients undergoing revascularization compared to patients with untreated OSA.

Abnormal endothelial function may play an important role in increased cardiovascular risk associated with OSA. Patients with OSA have impaired endothelial function compared to matched controls, and have increased markers of vascular inflammation, suggesting that OSA may directly impair endothelial function. Furthermore, treatment of OSA with CPAP improves endothelial function and is associated with reduction in CV events. Thus OSA may directly impair endothelial function by promoting vascular inflammation and may serve as a marker of increased risk of adverse events in patients presenting with ACS. In turn, endothelial dysfunction may serve as an index to the vascular impact of OSA.

Clinical Relevance of Therapeutic Improvement in Endothelial Function Until recently, there has also been a lack of direct proof that therapeutic improvement in endothelial function translates into lower CV morbidity and mortality. Thus to date, endothelial function has not been considered a primary therapeutic target in the prevention of atherosclerotic disease.

A recent study however, showed that improvement in endothelial function in hypertensive postmenopausal women is associated with an improvement in CV prognosis. Kitta and colleagues also showed that patients presenting with ACS after revascularization have a worse CV prognosis if they had persistent impairment of their endothelial function at 6 months of optimized medical therapy compared to patients whose endothelial function did not improve with medical therapy. The study showed persistent endothelial dysfunction measured remotely in the peripheral vasculature provided a better prognostic assessment of future CV events in this population than traditional risk factors. Thus endothelial dysfunction may serve not only as a marker for CV events but also as a therapeutic target.

Thus, functional vascular response may serve as surrogate marker for identifying patients at risk for CV events. Moreover, the assessment of endothelial function may help reclassify patients to different risk groups compared to the Framingham risk score alone.

Functional Risk Factors

We propose a comprehensive model of future risk assessment in patients with ACS after revascularization and optimal medical therapy that incorporates not only traditional risk factors but also functional risk assessment (Figure 1). Specifically, we propose the assessment of 3 phenotypes of clinical presentation of endothelial function: (1) peripheral endothelial tonometry, (2) vascular response to mental stress and (3) sleep apnea as non-invasive measures of functional risk assessment. This model would provide incremental value in predicting future CV events in patients with ACS who have undergone PCI and will help to further identify high-risk patients for targeted therapy.

Clinical Assessment of Endothelial Function

Peripheral Arterial Tonometry (PAT)

Measurement of peripheral vasodilator response with a finger-
tip pulse amplitude tonometry (PAT) device is an FDA-approved method for assessing vascular health. In response to hyperemic flow, digital pulse amplitude increases, which is a multifactorial response, but has been shown to depend in part on nitric oxide synthesis, thus considered as endothelial dependent. Augmentation of pulse amplitude in the finger with hyperemia is a complex response to ischemia and reflects both changes in digital blood flow and digital microvascular dilatation. In prior clinical studies, impairment of pulse amplitude hyperemic response was associated with the presence of coronary artery endothelial dysfunction. It is also related to multiple traditional and metabolic risk factors. In addition, we recently showed that the presence of peripheral endothelial dysfunction as detected by endoPAT in patients with intermediate Framingham risk score followed for a mean of 5 years is an independent predictors of adverse CV events (Figure 2). The applicability of PAT to predicting clinical outcome in patients with ACS and revascularization may provide important information that further enhances the risk stratification in those patients.

Acute Mental Stress
Acute mental stress tests and the response of the peripheral circulation are used to simulate mental stress-induced myocardial ischemia that patients may encounter in their daily lives. In multiple studies, the response mental stress testing was shown to have significant prognostic value in cardiac diseases and future cardiac events. The association between mental stress and ACS is underscored by the unique syndrome, ABS. The majority of patients with ABS provide a history of a preceding strong emotional or psychological trigger. Psychosocial stressors of daily life that trigger emotions are closely associated with the increased morbidity and mortality in women with CV disorders. The clinical presentation mimics acute MI, and is accompanied by reduced ejection fraction without obstructive CAD. Although the cardiomyopathy is reversible, we demonstrated a significant recurrence rate, which may indicate an underlying substrate that predisposes individuals to developing the syndrome. Moreover, we have recently reported that women with a history of ABS exhibit abnormal vascular response to mental stress, underscoring the potential role of endothelial dysfunction in identifying these patients at risk. Thus, the assessment of the vascular response to mental stress may have a significant effect on the stratification and potential future treatment of patients following ACS.

Sleep Apnea
Measurement of endothelial function in patients during hypopnea and apnea episodes could give important prognostic information of asymptomatic patients with OSA. Vascular function in response to apnea and hypopnea events measured non-invasively during sleep can be correlated with desaturation on pulse oximetry and heart rate to detect respiratory events. These data can then be analyzed with an automated computerized algorithm that calculates the frequency of respiratory events per hour sleep. Patients with increased respiratory events meeting the criteria for OSA would need further evaluation and treatment as they would have a worse prognosis.

Conclusion
Endothelial dysfunction is a systematic disorder and an early marker for vascular injury, and may be regarded as the vascular expression of CV risk factors, indicating an integrated index of both the overall CV risk factor burden and the sum of all vasculoprotective factors in any given individual. Traditional risk factors as identified in the Framingham study have shown inconsistent results in predicting CV events when applied to different populations. Endothelial dysfunction is an independent predictor of adverse CV outcome and may provide additional value of predicting future CV events than the traditional risk factors alone. Measurement of peripheral endothelial function has been shown to predict events in distal vascular beds, including coro-
nary and cerebral vessels. Functional vascular assessment using minimally invasive peripheral measures of endothelial function, vascular response to mental stress and sleep apnea may provide better prognostic information in patients with ACS after revascularization than traditional CV risk factors alone. Serial measurement of these functions may provide even better prognostic information, as improvement in endothelial function has recently been linked to improved CV outcomes.

Disclosures
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References


