

Normal Endothelial Function

Mini Review

Endothelium is a monolayer of cells covering the inner surface of blood vessels, and it acts as a functional and structural barrier between bloods and the vessel wall, preventing platelet and leukocyte adhesion and aggregation, controlling permeability to plasma components, and modulating blood flow. The healthy endothelium is a dynamic organ that regulates vascular tone by balancing production of vasodilators and vasoconstrictors in response to a variety of stimuli [1]. Nitric oxide (NO), the predominant mediator of normal vascular function, is released by the endothelium and diffuses within the vessel wall, causing smooth muscle dilation and myofibrillar relaxation in response to stimulation by endogenous factors such as bradykinin, acetylcholine, and catecholamine, as well as ischemia, temperature change, and mechanical stimuli, including shear stress [2]. Endothelium also provides anti-proliferative and anti-inflammatory actions, and regulates fibrinolysis as well as the coagulation pathway through the balanced production of anticoagulant (e.g. tissue plasminogen activator, thrombomodulin) and pro-coagulant (e.g., tissue factor, von Willebrand factor) factors, which maintain haemostatic properties of blood vessels [3].

Central role of NO

NO is synthesized from L-arginine by NO synthase (NOS) [4]. The 3 main NOS isoforms including constitutive endothelial NOS (eNOS or NOS3), neuronal NOS (or NOS1), and inducible NOS (iNOS) that are differently coexpressed in NO-producing cells and also inducible by immunological stimuli [5]. Although NO produced by all 3 pathways regulates normal physiology, large amounts of NO produced by iNOS may have acytotoxic effect and inhibit myocardial contractility [6]. Because HF triggers changes in myocardial NO production, shifting from spatially and temporally regulated NO production by eNOS to excessive release by iNOS, the distinction between NO produced by eNOS/neuronal NOS or iNOS is important [7,8]. In the intact endothelium, hormonal and physical stimuli cause the constitutively expressed eNOS to generate NO, which then diffuses into smooth muscle cells and stimulates soluble guanylate cyclase (sGC) to produce cyclic guanine monophosphate, which causes smooth muscle relaxation and also has antiproliferative effects. In addition to these smooth muscle cell mediated vascular effects, NO targets neighboring extra vascular tissues, including myocardium [9]. Release of endothelial progenitor cells from bone marrow, which has been shown to repair damaged endothelium, is also partially NO dependent [10]. Furthermore, NO can act as an endocrine vaso-regulator, modulating blood flow in the microcirculation when vehiculated by S nitroso-hemoglobin, which transports and releases NO to areas of tissue hypoxia or increased oxygen extraction [11]. Importantly, disruption of NO delivery to the microcirculation contributes to vasoconstriction and uncoupling of oxygen delivery in skeletal muscle. Given the pivotal role of NO in mediating endothelial function, impairment of vasodilation due to decreased NO availability is often used as a measure of endothelial function [12,13].

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Endothelial dysfunction in HF

Although endothelial dysfunction has traditionally been associated with systemic vasoconstriction in advanced HF, newer insights suggest a more central role in HF pathogenesis [14,15]. The failing heart is characterized by an altered redox state with over production of reactive oxygen species, and there is increasing evidence to suggest that the abnormal cardiac and vascular phenotypes characterizing the failing heart are caused in large part by imbalances between NO bioavailability and oxidative stress [16]. In HF, neurohumoral activation, release of inflammatory messengers from the myocardium, and altered local shear forces modulate gene expression and promote atherogenesis, increasing oxidative stress and reducing production of NO [17,18].

The resulting endothelial dysfunction triggers an increase in the production of cytokines, down-regulation or uncoupling of eNOS [19,20], and further increases in oxidative stress [21,22]. These processes culminate in reduced NO bioavailability and worsening endothelial dysfunction, which in turn propagates development and progression of HF [23-26]. These abnormalities have emerged as a common pathophysiological element in the development and progression of HF and are also associated with HF risk factors [27]. Within this construct, myocardial adverse effects and endothelial dysfunction related to oxidative stress represent a unifying feature that drives both the symptoms and unfavorable outcomes associated with both ischemic and non-ischemic [28].

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