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Review Article

Endothelial function and dysfunction: clinical significance and assessment

Shaghayegh Haghjooyejavanmard, Mehdi Nematbakhsh***

Abstract

Over the past two decades, investigators have increasingly recognized the importance of the endothelium as a central regulator of vascular and body homeostasis. The endothelial lining represents an organ of 1.5 kg in an adult, which is distributed throughout the body. The endothelium is versatile and multifunctional. In addition to its role as a selective permeability barrier, it has many synthetic and metabolic properties, including modulation of vascular tone and blood flow, regulation of immune and inflammatory responses, and regulation of coagulation, fibrinolysis and thrombosis. Endothelial dysfunction (ED) is a frequently used term, which can be referred to abnormalities in various physiological functions of the endothelium, and it is known as a key variable in the pathogenesis of several diseases and their complications. Finding suitable markers for endothelial damage or ED is certainly of interest. Established and emerging techniques to detect ED are divided into three large families of functional, cellular, and biochemical markers. Instead of performing single assessments, it may be much more valuable to determine various biological aspects of endothelium. It seems that there is likely a spectrum between normality, endothelial activation (by inflammatory cytokines), endothelial dysfunction (e.g., impairment of nitric oxide, resulting in loss of regulation of vascular tone) and endothelial damage (e.g., atherosclerosis). In this review we review the importance of endothelium and its activation, biomarkers and dysfunction.

KEYWORDS: Endothelial function, endothelium, Disease.

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A Computer search of international database of Pub Med shows that since 1980, the number of entries containing the term "endothelial dysfunction" (ED) as a keyword has been exponentially increased. The modern usage of the term is related to the Ludmer and co-workers observation that reported the acetylcholine-induced vasorelaxation is impaired, even reversed, in atherosclerotic coronary arteries.[1] It also has reported a similar angiographic pattern after coronary injection of acetylcholine in recipients of cardiac transplants.[2] They assumed that the "impaired response to acetylcholine is a common early finding in heart transplant patients and emphasizes the potential importance of ED in the development of atherosclerosis." A mass of studies by other investigators has confirmed these observations.[3-6] The last 27 years have established that the vascular endothelium, rather than being a mere barrier between intravascular and interstitial compartments, is a widely spread organ with various important functions responsible for vascular homeostasis.[7-15] It is well known that the inner lining of all blood vessels consists of a monolayer of flattened, orthogonal cells referred to as the endothelium, positioned on the internal elastic lamina. These cells function as a protective biocompatible barrier between all tissues and the circulating blood. The endothelial cells (ECs) also function as a selective sieve to facilitate bidirectional passage of macromolecules and blood gases to and from tissues and blood. The strategic location of the endothelium allows it to be sensitive to changes in hemodynamic

*MD, PhD, Applied Physiology Research Centre and Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran.
**Professor of Physiology, Applied Physiology Research Centre and Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran. e-mail: nematbakhsh@mui.ac.ir (Corresponding Author)

forces, blood-borne signals, and underlying tissue signals. It responds to these changes by releasing several autocrine and paracrine substances. A balanced release of these bioactive factors facilitates vascular homeostasis.[7,8] According to these broad ranges of function and body-wide distribution, the endothelium contributes importantly in homeostatic mechanisms throughout the body. In the past few years, researchers could attribute few diseases to the endothelium. Today, the list of disease states with endothelial involvement either as a primary determinant of pathophysiology or as a "victim of collateral damage" is extended (table 1).

Table 1. Endothelial involvement in human diseases.

Disease	Selected references
Neurology	
Stroke	16-18
Multiple sclerosis	19,20
Alzheimer	21,22
Cardiovascular disease	
Atherosclerosis	23-26
Myocardial infarction	27-29
Congestive heart failure	30-32
Peripheral arterial disease	33-34
Pulmonary Disease	
Asthma	35-36
COPD	37-38
Pulmonary hypertension	39-41
ARDS	41-43
Sleep apnea	44-46
Gastroenterology	
Peptic ulcer disease	47-49
Inflammatory bowel disease	50-51
Fatty liver disease	52-53
Hepatitis	54-55
Cirrhosis	56-57
Pancreatitis	58-59
Rheumatology	
Rheumatoid arthritis	60-61
Scleroderma	62-63
lupus erythematosus	64-66
Antiphospholipid syndrome	66-67
Endocrinology	
Diabetes	68-71
Haematology–oncology	
Cancer	72-73
SSD	74-77
Thalassemia	78-79
Myeloproliferative diseases	80-81
Bone marrow transplantation	82-83
TTP/HUS	84-85
Coagulation	86-87
Nephrology	
Acute renal failure	88-89
Chronic renal failure	90-91
Infectious disease	
Infection	92-94
Sepsis	95-97
Other	
Pre-eclampsia	98-100
Polycystic ovary syndrome	100-102
Periodontitis	103-104

SSD: sickle cell disease; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic uremic syndrome; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome.

1. Cell activation and endothelial cell dysfunction

Many terms have been used to explain the endothelium in disease, including activation, dysfunction, damage, injury, necrosis, derangement, and denudation. Of these descriptors, EC activation and EC dysfunction are perhaps the most commonly used and misused. A change in the constitutive phenotype of the endothelium to an 'activated' phenotype can be induced by physiological levels of inflammatory cytokines, and this is reversible. EC activation, driven by inflammatory cytokines, is characterized by the increased or de

novo expression of leukocyte adhesion molecules, a change in phenotype from antithrombotic to prothrombotic states, cytokine and growth factor production, and upregulation of HLA (human leukocyte antigen) molecules.[7,105] Upregulation of leukocyte adhesion molecules such as E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) allows leukocytes to adhere to the endothelium and then, move into the tissues.[106-109] The prothrombotic effects of EC activation include loss of the surface anticoagulant molecules (thrombomodulin and heparin sulphate), reduced fibrinolytic potential, loss of platelet antiaggregatory effects of ecto-adenosine diphosphatase and prostacyclin, and the production of platelet-activating factor.[105,109] Furthermore, following endothelial activation, syntheses of cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8) and monocyte chemo-attraction protein-1 (MCP-1) are activated.[7] Expression of class II HLA molecules allows ECs to act as antigen-presenting cells, permitting cross-talk with T lymphocytes in antigen clearance.[7] According to Hunt, there are two stages of EC activation by inflammatory cytokines.[110] First, EC "activation type I" requires neither de novo protein synthesis nor gene upregulation, and occurs rapidly. Consequent events include the retraction of ECs (thus exposing the subendothelium) and exocytosis of the Weibel–Palade body with subsequent surface expression of P-selectin and release of von Willebrand factor (vWF) into the plasma.[111] Second, EC "activation type II " requires time for the stimulating agent (histamine, thrombin, cytokine) to interact with its receptor and thus cause an effect via gene transcription and protein synthesis. The genes involved include those for adhesion molecules, cytokines and tissue factor.[111] Indeed, there are many instances in which endothelial activation is a welcome reaction, including wound healing, physiologic angiogenesis, and local defense against pathogens and foreign bodies.[87] It would be expected that the eventual elimination of the stimulus to EC activation (e.g., cholesterol lowering or the removal of the bacterium) leads to a gradual return of the endothelium to its normal, resting state as inflammatory cytokines subside. If this does not occur, excessive or chronic stimulation of these cells may lead to other changes that extend beyond the normal physiological response to insult. Under these conditions, the endothelium may fail to behave correctly and frank damage, and thus dysfunction, may occur.[111] So, chronic activation of the endothelium may result in a vicious cycle or 'dysfunction', which is the failure of the endothelium to adequately perform its physiological duties, and may result ultimately in severe pathological changes.[111,112] Based on the diversity of endothelial functions, it is logical to expect that the definition of the syndrome of "ED" should be broad enough to encompass disturbances in the barrier function of the vascular endothelium, perturbation of synthetic functions, impairment of antithrombogenic properties, perturbation of angiogenic competence, inappropriate regulation of vascular smooth muscle tonicity, proliferative capacity, and migratory properties, and deterrence of neutrophils and monocytes from diapedesis.[14,15]

2. Endothelial function and dysfunction: testing and clinical application

Despite pivotal role of endothelium in a wide variety of disease states, endothelium remains overlooked in clinical practice. [87] Since ED precedes the development of clinical manifestations of several diseases (table 1), ED assessment has potentially diagnostic and prognostic significances. For example, identification of ED may help targeting asymptomatic individuals who are at risk for cardiovascular diseases and would likely benefit from preventive measures. Furthermore, it has recently been demonstrated that ED may be reversible. This is an attractive possibility; if such strategies could be implemented early in the disease process, it might be possible to prevent or retard the disease. Even in advanced disease, modification of ED might decrease the progression of the disease or modify disease complications. The

endothelium has emerged as the key regulator of vascular homeostasis, which acts as an active signal transducer for circulating stimuli that modify the vessel wall phenotype in health and disease. [7-15] Appreciation of the central role of the endothelium throughout the wide variety of disease processes has led to extensive inquiries about the proper methods to test different aspects of its functions. Hence, developing novel tools for interrogating the endothelium is an important goal in vascular biology. These attempts have provided not only novel insights into pathophysiology, but also a clinical opportunity to detect the diseases from the early stages, and reduce later adverse events in patients. Established and emerging techniques to detect ED are divided into three large families: functional and structural markers of EC dysfunction, cellular markers of ED, and surrogate markers of EC dysfunction.

2.1. Functional diagnosis of EC dysfunction

This category includes tests of endothelium-dependent vasorelaxation, arterial stiffness and pulse wave propagation. Endothelial-dependent vasomotion has been the most common used clinical assessment of endothelial function. These tests investigate pharmacological and/or physiological stimulation of endothelial release of nitric oxide (NO) and other vasoactive compounds, and often a comparison of vascular responses to endothelium-independent dilators such as nitroglycerine. Initial studies were carried out in the coronary circulation, with measurement of the change in vessel diameter by quantitative coronary angiography.[112] Subsequently, this method has been refined with the use of flow-mediated vasodilatation (FMD). This method uses high-resolution ultrasound equipment to measure post-occlusive increase in the diameter and flow of brachial or radial arteries, reflective of the shear stress-stimulated production of NO.[113] Briefly, a sphygmomanometer cuff placed on the forearm distal to the brachial artery is inflated to 200 mmHg and subsequently, released 4 to 5 minutes later. FMD occurs predominantly as a result of local endothelial release of NO.[114] The abnormality of FMD reports ED, which serves as a preclinical marker and may have prognostic value.[115,116] FMD tests reflect in part the synthesis and bioavailability of NO. There is emerging technology for direct measurement of NO using electrochemical sensors, which have recently been miniaturized to submicron diameter size.[117,118] These probes can be inserted into catheters for in-vivo measurements. The measurement of aortic stiffness is accomplished by noninvasively testing arterial-wall motion, pulse-wave contour or most frequently, pulse-wave velocity (PWV), which is a technologically advanced version of pulse pressure measurement.[115,116] The PWV is a function of the elasticity of the vessel wall, its thickness and density, and thus in essence reports on the structure-functional properties of a vessel. Carotid intima-media thickness as determined using high-resolution ultrasound represents the index of atherosclerotic structural remodeling of the blood vessel. It is especially informative when measurements are performed in carotid bifurcation and internal carotid artery.[115] Coronary calcification is detected using a variety of techniques, including plain X-rays, two-dimensional echocardiography, electron beam computed tomography and spiral computed tomography. Coronary calcification reports the structural vascular abnormality associated with atherogenesis.[10] Ankle-brachial index (ABI), a ratio of systolic blood pressure in the legs and brachial arteries, as detected using a Doppler sensor, is another non-invasive means to screen patients for peripheral arterial disease.[10,115] Recent work has demonstrated that ABI correlated with the level of serum markers of inflammation such as C-reactive protein (CRP). In a prospective study, abnormality of both parameters (ABI and CRP) was associated with a fourfold increased risk for myocardial infarction, stroke or death.[116]

2.2. Cellular marker of ED

The notion that endothelial function reflects the net balance between injury and repair has

led to the development of assays to quantify the detachment of mature Ecs, circulating ECs (CECs) and circulating endothelial progenitor cells (EPCs). Determination of the number of CECs reflects the endothelial injury and determining the number and functional characteristics of EPCs reflect the endogenous repair potential. The number of both CEC and EPC can be measured in the circulation by flowcytometry and/or combination of magnetic bead selection and fluorescent microscopy.[119] Mature CECs can be distinguished from circulating EPCs by virtue of their sizes and the expression of surface markers.[120] The increased levels of CECs in several diseases associated with ED and vascular inflammation suggest a direct relationship between the number of these cells in the peripheral circulation and the extent of endothelial injury.[120-123] Endothelial microparticles are vesicles formed by the cell membrane after endothelial activation, and their composition can be used to characterize the status of the parent EC. Elevated circulating microparticles have been seen in a variety of conditions associated with endothelial activation or apoptosis.[124-126] It has been shown that increased number of apoptotic endothelial microparticles correlated with the severity of coronary ED.[124-126] A separate entity is represented by the EPCs. The circulating EPCs can be characterized by the coexpression of a hematopoietic progenitor cell surface markers such as CD 34, which is an EC surface marker detectable by flowcytometry.[127] Further methods to characterize EPC functions include quantification of the potential to differentiate into an EC phenotype, migration, adhesion, formation of vascular tubules, and the ability to attenuate ischemia in animal models.[127-129] It has been demonstrated that cardiovascular diseases (CVD) risk factors, ED and aging reduce the number of EPCs, and impair their functions.[130,131] Thus, measurement of CECs and circulating EPC levels provides a novel and exciting means to follow the determinants of endothelial injury and repair. The balance of these two cell populations has already been linked to other in vivo measures of endothelial function, and has been shown to be associated with future cardiovascular events.[132-134]

2.3. Circulating biomarkers of EC dysfunction

A broader appreciation of the numerous functions of the endothelium can be obtained by study of the levels of molecules of endothelial origin in circulating blood. When the endothelium is activated, the direct products of ECs such as NO metabolites, inflammatory cytokines, adhesion molecules, regulators of thrombosis, and markers of endothelial damage and repair are existed. In this context, these measures can provide important information regarding mechanisms and severity of ED.[135] As a result of biological and assay availability and variability, these factors currently have only a very limited routine clinical use.

2.3.1. Circulating NO pool: assessment of nitrite, nitrate and nitroso species in ED

NO is one of the endothelial biomarkers which decreases in condition of ED. Determination of the NO radical is difficult because of its radical nature and very short half-life; so measurements of plasma nitrite, nitrate and nitrosylated proteins are increasingly being mentioned as markers for determining NO bioavailability.[136-138] Circulating levels of nitrites and nitrosylated proteins in part reflect (not always) endothelial generation of NO, but they are difficult to measure.[139,140] Specifically, values may be perplexed by other sources of NO formation and variation in dietary NO.[141] Nitrite, has previously been reported to be a good marker of endothelial NO production.[141] It has been shown that up to 70–90% of plasma nitrite is derived from eNOS activity in fasted humans and other mammals.[27,141] Other studies demonstrated that plasma nitrite levels progressively decrease with increasing cardiovascular risk load.[141] Furthermore, NOS-inhibition in humans, pigs, dogs, and mice led to significant decreased plasma nitrite concentration.[142] In contrast to nitrite, it has been demonstrated that plasma nitrate levels do not change and thus, do not correlate with FMD—neither at rest nor during inhibition or stimulation of

NOS.[143] The plasma nitrate level is known to be influenced by a variety of NOS-independent factors, including dietary nitrate intake, saliva formation, bacterial nitrate synthesis within the bowels, denitrifying liver enzymes, inhalation of atmospheric gaseous nitrogen oxides, and renal function.[142]

2.3.2. Inflammation biomarkers in ED

ED is characterized by a shift of the actions of the endothelium towards a pro-inflammatory state.[144,145] Activation of the inflammatory process after endothelial injury leads to the production and release of primary pro-inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα). These induce activation of endothelial cells with release of adhesion molecules and chemokines that lead to local recruitment of circulating inflammatory cells. Moreover, IL-1β and TNFα stimulate the production of secondary cytokines, mainly IL-6, which leads to the activation of the acute-phase reaction and release of inflammatory mediators from the liver such as CRP, amyloid A, and fibrinogen.[146,147] CVD risk factors induce upregulation of endothelial adhesion molecules such as VCAM-1, ICAM-1, selectins (L, E and P), and integrins.[146] These molecules are thought to regulate the attachment and transendothelial migration of inflammatory cells into the intima (mainly monocytes and T-lymphocytes). These cells are directed to the site of the injury by chemoattractant factors such as monocyte chemoattractant protein-1 (MCP-1).[147] Other molecules such as lipoprotein-associated phospholipase A2 (Lp-PLA_2), CD40 and CD40 ligand have been also noticed as inflammation biomarkers.[146-148] Lp-PLA_2 is secreted by macrophages and promotes inflammation via generation of lysophosphatidyl choline, suppression of eNOS and upregulation of CD40 ligand expression in T lymphocytes.[148] CD40 is a membrane protein of the TNF receptor family, and CD40 ligand is a member of the TNF family, both of which are coexpressed by macrophages, T-lymphocytes, platelets, and endothelial and smooth muscle cells in atherosclerosis.[147] Inflammatory markers shed into the bloodstream provide a window into proinflammatory state (endothelial anti-inflammatory dysfunction) in atherosclerosis.[147] The relations between ED and inflammation are bidirectional, thus the markers of inflammation have a good chance of reporting on the severity of ED.[146] Among all above-mentioned markers, CRP has been studied more than others.[149-152] Several studies have shown, in different populations, that modest elevation of plasma CRP is a strong predictor of future vascular events.[151] Elevated plasma CRP concentrations are also associated with an increased risk of cardiovascular events and an increased risk of fatal and nonfatal cardiovascular events in ischemic stroke patients. It has been reported that the level of CRP significantly contributed to the Framingham score in predicting the risk of coronary events. These epidemiological and clinical observations suggest that determination of plasma CRP concentrations could be used as an adjunct for risk assessment in primary and secondary prevention of cardiovascular disease and be of prognostic value.[149-152]

3. Haemostatic abnormalities in ED

The vascular endothelium damage results in the rapid adhesion and aggregation of platelets at the site of the injury and in the activation of the coagulation cascade.[153] The consequences of a dysfunctional endothelium may include changes in the ability of the cell to participate adequately in both coagulation and fibrinolysis, and these may predispose to arterial thrombosis.[154] The procoagulant consequences of endothelial activation can be measured as a change in the balance of tissue plasminogen activator and its endogenous inhibitor, PAI-1.[155] Among procoagulant products of the endothelium, vWF is a high molecular weight glycoprotein, which is released into the circulation by activated ECs. vWf is synthesized exclusively in ECs and megakaryocytes. vWF plays a vital role in mediating platelet adhesion to damaged arterial walls.[156] When ECs are injured, vWF is released from endothelial

Weibel–Palade bodies. vWF, considered a gold standard in the measurement of endothelial damage and dysfunction.[157] Thrombomodulin is another molecule in this category. It plays a role as a protein C cofactor and has anticoagulant activity. Thrombomodulin can be released from injured ECs. The soluble thrombomodulin (sTM) has been shown to be a marker of EC damage.[158] Although the data for sTM are controversial, it is promising in some conditions such as peripheral arterial disease and in the treatment of risk factors.[158]

4. Oxidative stress biomarker in ED

Markers of oxidative stress are important contributors to eNOS uncoupling, representing a frequent pathway to development and progression of ED.[159] In addition to well-known markers of oxidative stress such as circulating oxidized low-density lipoprotein (oxLDL) and 8-iso-PGF2alpha, there are some techniques to measure redox state of albumin as a marker of oxidative stress.[160] The ratio of ubiquinone-10 to ubiquinol-10 (oxidized-to-reduced forms of coenzyme Q10) has been advocated as a sensitive circulating marker of oxidative stress.[161] The level of plasma thioredoxin is another marker of oxidative stress and showed independent association with the presence of CVD.[162] The level of plasma thioredoxin was elevated in patients with diabetes mellitus and glucose intolerance, and showed independent association with the presence of CVD.[162]

5. Prevention and treatment of ED

Of course, based on present knowledge, there is no unique procedure to prevent or to treat ED. The simplest way for the treatment is to think about administration of the endothelium products such as NO, L-Arginine as a NO donor, and investigate its effect on the endothelium.[3,163-170] Hormone therapy is another complex suggestion to repair ED or related parameters.[171-176] For purpose of prevention, searching about the material or the process that affect ED (or its related parameter) is interest of some researchers.[177-182] However, it seems that the correct prevention and treatment processes can absolutely achieve when more and more functional dimensions of endothelium are understood. In order to obtain this final goal, it is suggested to look the endothelium as a smart multi-vector system in which all of its vectors are related to each other, and should be considered together in future researches.

Conclusion

The endothelium occupies a unique and crucial position at the interface of the blood and the tissues. The endothelium distributes spatially in all tissues of the human body and therefore, requires the attention of all existing organ-specific disciplines. Clinical progress in EC biology will depend on several factors. First, clinicians should begin to view the endothelium as a distinct organ system— the one that has pathophysiologic determinants and diagnostic and therapeutic potentials. Second, there must be hard efforts to inform physicians about the endothelium, and train the next generation to develop and implement new diagnostic and therapeutic tools for observing and tracking the endothelium. The endothelium is hidden from view and is poorly accessible in the patient. It is not accessible by inspection, palpation, percussion or auscultation. Notion that ED is a diagnostic, preventive, and therapeutic target in several diseases finding appropriate endothelial markers is certainly of interest. Undoubtedly, ED should be investigated in multifaceted approach.[10,11,157] Limiting the diagnosis of ED to one or two markers may underrepresent the diversity of endothelial functions leading to false conclusions. The situation is like the blind men examining an elephant and reporting on individual body parts. Therefore, a reasonable solution is envisaged in the optimal selection of multiple markers characterizing various endothelial functions. It should be realized that the present choices of markers of ED are based on the random selection of candidates. Since the endothelium has several various functions, therefore ED has a variety of meaning. It should be appreciated that each marker usually touches

one aspect of endothelial function. However, cellular markers of ED, i.e., CECs and EPCs, can be potentially different. They are endothelial system explorers, which can let us know endothelial "general appearance" and give us the opportunity to examine endothelial system. However, the phenotype and functional capacity of these cells need to be further elucidated, and their use in a clinical setting is on the horizon. At the present a panel of markers, including CECs, vWF/ E-selectin and IMT ratio may be optimal to gauge ED. Hopefully, future efforts overpass the "Bench-to-Bedside Gap" in endothelial researches, and look the endothelium as a multi-potential and multifaceted system not as a simple barrier.

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