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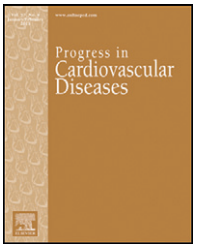

Treating Coronary Disease and the Impact of Endothelial Dysfunction

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ABSTRACT

Ischemic heart disease is the leading cause of morbidity and mortality throughout the world. Many clinical trials have suggested that lifestyle and pharmacologic interventions are effective in attenuating atherosclerotic disease progression and events development. However, an individualized approach with careful consideration to comprehensive vascular health is necessary to perform successful intervention strategies. Endothelial dysfunction plays a pivotal role in the early stage of atherosclerosis and is also associated with plaque progression and occurrence of atherosclerotic complications. The assessment of endothelial function provides us with important information about individual patient risk, progress and vulnerability of disease, and guidance of therapy. Thus, the application of endothelial function assessment might enable clinicians to innovate ideal individualized medicine. In this review, we summarize the current knowledge on the impact of pharmacological therapies for atherosclerotic cardiovascular disease on endothelial dysfunction, and argue for the utility of non-invasive assessment of endothelial function aiming at individualized medicine.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality all over the world. Atherosclerosis results from a complex interaction between genetic and environmental factors that causes the arterial wall to respond to inflammatory stimuli. It begins in childhood progressing over decades with a long subclinical phase and affects essentially all arterial beds.[1] On occasion, atherosclerosis can cause sudden arterial occlusion from unstable lesions leading to acute clinical events. In order to reduce morbidity and mortality related to ASCVD, increased emphasis is being placed on early identification of at risk patients and their optimal treatment to stabilize, halt, or even modestly regress atherosclerosis.[2] Owing to results from large randomized clinical trials, significant advancements have been made, over decades, to define effective treatment for ASCVD. However, there is a notable inter-individual heterogeneity in response to risk factors and cardiovascular (CV) drugs, affecting efficacy. Emerging paradigms that manage individual patients based on their comprehensive vascular health assessment have the potential to unveil novel mechanisms in disease pathogenesis.

Endothelial dysfunction is associated with unfavorable physiological vascular changes such as vasomotor tone alterations, thrombotic dysfunctions, smooth muscle cell proliferation and migration, as well as leukocyte adhesion, and plays a pivotal role

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Abbreviations and Acronyms

ACEI = angiotensin converting enzyme inhibitor

ACS = acute coronary syndrome

AMPK = 5' adenosine monophosphate-activated protein kinase

Apo = apolipoprotein

ARB = angiotensin II receptor blocker

ASCVD = atherosclerotic cardiovascular disease

βB = β adrenergic receptor blocking agent

CCB = calcium channel blocker

CETP = cholesterol ester transfer protein

CHD = coronary heart disease

CV = cardiovascular

DHP = dihydropyridine

DPP4-I = dipeptidyl peptidase 4 inhibitor

FMD = flow mediated vasodilatation

GLP-1 = glucagonlike peptide-1

HDL = high-density lipoprotein

LDL = low-density lipoprotein

Lp-PLA$_2$ = lipoprotein-associated phospholipase A_2

MAPK = mitogen-activated protein kinase

MI = myocardial infarction

NO = nitric oxide

PI-3 K = phosphatidylinositol 3-kinase

RAAS = renin–angiotensin–aldosterone system

RH-PAT = reactive hyperemia–peripheral arterial tonometry

T2D = type 2 diabetes

in the initial development and progression of atherosclerotic plaque and occurrence of atherosclerotic complications.[3,4] Most CV risk factors have the potential to initiate endothelial cell injury causing endothelial dysfunction.[5] Moreover endothelial function is not determined solely by the individual risk factor burden but rather, may be regarded as an integrated index of all atherogenic and atheroprotective factors present in an individual, including unknown factors and genetic predisposition (Fig 1).[6] Increasing body of evidence suggests that improvement of endothelial function in response to therapy is associated with reduction in future events.[7,8] Therefore, assessment of endothelial function not only reflects ongoing CV risk but also success of therapy.

This review will present the current knowledge on the impact of therapeutic interventions, currently available and under development, on endothelial function. Clinical management strategies for ASCVD with endothelial function assessment might enable more accurate risk assessment guiding the indication of pharmacological therapy and more accurate evaluation of treatment efficacy guiding the selection or adjustment of a given pharmacological therapy. Thus, the introduction of endothelial function assessment into clinical practice will bring the development of more tailored medicine in both primary and secondary prevention settings.

Endothelial function assessment for individualized medicine

Common approaches to ASCVD risk assessment are based on identifying and quantifying the established risk factors for atherosclerotic diseases to estimate 10-year risk for ASCVD.[9] This process represents a uniform, validated and robust method to identify individuals at high-risk for ASCVD. However, many individuals with coronary heart disease (CHD) have only one, or none, of the classic risk factors,[10] and these risk factors overall are thought to account for only 50% of CHD,[11] indicating the existence of non-traditional risk factors for atherosclerosis (i.e., mental stress, physical inactivity/fitness, genetic factor) (Fig 1). Thus, the current patient-specific approaches may have limitations that derive from the insufficiency of established risk factors to accurately identify individual risk or etiologic causes of atherosclerosis. Direct assessment of vascular damage by measuring endothelial function rather than risk factor estimation could be a reliable method to identify the functional significance of the risk factors. Precise detection of a risk profile will potentially allow both early identification of individuals susceptible to disease and discovery of potential targets for pharmacological or lifestyle intervention.

In addition to risk assessment, providing and adjusting optimal treatment in each individual is the goal of individualized medicine. In clinical practice, it is necessary for clinicians to translate scientific evidence from large clinical trials to the treatment of individual patients. Most clinical trials report relative risks or hazard ratios, which are obtained from treating a heterogeneous group of participants.[12] In current practice, the same treatment is administered to a wide range of patients who are all assumed to be the "average" patient based on the single point estimate of treatment effect. However, the absolute treatment effect in each patient can largely be affected by individual characteristics. Endothelial function might be reversible at every phase of atherosclerosis, from initiation to atherothrombotic complication.[13] Thus it can be a potentially useful clinical strategy, for both physicians and patients, to consider endothelial function in the assessment of atherosclerosis to prevent ASCVD and to determine the efficacy of current ongoing treatments (Fig 2). For example, if a patient had abnormal endothelial function even under optimal medical treatment for traditional risk factors, we need to consider changing therapy and searching other non-traditional risk factors in order to prevent CV events.

Non-invasive assessment of peripheral endothelial function

Several invasive and noninvasive techniques have been developed for endothelial function testing into clinical practice. The features of commonly used methods to assess endothelial function are summarized in Table 1.[14] Invasive assessment by catheterization is considered the reference standard for evaluating coronary endothelial function.[14] Catheterization involves intra-arterial administration of