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Review

The clinical significance of endocardial endothelial dysfunction

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ARTICLE INFO

Article history:
Received 13 February 2017
Received in revised form
7 August 2017
Accepted 29 August 2017
Available online 21 September 2017

Keywords:
Endocardial endothelium
Dysfunction
Heart failure
Nitric oxide
Endocardial endothelial cells

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

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http://dx.doi.org/10.1016/j.medici.2017.08.003

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].

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 released from myocardial capillary endothelium and endocardial endothelium directly regulates local myocardial metabolism [18]. At the same time, NO inhibits platelet aggregation and blocks binding of neutrophils to endothelium which is of vital importance in the prevention of cardiovascular diseases.

Catecholamines and neurohormones modulate the contractility of the heart and can be the cause of heart remodeling. Vasostain-1 exhibits beneficial effects on the heart by enhancing the activation of the eNOS–cGMP–PKG pathway. This process was used for the inhibition of hypertrophy, fibrosis, and ventricular remodeling while improving the cardiac function in the experimental heart models of rats that were injected with isoprenaline [19]. Despite the increased capacity for NO synthesis in isoproterenol-induced HF, NO does not sustain contractility of failing myocytes. NO may contribute to the decreased basal heart rate and it may accelerate beta-adrenergic stimulation [20].

ET-1 is a mediator with a potent positive inotropic effect exhibited through an increased sensitivity of myophilaments to Ca^{2+} [21]. A positive inotropic effect is the result of the activation of protein kinase C (PKC) and protein kinase A (PKA) [22]. EECs are a major source of ET-1, and cardiomyocytes are its primary target. When ET-1 synthesis and secretion are not stimulated, it exhibits an autocrine effect by binding itself to ETB receptors of the endocardial endothelial cells. Small concentrations of ET-1 may have an important protective role in adult heart by stimulating the release of nitrogen oxides and PGI_2 [23].

In pathophysiological conditions, a large number of nonendothelial cells in the heart, including cardiomyocytes, can also synthesize ET-1 in response to a myocardial stretch, ANG II, and norepinephrine [24]. ET-1 exhibits an antagonizing effect. It enhances myocardial oxygen consumption and thus emphasizes the inotropic effect, while at the same time it decreases oxygen supply through its powerful coronary vasoconstrictive effect [25].

Cardiac endothelial cells synthesize and release prostaglandins in response to various humoral, chemical, immunological, and mechanical stimuli. Cyclooxygenase (COX-1 and COX-2) that plays a key regulatory role in prostaglandin synthesis (PGE_2, $PGF_{2\alpha}$, PGI_2) is constitutively expressed in all endothelial cells in the heart and is believed to provide cytoprotective effects.

The activity of COX-1 is twice as high in the endocardial zone compared with the myocardium. However, the positive inotropic effect of prostaglandin (PGE_2 and $PGF_{2\alpha}$) can completely be canceled after the removal of EE in the atria of the heart. The positive inotropic effect is due to the release of prostaglandins from EECs upon the activation of muscarinic M3 receptors [26]. Myocardial responses to PGI_2 and PGE_2 range from increased inotropy [27], to no effect [28] to negative inotropy [29].

The effect of angiotensin II on cardiac growth and contractile performance is the result of locally produced ANG II. ANG II is synthesized locally through ACE and an ACE-independent kinase pathway, both of which are expressed predominantly in coronary vascular and cardiac endothelial cells [30]. ANG II generally exerts a positive inotropic effect, which may not always be the case as different effects are obtained in different conditions. The inconsistencies in the results of the conducted trials may reflect the many interactions of the cardiac synthesis, release and activity of ANG II with a bradykinin-NO and PGI_2 pathways, as well as with ET-1. ANG II and ET-1 [31], for example, elicit a synergistic effect on the heart while their receptors on cardiomyocytes are also coupled, through similar G proteins, so that their intracellular signaling pathways may be similar [23].

An increasing importance is attached to peptide growth factors that have a role in cell proliferation and angiogenesis, such as platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor and vascular endothelial growth factor. VEGF plays a role in promoting arteriogenesis and the conversion of endocardial endothelial cells into coronary endothelial cells, particularly after acute myocardial infarction. EECs are a source of endothelial cells in the process of arteriogenesis in pathological conditions [32].

Neuregulin is mainly synthesized in endocardial endothelial cells and myocardial capillary endothelium. ErbB3 receptors are distributed in endothelial cells and ErbB2/ErbB4 receptor complex in cardiomyocytes. Soluble NRG-1 induces a substantial increase in embryonic cardiac myocyte proliferation, as well as an increased survival and inhibition of apoptosis of cultured cardiomyocytes and could also induce hypertrophic growth in both neonatal and adult ventricular cardiomyocytes [33]. NRG is essential for endothelial-myocardial signaling for normal cardiac function [7,34]. Just like neuregulin-1, insulin-like growth factor 1 (IGF-1), fibroblast growth factor 1 (FGF-1), fibroblast growth factor 2 (FGF-2), urocortin, vascular endothelial growth factor (VEGF), transforming growth factor beta -1 and cardiotrophin-1 are all associated with the inhibition of apoptosis in the heart.

In the preservation of homeostasis of the heart and blood vessels, the endothelium creates a balance between antithrombotic factors (NO, prostacyclin, plasminogen activator, protein C, tissue factor inhibitor and pro-thrombotic factors (ET-1, oxidant radicals, plasminogen-activator inhibitor-1, thromboxane A2, fibrinogen, tissue factor).

4. Endocardial endothelium dysfunction

Numerous diseases of the cardiovascular system can be a consequence but also the cause of endocardial endothelial dysfunction. Selective damage to the endocardial endothelium and subendocardium occurs in arrhythmia, atrial fibrillation, ischemia/reperfusion injury, cardiac hypertrophy and heart failure [35]. Typical lesions of endocardial and microvascular endothelium have also been described in sepsis, myocardial infarction, inflammation, thrombosis, and in hypertensive patients [36].

In sepsis, endocardial endothelium displays a proinflammatory phenotype. Higher levels of the proinflammatory transcription factor NF-kB, promote the adhesion of polymorphonuclear cells to EECs, and their migration into the subendocardial space and the interstitial space of the heart. Polymorphonuclear cells adhered to EECs induce oxidative

stress in EECs and cardiomyocytes, which can affect the contractility of the heart [37].

Under physiological conditions, the endothelium prevents the formation of thrombus. In cardiac insufficiency, the ventricular endocardial endothelium exhibits prothrombotic properties. This causes frequent thromboembolic complications in patients with HF. However, endothelial dysfunction in HF caused by to the increased release of the sympathetic mediators and vWF can be corrected by the use of galanin. Our study confirmed that neuropeptide galanin promotes an anti-thrombotic phenotype on endocardial endothelial cells [38]. The preserved function of EECs is necessary in the revascularization of the areas damaged by a myocardial infarction. In the infarcted area, EECs were identified as a source of endothelial cells used to promote vascularization. The plasticity of endocardial endothelial cells plays a major role in the revascularization of ischemic heart tissue [32]. EE dysfunction or the dysregulation of the transforming growth factor in EECs can lead to their transition into mesenchymal cells. This occurs in endocardial fibroelastosis, a form of fibrosis where a de novo subendocardial layer is formed that encapsulates the cardiomyocytes and stops heart growth [39].

Fully removing or partially damaging EECs directly effects contractile cardiac performance and causes a lower contractility of cardiomyocytes. The inotropic effect of EE is achieved through the synthesis and release of endothelial mediators, the sensory ability to detect changes in blood plasma and the quality of blood-heart barrier to control transendothelial transport. Thus, EECs have a role in Na^+ transport. Increased Na^+ plasma concentrations and high levels of aldosterone lead to an increased entry of Na^+ into EECs and the transition to subendocardial space, endothelial glycocalcax and glycosaminoglycan network. Increased levels of Na^+ in EECs alter their properties and lead to a decrease in NO synthesis. At the same time, higher Na^+ levels in the subendocardial zones lead to an accumulation of fluids.

EE dysfunction is significant in the pathogenesis of numerous CVDs and we will try to explain the importance of EE dysfunction in atrial fibrillation, coronary disease and cardiac failure.

5. Endocardial endothelial dysfunction in atrial fibrillation

Atrial fibrillation [AF] is an arrhythmia whose most common trigger is the automatic ectopic activity of left atrial cardiomyocytes with altered electrophysiological properties due to the influence of congenital and/or acquired conditions and diseases. AF is the most common sustained arrhythmia in adults [40]. Remodeling of the left atrium includes a series of morphological and functional changes that occur as an adaptive response to factors that lead to atrial fibrillation. The endothelial cells contribute to fibroblast accumulation through an endothelial-mesenchymal transition in the atrium of patients with atrial fibrillation. Immunofluorescence multilabeling experiments identified that heat shock protein 47, prolyl-4-hydroxylase, and procollagen type 1 co-localized with snail and S100 calcium-binding protein A4 (S100A4) within the endothelial cells of the left atrium, indicating the mesenchymal phenotype to produce collagen [41,42].

Adaptive changes in left atrium depend on the duration of arrhythmias, the presence of other adverse effects such as heart failure, myocardial ischemia due to coronary insufficiency and proinflammatory conditions. In addition, changes in the electrophysiological properties of cardiomyocytes create conditions for the reoccurrence and the formation of permanent forms of atrial fibrillation. With the changes in the structure and the function of the myocardium, there are simultaneous changes in the left atrial endocardium that due to dilation and hypocontractility predispose thrombosis [43]. Diseases and conditions that gradually lead to structural changes in myocardium and endocardium, the increased volume [dilatation] and reshaping of the left atrium and its auricle, as well as the reduced contractile ability of the myocardium cause the loss of anticoagulant features of the left atrial endocardium [44].

Structural changes in the atrial endocardial endothelium in AF are manifested by endothelial cells edema and fibrinous transformation. At the same time, there are small areas of endothelial denudation with the formation of platelet aggregates, especially in the left atrium appendage, which can be seen as precursors for thrombosis. This gives endothelium a rough and wrinkled appearance [45]. Changes in the structure of atrial endocardial endothelium are followed by functional changes characterized by different synthesis and secretion of mediators.

Endothelial dysfunction in AF is characterized by a reduced synthesis of mediators with anticoagulant, antithrombotic, anti-inflammatory and anti-proliferative effects: NO, prostacyclin and tissue plasminogen activator and the increased production of procoagulant factors: von Willebrand factor, tissue factor, plasminogen activator inhibitor. At the same time, there is an increased expression of adhesion molecules, the release of chemoattractants, growth factors and free oxygen radicals [46]. The more intense expression of vWF by left atrial appendage (LAA) tissue is a significant predictor of postoperative AF. This points toward a possible role of endothelial damage/dysfunction [as reflected by VWF changes] in the pathogenesis of postoperative AF [47]. Impaired protein C activation on the left atrial endocardium attributable to low thrombomodulin expression may explain its higher thrombogenicity and play a role in cardioembolic stroke [48].

In AF, the eNOS activity is reduced, the release of von Willebrand factor is increased, as well as the presence of inflammatory infiltrates in endocardium and myocardium, the synthesis and release of proinflammatory cytokines and acute phase reactants [CRP], and the presence of products of oxidative modification and markers of hypoxic damage to atrial tissue [49]. EE cells of the left atrium synthesize and release nitric oxide [NO] that plays an important role in the regulation of platelet activity, the inhibition of expression of adhesion and procoagulant molecules on the surface of endothelial cells, and the modulation of inflammation and oxidative stress [50]. In physiological conditions, NO production in the left atrium is significantly higher than its production in any other part of the cardiovascular system. Systemic vascular endothelium produces NO in the conditions of laminar blood flow. Turbulent blood flow reduces the activity of eNOS and the production of NO [31]. The entire

cardiac output passes through the left atrium, and the atrial endocardium represents an endocrine organ whose NO synthesis, through the formation of nitroso-thiol compounds, provides circulating NO donors in the systemic circulation [49,51]. Thus, the atrial endocardial dysfunction with a reduced NO synthesis may have an adverse effect on the function of systemic blood vessels.

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 [43,52]. These mediators can induce, along with paracrine effects, the adverse effects on distant tissues and organs, and promote the development of cardiovascular diseases.

6. EE dysfunction and coronary artery disease

Endothelial dysfunction is closely associated with the progression of atherosclerosis and represents a transitional stage in the development of a coronary artery disease. Oxidative stress lies at the basis of the progression of endothelial dysfunction toward atherosclerotic lesions [52]. Endothelial function of coronary artery worsens in the early stages of atherosclerosis as an early marker when a routine angiography cannot detect any changes. Therefore, not surprisingly, patients with or without coronary artery obstruction show a reduced coronary vascular function that coincides with cardiovascular and cerebrovascular events [53].

An impaired synthesis of vasodilator mediators such as NO and prostacyclin is a potential initiator of endothelial dysfunction [18]. Vasoconstrictors such as ET-1, are increased in endothelial dysfunction. Since the myocardial consumption of oxygen peaks in basal conditions, any additional metabolic disorders will lead to increased blood flow in the myocardium and increased vasodilation of coronary arteries. A reduced vasodilation of coronary arteries results in an inadequate blood flow, especially in patients with an acute coronary syndrome [54].

There is an increased ET-1 production in ischemic cardiomyocytes and endocardial endothelial cells in acute coronary syndrome. ET-1 binds to ET_A receptors, promotes the release of catecholamine from the adrenal gland and modulates the release of noradrenaline from the sympathetic fibers in atrial myocardium, resulting in an increased adrenergic activity [55]. In contrast, the activation of ET_B reduces the effect of sympathetic mediators. ET-1 contributes to the ventricular arrhythmogenesis which is increased with an amplified receptor-mediated activity of inositol 1,4,5-triphosphates leading to an increased release of calcium. Studies have pointed to a higher activation of these receptors during painful conditions in acute coronary syndrome, a heart failure or a mitral valve disease [56].

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 [57].

7. EE dysfunction and heart failure

Congestive heart failure is a common end result of progressive cardiovascular diseases. Many compensatory mechanisms, both cardiac and noncardiac, such as dilation or myocardial hypertrophy, neurohumoral factors, cytokines and the activation of endothelial cells, provide an adaptation that can progress to a maladaptive response ultimately leading to decompensation and heart failure. Maladaptation manifests itself through hemodynamic abnormalities, neurohumoral imbalance, excessive release of cytokines and endothelial dysfunction [58].

EE becomes dysfunctional if a desensitization of receptors is developed. Desensitization of adrenergic α_1 receptors in heart failure has been demonstrated in MVEC isolated from the biopsy samples of patients with different forms of cardiomyopathy with a reduced NO production, in response to acetylcholine, bradykinin, and alpha agonists [59]. There is a deficiency of other signs of MVEC activation such as an expression of adhesion molecules vascular cell adhesion protein-1 (VCAM/-1) and E-selectin or transforming growth factor-β and Endoglin (TGF-β endoglin) [60].

Cardiac endothelial dysfunction is, similarly to coronary endothelial dysfunction, an early event that leads to the progression of heart failure. In a moderate pressure load in the left atrial hypertrophy of shams, ventricular relaxation is completely suppressed due to the deficiency of endothelial NO release [61].

In heart failure, increased neuroendocrine activity [sympathetic nervous and renin–angiotensin–aldosterone systems] is associated with oxidative stress in the myocardium and vasculature. Oxidative stress causes endothelial dysfunction through O_2^- scavenging of NO to produce $ONOO^-$, followed by uncoupling of oxygen reduction from NO synthesis by eNOS, causing it to produce not NO but O_2^-.

The inducible form of nitric oxide synthase [iNOS] is expressed in the vasculature in pathological states [inflammation, sepsis] that lead to heart failure. iNOS produces excessive amounts of NO and mediates impaired vasoconstriction and endothelium-dependent vasodilation. Impaired vasodilation may be further worsened by decreased eNOS activity, resulting from competition with iNOS for BH_4 (essential cofactor considered a significant cause of eNOS uncoupling) and NO scavenging by O_2^- [62].

In insufficient hearts, the heart muscle cells behave as cardiomyocytes without endocardial endothelium. Preclinical and clinical studies emphasize the importance of coronary endothelial dysfunction in heart failure. Basically, the identified reduced vasodilator response is supported by the fact that the reduction of NO reduces myocardial perfusion and indirectly contributes to the progression of heart failure. High concentrations of neurohormones cause selective damage to EE and MVE and the reduction in mechanical performances of the neighboring cardiomyocytes. Thus, the activation of β_1 adrenergic protein kinase A and ET-1 protein kinase C is crucial in a positive modulation of the full development of amplitude–frequency responses in the heart, and a dysregulation of the balance between amplitude and frequency is one of the signs of heart failure [7,63]. The independence of initial pathological

mechanisms in heart failure and the endothelial dysfunction play a major role in the progression of the disease and have an important prognostic value for clinical outcome.

8. Concluding remarks

Intact endocardial endothelium is essential in the embryonic development of the heart, the optimal contractility and rhythm as well as the remodeling of the heart. Endocardial endothelial dysfunction and impaired communication between the EE cells and cardiomyocytes lead to the development of heart and blood vessels diseases. The result of endothelial dysfunction is the weakening of the endothelial barrier regulation and the electrolyte disbalance of subendocardial interstitium. In addition, in endothelial dysfunction there is a change in the synthesis of endothelial mediators with a primary influence on cardiomyocyte performances. The deficiency in EE reduces its sensory ability and the response of cardiomyocytes to circulating mediators or hormones.

Endothelial dysfunction can be assessed by determining the biomarkers of endothelial dysfunction (vWF, soluble thrombomodulin, CRP, cytokines, vascular cell adhesion molecule-1 [VEGF-1], intercellular adhesion molecule-1 [ICAM-1], selectins P and E, asymmetric dimethyl arginine, circulating endothelial cells and microparticles). Along with markers of plaque destabilization and/or markers of ischemia or myocardial necrosis, they may provide additional prognostic information.

To date, a large number of endothelial biomarkers has been identified, most of which await a key analytical and clinical evaluation and are a long way from a broader application in clinical practice. 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 prevent the onset of cardiovascular diseases by preserving endothelial function. Above all, a clear emphasis must be put on the impact of endocardial endothelial cells on the contractility of cardiomyocytes and remodeling of the heart and this information should guide the diagnosis and treatment of heart and cardiovascular diseases.

Conflict of interest

The author states no conflict of interest.

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