Endothelial Dysfunction: A Crystal Ball Prediction for Enhanced Cardiovascular Risk?

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The endothelium, the largest autocrine, paracrine and endocrine organ, plays a central role in the regulation of vascular homeostasis by releasing paracrine factors that influence vascular tone, platelet activation, monocyte adhesion, thrombogenesis, inflammation, lipid metabolism, and vessel growth and remodeling [1–6]. In response to physical and humoral conditions, the endothelium secretes several biologically active substances that control these processes [1–7]. Nitric oxide, synthesized from L-arginine, is the predominant vasodilator, while endothelin-1, angiotensin-II and thromboxane are the predominant vasoconstrictors. Dysfunctional endothelium promotes atherosclerosis through vasoconstriction, platelet activation, leukocyte adhesion, thrombogenesis, inflammation, smooth muscle cell proliferation and collagen breakdown. In human subjects this maladaptive endothelial phenotype manifests itself prior to the development of frank atherosclerosis, and is associated with traditional risk factors such as hypercholesterolemia, hypertension and diabetes mellitus, as well as with emerging risk factors such as hyperhomocysteinemia, obesity and systemic inflammation [8,9]. Endothelial dysfunction is therefore a systemic disorder and a key variable in the pathogenesis of atherosclerosis and its complications.

Recent studies have shown that impaired vasodilation, assessed via intraarterial infusion of endothelium-dependent vasodilator acetylcholine in a coronary or peripheral artery, identifies individuals at increased risk for future cardiovascular events [10–12]. However, their invasive nature has limited widespread clinical application. Over the past decade a non-invasive technique has been developed to evaluate endothelium-dependent, brachial artery flow-mediated dilation [13–15]. This stimulus provokes the endothelium to release nitric oxide with subsequent vasodilation that can be imaged and quantitated as an index of vasomotor function. This high frequency ultrasonographic imaging of the brachial artery is non-invasive and also has the advantage of easily repeated measurements [15]. On the basis of these findings, investigators have proposed that brachial artery flow-mediated vasodilation might prove useful as a surrogate marker for cardiovascular risk [15].

In addition to its role in early atherosclerosis, there is growing recognition that endothelial dysfunction also contributes to the later stages of the disease when patients develop clinical symptoms. Cross-sectional studies have demonstrated the most severe impairment of endothelial function in arteries containing a culprit lesion that precipitates unstable angina or myocardial infarction [16,17]. Furthermore, endothelial dysfunction promotes pathologic vasoconstrictor responses in situations known to provoke ischemia, including physical and emotional stress [18]. An additional line of evidence supporting the pathophysiologic role of endothelial dysfunction is provided by intervention studies [19]. The ability to improve endothelial function is a common feature of many otherwise diverse interventions proven to reduce cardiovascular risk. For example, lipid-lowering therapy, angiotensin-converting enzyme inhibitors, smoking cessation and physical exercise have all been shown to reduce cardiovascular risk and to improve endothelium-dependent vasodilation in the coronary and peripheral circulations [8,20].

In the present issue of *IMAJ*, Blum et al. [21] review the current etiology and future non-invasive assessment of preeclampsia and eclampsia. The authors speculate that maternal vascular endothelial dysfunction is the final common pathway of preeclampsia and eclampsia. Vascular endothelial dysfunction is associated with increased platelet reactivity and thrombogenicity, inflammation, increased vascular adhesion molecules, generalized vasoconstriction and hypercoagulability. If endothelial function is the final common pathway of preeclampsia and eclampsia, the authors suggest early detection of endothelial function using high resolution ultrasound of the brachial artery [15] in women at high risk of developing eclampsia in the early stage of pregnancy.

There are few reports in the literature that utilize the BRT method to demonstrate endothelial dysfunction in preeclampsia and eclampsia. In a case-controlled study conducted at three hospital maternity units in London, Chambers et al. [22] demonstrated that BRT was impaired in women with previous preeclampsia and unexplained by established maternal risk factors, but was reversed by antioxidant ascorbic acid administration. Yoshida et al. [23] found that flow-mediated vasodilatation was significantly impaired in preeclamptic women than in women with normal pregnancies. The authors also demonstrated that flow-mediated vasodilatation showed significant negative correlation with plasma fibronectin levels. Recently vanWijk et al. [24] postulated that two stages of vascular dysfunction seem to be involved: in the early stage suboptimal development of the placenta and a hemodynamic

BRT = brachial artery vasoreactivity testing

maladaptation to pregnancy exist. At this stage maternal constitutional factors such as genetic and immunologic factors and preexisting vascular diseases may play a role. Due to this defective placentation a factor is released from the placenta, supposedly under the influence of ischemia. This factor then results in the late vascular dysfunction characterized mainly by generalized endothelial dysfunction, leading to the clinical syndrome of preeclampsia. Early detection of peripheral endothelial dysfunction by BRT in pregnant women at high risk for preeclampsia and eclampsia may therefore be a useful test. Nevertheless, the association of endothelial dysfunction assessed by BRT and an adverse clinical outcome in preeclampsia and eclampsia has yet to be elucidated.

Obesity is a worldwide epidemic that has a negative impact on healthcare programs and survival. The metabolic syndrome composed of hypertension, obesity, insulin resistance and dyslipidemia is much more common than obesity alone, and is present in nearly 50% of patients with coronary artery disease. Endothelial dysfunction is the common pathway of most, if not all, CAD risk factors and is thought to be an important element in the development of atherosclerosis, hypertension and heart failure, linking metabolic syndrome and enhancing atherosclerosis and CAD. Therefore, restoration of endothelium-derived nitric oxide bioavailability and endothelial function is now proposed as a therapeutic target [25].

In the past, most of the evidence suggesting a causal relation between endothelial dysfunction and clinical events related to atherosclerosis was circumstantial. Recently, this evidence has been strengthened by a series of outcome studies showing that endothelial dysfunction predicts future events. Endothelial function has been found to be an accurate tool for CAD detection and severity in healthy subjects and in patients with CAD. Schroeder et al. [26] evaluated endothelial function by BRT, exercise testing and myocardial perfusion imaging in 122 patients who were scheduled for coronary angiography, and found that BRT carries a sensitivity of 71% and specificity of 81% in detection of CAD. Similarly, Neunteufl et al. [27] found that endothelial function assessment by BRT carries a sensitivity of 89% and specificity of 77% for the presence of CAD. In a mean follow-up of 5 years they found three times more cardiovascular events (need for PTCA, CABG and non-fatal myocardial infarction) in patients with endothelial dysfunction compared with patients having normal endothelial function, and therefore concluded that normal endothelial function in the brachial artery of patients with chest pain appears to be associated with low risk of cardiac events.

Murakami and Ohsato recently demonstrated that endothelial dysfunction, assessed by BRT, was associated with 9.8-fold cardiovascular and 7.4-fold non-cardiovascular death for a mean follow-up period of 45 months in 518 ambulatory patients with suspected CAD. Gokce et al. [29] also recently demonstrated that endothelial function assessment is important in CAD patients with prior dysfunctional endothelium. In 187 CAD patients who had undergone major vascular surgery, BRT prior to the vascular surgery was associated with a sensitivity of 95%, a specificity of 37%, and a negative predictive value of 98% for postoperative short-term (30 day) cardiac events, including cardiac death, myocardial infarction, unstable angina and stroke. More recently, they also reported on a long-term (mean of 1.2 years) follow-up of those patients [30] who had recovered from the immediate stress of vascular surgery, and found that impaired preoperative BRT flow-mediated dilation was independently and significantly associated with a ninefold increase in cardiovascular events. The authors concluded that the strong negative predictive value of preserved endothelial function raised the possibility that assessment of endothelial function by BRT would be a useful risk stratification non-invasive test in the management of CAD patients undergoing vascular surgery [29,30].

Dysfunction of either the coronary or peripheral vascular endothelium was shown to constitute an independent predictor of cardiovascular events, providing valuable prognostic information additional to that derived from conventional risk factor assessment. Interventions, such as risk factor modification and treatment with various drugs, including statins [31] and angiotensin-converting enzyme inhibitors [32], may improve endothelial function and subsequently prognosis [33]. Hence, given its reversibility and potential to identify patients at risk and control the efficacy of therapy in clinical practice, endothelial dysfunction may be an attractive primary target in the effort to optimize individualized therapeutic strategies, thereby reducing cardiovascular morbidity and mortality [34]. This BRT technique could be used to frame specific therapeutic patient care decisions, although further studies are needed before this technique can be routinely introduced into clinical practice. Despite its widespread use, technical and interpretive limitations still exist. Currently there is considerable center-to-center variation in how flow-mediated vasodilation is measured, emphasizing the necessity for a standardized approach [15,33].

CAD = coronary artery disease

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