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Review

The clinical significance of endocardial endothelial dysfunction

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ABSTRACT

Endocardial endothelium (EE) is essential in the embryonic development of the heart, the optimal contractility and rhythm as well as the remodeling of the heart. Endocardial endothelium affect the contractility of cardiomyocytes through paracrine signaling substances such as nitric oxide (NO), endothelin (ET-1), prostaglandins (PGI2, PGF2, PGE2) and angiotensin II (ANG II). Typical lesions of endocardial endothelium have been described in atrial fibrillation, ischemia/reperfusion injury, cardiac hypertrophy, heart failure, sepsis, myocardial infarction, inflammation and thrombosis. In patients with atrial fibrillation, there can be a systemic endothelial dysfunction that combines endocardial and vascular endothelial dysfunction and leads to increased hemodynamic load of the left atrium and increased synthesis and release of natriuretic peptides, angiotensin II, aldosterone and growth factors from the atrial myocardium. A dysfunction of endothelial cells in the local inflammatory status can lead to increased plaque vulnerability, which contributes to plaque rupture and favors the formation of thrombus. Preserving the endocardial-myocardial integrity plays a significant role in the prevention of a coronary artery disease. Endocardial endothelial dysfunction is, similarly to coronary endothelial dysfunction, an early event that leads to the progression of heart failure. Multimarker strategy, that would include a different set of biomarkers, could significantly help in the assessment of patients with cardiovascular diseases. The challenge lays in finding new therapeutic strategies that would, by preserving endothelial function, prevent the onset of cardiovascular diseases.

1. Introduction

Endocardial endothelium, a natural biological barrier between the circulating blood in heart ventricle and cardiomyocytes, creates a complex yet finely tuned balance of interactions between these units. The complex cavitary surface of the cardiac wall is completely lined by the endocardial endothelium that extends over the surface of the valve and continues on to form the lining of large blood vessels. Cardiac endothelial cells are endocardial endothelial cells (EECs) and microvascular endothelial cells (MVECs), while the vascular endothelial cells line the interior surface of blood vessels [1]. The physiological relevance of endocardial endothelial cells and their effect on cardiomyocytes, terminal network of Purkinje fibers and subendocardial nerve plexus (SNP) is reflected in their endocrine and sensory role and their role in the formation of a blood-heart barrier [2].

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The contractility of the heart is significantly modified by the presence of an intact endocardial endothelium. Selective damage or dysfunction of endocardial endothelium change the appearance of the contraction curve. The impact of the vascular endothelium on the vascular smooth muscle contractility was first described in studies of Furchgott and Zawadski in 1980 [3] and was later confirmed for the endocardial endothelium as well [4–6]. The intact endocardial endothelium improves the contractility of the heart muscle by increasing the sensitivity of myofilament to Ca^{2+} ions through the release of endothelial mediators [6].

Endocardial endothelium and myocardial capillary endothelium affect the contractility of cardiomyocytes through autocrine or paracrine signaling substances such as nitric oxide (NO), endothelin (ET-1), prostaglandins (PGI_2, PGF_2, PGE_2) and angiotensin II (ANG II). A potential participation of other endothelial mediators, such as fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), neuregulin (NRG-1) and angiopoietin [1,7], in the modulation of cardiac inotropic state is also noted.

The formation of endocardial endothelium and the endothelium of blood vessels occurs simultaneously during embryonic development. Endocardial endothelium plays a role in heart development and is essential for the proper formation of trabecular myocardium. It is important for the transdifferentiation of myocytes into the Purkinje's fibers and heart conduction system cells. Endocardial cells are involved in endocardial-mesenchymal transformation and the formation of endocardial cushions. The endocardial cushions give rise to several important structures within the heart, including the valves, the membranous portion of the interventricular septum, and the atrial septum [1].

2. The morphology of endocardial endothelial cells

Endocardial endothelium cells and myocardial capillary endothelium have different embryonic origin and functional morphological traits. The effects of EECs and MVECs on myocardial contractility, rhythm and remodeling are not identical. The distribution of receptors for these two endothelial types is different. At the same time, EECs and MVECs have different cytoskeletal characteristics, such as the presence of contractile bundles of actin filaments (stress fibers) and vimentin and microtubule filaments. Due to greater shear stress exposure, MVEC have more actin filaments. Endocardial cells have well developed organelles, especially Golgi apparatus, and a greater ability to synthesize endothelial mediators in comparison to microvascular endothelium.

EECs are slightly larger than endothelial cells in almost all the other parts of the circulatory system [8]. There is no proven link between the morphologies of endocardial cells and cardiomyocytes; therefore, the endocardial-myocardial interaction depends on the intercellular distance. Depending on animal species, the closest distance of EECs from cardiomyocytes varies in different parts of the heart and is less than 1 μm in small mammals and goes as high as 50 μm in the atria of humans. The specificity of EECs is characterized by the presence of specific cellular connections and intracellular spaces compared to vascular or microvascular endothelial cells [8,9]. Transendothelial permeability is controlled by one or more close junctions and many complex structural gap-junctions. Gap junctions permit a quick passage of charged ions (primarily Ca^{2+}), secondary messenger molecules and small metabolites.

Cardiomyocytes and EECs are not interconnected by a gap junction. Although there is no functional link between EECs, cardiomyocytes and Purkinje fibers, the electrochemical signal propagation is still present. Plenty of gap junctions in endocardial endothelium, which are not so numerous in other endothelial structures, allow for a functional connection and the behavior of endocardial endothelium as a single entity. Transcellular ion transport from the blood to the cardiomyocytal interstitium occurs via passive diffusion through ion channels (inward rectifier K^+ channels, Ca^{2+} activated K^+ channels, voltage-gated K^+ channels, volume activated Cl^- channels, stretch-activated cation channels) and via active transport (Na^+/K^+-ATPase) [10]. The abundance of vesicles in myocardial capillary endothelium in relation to a small number of vesicles in the 3 endocardial cells similarly indicates that the vesicular transport would be more prominent in myocardial capillaries [1,9].

All endocardial endothelial cells act as a functional syncytium. After the activation of individual EECs, secondary messengers pass many gap junctions, activating the neighboring endocardial endothelial cells and amplifying their sensory capacity.

3. Endocrine role of endocardial endothelium

Cardiac endothelial cells synthesize and release mediators that influence cardiac growth, metabolism, contractility and rhythm, primarily NO, whose synthesis is catalyzed by endothelial, neural and induced nitric oxide synthase (NOS) [11]. Endothelium constitutive nitric oxide synthase (eNOS) is present in the coronary endothelium, myocardial capillary endothelium, endocardial endothelium and to a lesser extent in cardiomyocytes [12]. Neuronal NOS (nNOS) is present in cardiac myocytes and in a subpopulation of intracardiac ganglia and nerve fibers in the atrial tissue and in the perivascular nerve fibers of the ventricular myocardium [13]. Inducible NOS (iNOS) is active only under the influence of stress and cytokines [14].

The activity of eNOS and NO synthesis depends on the cyclical changes in the heart during systole and diastole. There is a cyclical release of NO in the heart, mostly in the subendocardial regions, indicating endocardial endothelium as its main source, reaching peak values during ventricular relaxation and early rapid filling [14,15]. The endothelial-borne reactive oxygen species (ROS), such as superoxide, can directly quench NO produced by the endothelial cells, without affecting the expression of eNOS [16]. In physiological and pathophysiological conditions, exogenous and endogenous NO decreases myocardial tissue oxygen consumption [17]. NO ability to reduce myocardial oxygen consumption indicates its potential cardioprotective effect. It can reversibly compete with oxygen for a common binding site on cytochrome-c oxidase, inhibiting electron transfer to oxygen. Nitric oxide

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