Role of Endothelial Dysfunction in Cardiovascular Disease: Potential Therapeutic Target

Korzh Oleksii
Kharkiv Medical Academy of Postgraduate Education, Department of General Practice-Family Medicine, Kharkiv, Ukraine.

ABSTRACT
Introduction: The vascular endothelium is a layer of endothelial cells lining the lumen of blood vessels, lymphatic vessels, the heart and other organs. Normal endothelium protects cardiovascular diseases, while vascular endothelial pathology is the main cause of many cardiovascular diseases.

Aim: Here we summarize current knowledge about endothelial function from bench to bedside.

Methods: We review the studies demonstrating the significance of vascular endothelium and evaluating the potential role of drugs targeting endothelial function in the management of cardiovascular diseases.

Results: Endothelial dysfunction is a discovered phenomenon that makes a significant contribution to the pathophysiology of numerous cardiovascular conditions associated with vasoconstriction, thrombosis and inflammatory conditions. In clinical settings, the assessment of endothelial functions is attracting increasing attention due to its growing importance for cardiovascular diseases. Since cardiovascular endothelial dysfunction is also detected in patients with heart failure, it is expected to play an important role as a predictive predictor of cardiovascular events. Moreover, vascular endothelial function may be the goal of a comprehensive treatment of diseases for the prevention of cardiovascular diseases.

Conclusion: Recent publications have highlighted emerging modulators of endothelial functions, and potential therapeutic and diagnostic goals with major clinical consequences.

Key Words: Endothelium, Endothelial dysfunction, Cardiovascular disease, Hypertension, Treatment, New agents, A terap glucagon-like takimoto peptide jmc-1 receptor agonist

INTRODUCTION
The endothelium consists of a monolayer of endothelial cells (EC), which acts as a semi-selective barrier between blood flow and the wall of blood vessels and modulates blood flow, blood coagulation, inflammation and plasma permeability. The vascular endothelium regulates vasomotor tone, coagulation factors and inflammation. In particular, a healthy vascular endothelium regulates vascular tone, balancing the production of vasodilators and vasoconstrictors, which affect the expansion of smooth muscles.

Endothelial dysfunction is a pathological condition characterized by loss of balance in all major endothelial mechanisms and can be the first step to cardiovascular disease. It was implicated in the pathophysiology of numerous cardiovascular diseases. Endothelial dysfunction is associated with reduced anticoagulant properties, as well as increased expression of adhesion molecules, the release of chemokines and other cytokines, as well as the production of reactive oxygen species from the endothelium. This leads to inflammation, migration and proliferation of fibroblasts inside the vessel wall, which play an important role in the development of atherosclerosis.

Endothelial dysfunction and atherosclerosis
Atherosclerosis, a chronic vascular disease of the large and medium arteries, involves various risk factors, including lipid deposition, hypertension, inflammatory factors and hy-
Endothelial dysfunction and pulmonary hypertension

Pulmonary arterial hypertension (PAH) remains a life-threatening disease that still requires a better understanding of the underlying mechanisms. To this date, several experiments were conducted. It has been demonstrated that endothelial-specific overexpression of cyclophilin A, which has been shown to cause vascular damage through a variety of mechanisms, including endothelial dysfunction and proliferation of vascular smooth muscle, causes spontaneous PAH in mice in vivo. A mechanism has been proposed for the development of CAD in patients with PAH; the expression of bromodomain-containing protein 4, which stimulates atherogenic processes through inflammatory reactions in ECs, was increased not only in the lungs of patients with PAH, but also in their coronary arteries, promoting vascular remodeling through enhanced proliferation and suppressed apoptosis in VSMCs. These data provide a key to understanding why patients with PAH can be complicated by CAD even in the absence of metabolic disorders. It has been shown that hypoxia-inducible factor-1 is an important downstream mediator of mitogenic factors induced by hypoxia, which contribute to the development of pulmonary hypertension, in particular, through the activation of pulmonary microvascular ECs, apoptosis and inflammation.

Endothelial dysfunction and heart failure

Endothelial dysfunction is involved in heart failure (HF), and the mechanistic relationships between them remain an important subject of study. HF is a complex syndrome that occurs as a result of structural and/or functional impairment of ventricular filling (diastolic dysfunction) or ejection of blood (systolic dysfunction), known as HF with preserved ejection fraction (HFrEF) and HF with reduced ejection fraction (HFrEF), respectively.

HFrEF characterized by a left ventricular ejection fraction (LVEF) of more than 50% is a new epidemic and is thought to account for up to 50% of patients with HF. It is important that recommended HF drugs (e.g., b-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin-receptor-neprilysin inhibitors, and aldosterone antagonists) target HFrEF or LVEF of 40% or less, and have yielded frustrating results in patients with HFrEF. These recommended medications or guideline-directed medical therapy, improve morbidity and mortality in patients with HFrEF, while the guidelines recommend diuretics and aldosterone antagonists in individual patients to improve symptoms and control blood pressure in HFrEF pending future clinical trials.

HFrEF develops as a result of damage to the heart, which can be ischemic due to myocardial infarction or non-ischemic (genetic or acquired), which leads to systolic dysfunction and eccentric hypertrophy. HFrEF can contribute to endothelial dysfunction through neurohormonal activation, altered shear stress, increased oxidative stress, and decreased NO production. Ultimately, HFrEF contributes to an altered redox state in which oxidative stress and inflammatory markers predominate. With such an imbalance of NO and oxidative stress (nitroso-oxidation-reduction imbalance), a subsequent decrease in coronary endothelium-dependent vasodilating ability occurs, which impairs myocardial perfusion, reduces coronary blood flow and worsens ventricular function. These processes lead to a decrease in the bioavailability of NO and a deterioration in endothelial dysfunction, which, in turn, contributes to the progression of chronic HFrEF.

In HFrEF there is no direct heart damage, but there are many concomitant diseases that can underlie etiology (e.g., hypertension, obesity, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, anemia, and iron deficiency). It has been well documented that endothelial function is impaired in patients with HFrEF. In this inflammatory state, endothelial cells transform into fibroblasts, also known as the epithelial-mesenchymal transition. The inflammatory state observed in these concomitant diseases can also cause a decrease in the bioavailability of NO, leading to a decrease in cGMP, altered phosphorylation of titin, and microvascular ischemia.

Novel therapeutic targets

Case-control studies have clearly documented the relationship between endothelial dysfunction and the progression of cardiovascular disease (CVD), emphasizing how endothelial dysfunction can be an important predictive tool for assessing the stages of CVD. These correlations contributed to the hypothesis that targeting endothelial dysfunction can lead to an improvement in CVD.

Clinical trials of statins have given encouraging results, reporting that statins improve endothelial function and hemodynamics in patients with HF, CAD, and atherosclerosis. Statins have been found to improve endothelial function, as measured by FMD, in patients with CAD. In addition, they reported a potential mechanism for this improvement, namely an increase in the bioavailability of NO caused by...
a decrease in uncoupled endothelial NOS-derived superoxide and an increase in the bioavailability of vascular BH4 through activation of guanosine triphosphate cyclohydrolase 1. The same group was later demonstrated that 4 weeks of treatment with atorvastatin significantly improved endothelial function (measured by FMD and endothelial-independent vasodilation) and EPC mobilization and reduced tumor necrosis factor-α in patients with ischemic HF. In addition, high doses of rosvastatin in 42 patients with HF led to a significant improvement in FMD, LVEF, vascular endothelial growth factor, circulating EPCs and capillary density, and that these effects were accompanied by a decrease in oxidized low-density lipoprotein.

Ezetimibe, a potent inhibitor of cholesterol absorption, is receiving increasing attention because of its potential role in reducing residual risk for patients taking statins. The CuVIC trial (Effect of Cholesterol Absorption Inhibitor Usage on Target Vessel Dysfunction After Coronary Stenting) is a multicenter randomized controlled clinical trial demonstrating that combination therapy with ezetimibe plus statins, compared with statin monotherapy, improves the coronary endothelial dysfunction in patients with CAD undergoing coronary stenting.

Based on the assumption that targeting a glucagon-like peptide (GLP)-1 may provide a better treatment for diabetes mellitus with pleiotropic protective cardiovascular effects, in addition to glycemic control, many clinical trials of GLP-1-based therapy have been conducted with varying effects on cardiovascular outcomes and others are ongoing. For example, in patients with type 2 diabetes, a 12-week treatment with a GLP-1 receptor agonist, liraglutide, or a dipeptidyl peptidase-4 enzyme inhibitor GLP-1, sitagliptin, was estimated to have a neutral effect on microvessel function, using capillary microscopy of the skin of the nail and laser Doppler flowmetry, implying that the antihypertensive effects of GLP-1 therapy are mediated by other mechanisms, in addition to improving microvascular functions.

Blood pressure medications have also been investigated, giving mixed results. In particular, nebivolol, a b1-selective receptor blocker with NO potentiating effects, has been shown to be effective in improving endothelial function. Conversely, metoprolol, a b1-selective receptor blocker, and spironolactone, an aldosterone antagonist, did not have a minimal effect on endothelial function.

In the modern literature, new pharmacological agents have begun to appear that improve endothelial function in different groups of patients. Among them, allopurinol as an xanthine oxidase inhibitor has shown some benefit for endothelial function, which is most noticeable in patients with HF. This is due to the fact that circulating xanthine oxidase can bind to the surface of the endothelium, where reactive oxygen species are formed to promote endothelial dysfunction, and because uric acid per se has been found to correlate negatively with FMD readings.

In a recent meta-analysis, which included 197 patients with HF with systolic LV dysfunction with ischemic and non-ischemic etiology (NYHA class II-III), a dose of allopurinol 300 mg administered over a period of 1 week to 3 months improved the endothelial function with a standardized mean difference of 0.776 (95% CI; 0.429–1.122, p<0.001).

**CONCLUSION**

Recent experimental and clinical studies have shown a close relationship between endothelial dysfunction and CVD. Although the question remains how to modulate endothelial functions to improve clinical outcomes, recent publications have highlighted emerging modulators of endothelial functions, a new understanding of CVD associated with endothelial dysfunction, and potential therapeutic and diagnostic goals with major clinical consequences, which makes a significant contribution to this goal. In conclusion, further characterization and a better understanding of the functions of the endothelium are necessary to develop new therapeutic strategies in cardiovascular medicine. This review provides a potential and a perspective for drugs targeting endothelial function in the management of cardiovascular diseases.

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