

# Prognostic significance of microvascular dysfunction

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## Abstract

Several studies have demonstrated a strong association between coronary vascular endothelial dysfunction and an adverse long-term cardiovascular prognosis. Both conduit arterial and microcirculatory endothelial function are predictive of outcome, independent of the presence of coronary artery disease and its risk factors. Thus assessment of endothelial function or its markers in patients with different cardiovascular disorders may help identify a subgroup of patients at high risk. Whether strategies that improve microvascular function will uniformly improve prognosis needs to be studied prospectively.

■ *Heart Metab.* 2008;40:11–14.

**Keywords:** Endothelial function, microcirculation, atherosclerosis, coronary arteries

## Introduction

The coronary microcirculation, which consists of resistance arterioles, capillaries, and small veins, plays a major part in the delivery of blood and nutrients to the myocardium. In addition to its physiologic role, the coronary microcirculation is affected in a variety of systemic and cardiac disorders [1]. Functional alterations, involving changes in the microvascular vasomotor response, may occur as a result of metabolic and autoregulatory changes and endothelial dysfunction. Alterations in the number and diameter of the coronary microvessels may further trigger structural alterations [1].

Studies of the microvascular responses to drugs and of the impairment of coronary microvessels in cardiovascular diseased conditions provide useful prognostic and therapeutic information [2]. In this article, the prognostic significance of microvascular dysfunction is discussed.

Several studies have demonstrated a strong association between coronary vascular endothelial dysfunction and an adverse long-term cardiovascular prognosis [2–5]. A multivariate analysis describing the association between coronary or peripheral endothelial dysfunction and cardiovascular outcome demonstrated that endothelial dysfunction is strongly and independently associated with cardiovascular events [2]. Both conduit arterial and microcirculatory endothelial function are predictive of outcome, independent of the presence of coronary artery disease and its risk factors [2].

## Microcirculation and acute myocardial infarction

According to the vulnerable patient concept [6], myocardial microcirculatory dysfunction may be the consequence of a primary epicardial event or

may contribute to the clinical course of the acute coronary event. Coronary microvascular dysfunction is responsible for the no-reflow phenomenon, which is known to be associated with a worse outcome [7]. In addition to predicting recovery of systolic function, the presence of no-reflow predicts acute complications after acute myocardial infarction (AMI). Patients with the no-reflow phenomenon form the highest-risk subgroup of patients undergoing reperfusion, with increased associated risks of early and sustained congestive heart failure and death [8]. Follow-up studies have documented that the no-reflow phenomenon is associated with malignant arrhythmias, reduced ejection fraction, and an increased risk of cardiac death [8]. Hombach et al [9] have shown that persistent microvascular obstruction has more prognostic importance than ejection fraction in predicting late left ventricular remodeling and survival after AMI.

The fact that coronary blood flow is reduced by 50% in the non-culprit coronary arteries in AMI before and after coronary intervention points to global, rather than regional, myocardial microcirculatory impairment [10]. Inflammation may be a common link between epicardial macrovascular and myocardial microvascular disease. Indeed, Neri Serneri et al [11] demonstrated an acute inflammatory process involving the coronary microvessels, but not the cardiomyocytes, in patients with unstable angina. They emphasized that, in this setting, inflammation of the myocardial microcirculation could not be the consequence of myocardial necrosis or even myocardial ischemia, but rather that of an immunological process, possibly by downstream spread of immunogenic material from ruptured plaques [11]. Intriguingly, widespread activation of neutrophils across the coronary vascular bed has been reported in patients with unstable angina, regardless of the location of the culprit stenosis [12].

Taken together, these observations demonstrate a growing body of multilayered evidence to suggest that the integrity of the coronary microcirculation plays an integral part in the evolution of AMI. In line with the concept of the primary significance of the myocardial microcirculation, pre-existing transient or permanent microcirculatory dysfunction may contribute to the development and prognosis of AMI via reduction in coronary blood flow, leading to an alteration in shear stress and thereby aggravation of endothelial function at the epicardial level, in addition to aggravation of thrombus formation.

## Microvascular dysfunction in patients without significant coronary stenoses

Coronary microvascular dysfunction is sufficiently severe to induce myocardial ischemia in at least

20% of patients with chest pain and normal or near-normal angiography [13]. In patients without obstructive coronary artery disease, future cardiovascular events (including acute coronary syndromes) were limited to those with a reduction in endothelium-dependent coronary blood flow [5].

Britten et al [14] confirmed coronary flow reserve, an indicator of the myocardial microcirculation, as an independent predictor of prognosis in patients with angiographically normal or minimally diseased coronary arteries over an average of 6.5 years. They noted a more than 3-fold greater cardiovascular event rate in patients in the lowest tertile of coronary flow reserve compared with the highest (18% compared with 5%,  $P=0.019$ ), with 36% of all events related to AMI [14]. Similarly, Marks et al [15] followed patients with chest pain/ischemic cardiac disease and normal coronary angiograms over a mean period of 8.5 years and demonstrated a 3-fold greater mortality for those patients with an abnormal coronary flow reserve (20% compared with 7%;  $P=0.016$ ). Hence, the presence of myocardial microcirculatory dysfunction is a strong predictor of clinical outcome, including future acute coronary events, even in the absence of hemodynamically significant epicardial disease.

Finally, microvascular dysfunction may play a prominent role in the unexpected prevalence of angina after the removal of obstructions in the major coronary branches [16].

## Microvascular dysfunction and hypertrophic cardiomyopathy

Patients with hypertrophic cardiomyopathy (HCM) have been shown to have abnormal small coronary resistance vessels. Intramural coronary arteries and subendocardial arterioles have thickened walls and narrowed lumens. The intima layer involving the endothelium is hypertrophied and endothelial cells are structurally abnormal, which provides a morphological substrate for functional impairment of the endothelium [17]. Accordingly, endothelium-dependent vasodilator dysfunction has been demonstrated, using the cold pressor test, in both symptomatic and asymptomatic patients with HCM without a left ventricular outflow tract gradient [17]. In patients with HCM, the degree of microvascular dysfunction is a strong, independent predictor of clinical deterioration and death. Severe microvascular dysfunction is often present in patients with mild or no symptoms, and may precede clinical deterioration by years [18,19].

## Coronary microcirculation and heart failure

The myocardial blood flow response to increased demand is a strong independent predictor for

the progression of heart failure [20]. Thus it may be speculated that endothelial dysfunction may lead to repeated episodes of myocardial ischemia and small infarcts that ultimately contribute to the development of heart failure. This hypothesis is supported by the observation that endothelial dysfunction is present both in patients with early asymptomatic heart failure [21] and in those with heart failure that is symptomatic [22].

### Coronary microcirculation after heart transplantation

Cardiac allograft vasculopathy continues to limit the long-term success of cardiac transplantation. Recent insights have underscored the fact that innate and adaptive immune responses are involved in the pathogenesis of cardiac allograft vasculopathy [23]. Vascular lesions are the result of cumulative endothelial injuries induced both by alloimmune responses and by non specific insults in the context of impaired repair mechanisms [23]. The prevalence of microvascular endothelial dysfunction increases with increasing time after heart transplantation. Early after transplantation, dysfunction is prominent in 20% of patients; it increases to about 30% during long-term follow-up [24]. As in the epicardial tree, dysfunction of the microvascular system is a variable phenomenon over time [25]. Importantly, there is no association between epicardial and microvascular vasomotor dysfunction after heart transplantation. Thus epicardial and microvascular cardiac allograft vasculopathy are two independent, distinct entities in terms of endothelial dysfunction and morphological involvement, reflecting different pathogenetic mechanisms [23].

In a study using serial intravascular ultrasound and Doppler flow-wire measurements, annual decrements in coronary endothelial function were found to be associated with progressive intimal thickening, whereas abnormal vasomotor response to acetylcholine preceded the development of clinical endpoints [26]. Together, these observations suggest that endothelial dysfunction may represent an early and potentially reversible stage of graft vasculopathy. However, sustained endothelial dysfunction may reflect permanent vascular injury, with or without structural abnormalities.

Importantly, an impaired coronary flow reserve was associated with subsequent reduction in left ventricular ejection fraction during a 2-year follow-up, suggesting that repetitive subendocardial ischemia during myocardial stress resulted in an impairment of left ventricular function after heart transplantation [27]. In addition, Wolford et al [28] demonstrated that an increased variability of coronary vasodilatory

reserve correlates with a significantly increased risk of cardiovascular events. ■

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