Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

October 2-4, 2002

Session 2

1. Topic and Author
Endothelial dysfunction and ischemia Amir Lerman, MD
2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Endothelial dysfunction is not just an unfavorable vascular condition that precedes the physical presence of overt atherosclerosis lesions. Rather, the presence of endothelial dysfunction may contribute to the development of myocardial ischemia and future an increased rate of adverse cardiovascular events. Recent studies established the association between endothelial function and ischemia and fulfilled several requirements.

Endothelial Dysfunction and Myocardial Ischemia

Given that endothelium-derived NO not only contributes to the maintenance of basal vascular tone but also is also essential for the metabolic vasodilation of both coronary epicardial and resistance vessels, it is not surprising that coronary endothelial dysfunction, which is characterized by impaired NO bioavailability, may be associated with myocardial ischemia. Both physical exercise and mental stress [38], two of the main triggers for an increase in myocardial demand, are associated with vasoconstriction of atherosclerotic coronary segments attributable to the presence of epicardial coronary endothelial dysfunction. On the other hand, diverse studies indicated an association between the presence of coronary microvascular endothelial dysfunction and chest pain in patients with angina pectoris and angiographically normal coronaries . Zeiher and colleagues extended these findings by demonstrating an association between impaired endothelium-dependent vasodilation of the coronary microvasculature and the occurrence of exercise-induced myocardial perfusion defects in patients without thermodynamically relevant CAD. We recently provided more evidence for a direct contribution of coronary endothelial dysfunction to myocardial ischemia by demonstrating the appearance of myocardial perfusion defects after intracoronary injection of acetylcholine in patients with minimally obstructive CAD. Although, direct comparison between PET scanning and coronary endothelial function is lacking, there is growing body of evidence to suggest that endothelial dysfunction may be associated with perfusion abnormalities on PET scanning. Hence, myocardial ischemia may result from endothelial dysfunction of either epicardial arteries or coronary microvessels.

Endothelial Dysfunction and Prognosis

Strong evidence for a role for endothelial dysfunction as a marker of atherosclerotic risk stems from several studies investigating the association between the presence of endothelial dysfunction in both the coronary and systemic circulation and prognosis. We recently reported the long-term follow-up results of patients with mild 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 severe coronary endothelial dysfunction during an average follow-up of 28 months. In contrast, individuals with normal or mildly impaired coronary microvascular endothelial function experienced no adverse events. These findings were extended to the epicardial coronaries by Schächinger and colleagues, who reported long-term follow-up results (mean follow-up period 6.7 years) of 147 patients with various stages of CAD in whom epicardial coronary endothelial function was assessed initially. In this study, patients who experienced cardiovascular events affecting the coronary or systemic circulation demonstrated significantly impaired endothelium-dependent epicardial coronary vasoreactivity at the initial examination. Moreover, multivariate analysis, which included traditional cardiovascular risk factors and angiographic evidence for atherosclerosis, identified the presence of epicardial coronary endothelial dysfunction as an independent predictor of future cardiovascular events.

Recently, three studies shed more light on the relation between the presence of systemic endothelial dysfunction and an adverse outcome. Taken together, these studies clearly indicate an association between the presence of both coronary and systemic endothelial dysfunction and an increased risk for future cardiovascular events, further underscoring the systemic nature of endothelial dysfunction. Interestingly, the fact that endothelial dysfunction of coronary and peripheral microvessels as well as that of the brachial artery, which hardly ever develop atherosclerotic lesions, is linked to an adverse outcome indicates that additional local or genetic factors play a fundamental role for the transition from a mere atherogenic milieu to overt disease. However, the prognostic impact of endothelial dysfunction in peripheral easily accessible arteries suggests that assessment of peripheral endothelial function may represent an additional means for risk stratification in patients at possible risk for cardiovascular events, as soon as standardized and reproducible techniques for peripheral endothelial function testing become available.

Although various interventions were shown to be associated with improvement of endothelial function,

little is currently known about the clinical and prognostic impact of therapeutic improvement of endothelial function.

Cholesterol lowering with statins and therapy with ACEI are also associated with a reduction of myocardial ischemia in patients with documented CAD. Moreover, we demonstrated that improvement of coronary small-vessel endothelial function by long-term L-arginine supplementation was associated with a significant reduction in anginal symptoms suggesting a reduction in myocardial ischemia in patients with nonobstructive CAD and coronary endothelial dysfunction. Taken together, these findings point out the clinical significance of therapeutic improvement of coronary endothelial function.

In summary, there is supportive data to suggest coronary endothelial dysfunction is associated with myocardial ischemia. Future research should focus on early diagnosis and treatment to prevent cardiovascular events and the potential deterioration to heart failure

3. Current challenges and the most important issues for future research

We still lack the direct proof that therapeutic improvement of endothelial function translates into lower cardiovascular morbidity and mortality and further prospective trials are required to answer the question, whether improvement of endothelial function should be considered a primary therapeutic endpoint. Moreover, the association of endothelial function with traditional risk factors should be explored.

The differential effect of each risk factor and gender effect should be studied in large population and new and genomic predisposition should be integrated into this area.

The development of a simple non-invasive technique to screen individual with abnormal endothelial function is crucial.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

The concept of endothelial function and the implications of early diagnosis and treatment.
Develop a mechanism to inform the public on scientific results.

5. Translating new findings to improved diagnosis and treatment/saving lives.

Addressing the concept the endothelial function should be a part of the general cardiovascular evaluation.
Addressing the role of sex and the traditional risk factors in atherosclerosis.
More NIH funding to support clinical studies addressing early detection and treatment of atherosclerosis
Multi center study addressing the role of endothelial function and the effect of sex at an early age

6. References.

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