Adv Exp Med Biol - Advances in Internal Medicine
DOI 10.1007/5584_2016_90

Endothelial Dysfunction and Hypertension

Dildar Konukoglu and Hafize Uzun

Abstract

In the past, endothelium was thought to be only a mechanical barrier. Today, endothelium is known to be a tissue regulating vascular tone, cell growth and the interaction between the leukocytes, thrombocytes and the vessel wall. It also synthesizes growth factors and thrombo-regulatory molecules and responds to physical and chemical signals. Even though the term "endothelial dysfunction" is generally used for deterioration of endothelium-dependent vasodilatation; the term also includes the abnormalities between endothelium and leukocytes, thrombocytes and regulatory molecules and conditions resulting in aberrant endothelium activation. Healthy endothelium is essential for cardiovascular control. Thus, it plays an important role in pathogenesis of many diseases and cardiovascular problems such as atherosclerosis, systemic and pulmonary hypertension, cardiomyopathies and vasculitides. The aim of this chapter is to explain endothelial dysfunction and the circulating molecules of endothelial cells as they become potential targets of therapeutic approach for hypertension. This chapter reviews the roles of endothelial dysfunction in hypertension by addressing (1) the nature of endothelial function, (2) mechanisms of endothelial dysfunction and its relationship with the diseases (3) also endothelial function testing (4) the role of endothelial dysfunction and hypertension and (4) the effects of antihypertensive therapeutic options on the endothelial dysfunction. In addition to these, the role of endothelial dysfunction in white coat hypertension has been discussed. The key connections between hypertension and endothelial dysfunction are vitally important for future studies to permit new interventions to be designed and released.

D. Konukoglu and H. Uzun (✉)
Cerrahpasa Medical Faculty, Department of Biochemistry, Istanbul University, Istanbul, Turkey
e-mail: huzun59@hotmail.com

Keywords
Endothelial dysfunction • Atherosclerosis • Hypertension • White coat hypertension • Coagulation • Fibrinolysis • Inflammatory mediators • Endothelium-derived relaxing factors • Endothelium-derived contracting factors: angiogenesis

1 Introduction

The term endothelial dysfunction is used to describe the altered metabolism of available nitric oxide (NO) or imbalance of several endothelium-derived relaxing and constrictor factors. Between the blood and the vascular wall, the endothelium forms both mechanical and biological barrier (Vanhoutte et al. 2009). Interactions between platelets and leukocytes with the vessel wall, impairment of vascular tone, inflammation, free radical formation and oxidation of lipids and vascular smooth muscle cell proliferation can be activate endothelial cells (ECs) (Lerman and Burnett Jr 1992). ECs function by secreting relaxing and/or contracting molecules. ECs are exposed to the shear stress resulting from blood flow and can convert mechanical stimuli into intracellular or biochemical signals (e.g., proliferation, apoptosis, migration, permeability, remodeling and gene expression) (Li et al. 2005a). As a result, endothelial dysfunction is related to several diseases including atherosclerosis, cancer metastasis, inflammatory diseases and hypertension (Rajendran et al. 2013).

Hypertension is defined as the presence of chronically elevated systemic arterial or diastolic blood pressure (BP) above a certain threshold whereas sustained hypertension is defined as systolic BP >140 mm Hg in medical environment and daytime ambulatory systolic BP >135 mm Hg, and/or medical environment diastolic BP >90 mm Hg and daytime ambulatory diastolic BP >85 mm Hg (Weber et al. 2014). Thus, the patients with sustained hypertension have increased BP levels in the medical environment (in clinics or office) and out of the medical environment (at home). Sustained high blood pressure is also an indicator of the age, diet, stress, sedentary lifestyle, all or the combination of these factors. It has been suggested that sustained hypertension is closely related to both target organ damage and organ function failure including heart, kidneys, and brain. Pathophysiology of hypertension is related to several factors, including genetics, activation of the sympathetic nervous system, the rennin- angiotensin (AT)- aldosterone system, endothelial dysfunction, impaired capillary blood flow and inflammatory mediators (Dawes et al. 2008; Oparil et al. 2003).

2 The Nature of Endothelial Function

Three layers of the artery wall from outside to inside comprise; tunica adventitia, tunica media and tunica intima. The layer of tunica adventitia; contains nerve endings, perivascular adipose tissue and connective elements, such as fibroblasts and collagen. It plays important roles in the vascular development and remodeling. The second layer, vascular smooth muscle, regulates the response of constriction and dilatation of the blood vessels. The mechanical stimuli, such as shear stress and pressure, or pharmacological stimuli activate the contraction of the vascular smooth muscle cells by increasing the intracellular calcium concentration. Tunica intima, the innermost layer of the vascular arterial wall, consists of monolayer ECs and connective tissues lie beneath the ECs. Substances can pass through the connection between ECs or are absorbed by the cells. As the vascular vessel sizes are about 60–80 nm in diameter, endothelium provides restriction for larger particles and

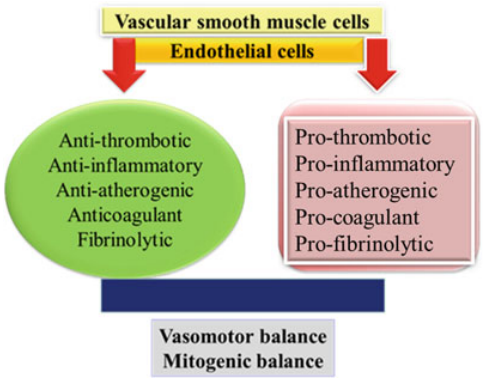

Fig. 1 Activities of endothelial cells. Vasomotor and mitogenic balance is provided by molecules secreted by endothelial cells and vascular smooth muscle cell. These cells have several paracrine functions by producing and secreting several molecules including vasoactive, inflammatory, vasculoprotective, angiogenic, thrombotic and antithrombotic

prevents the interaction between the blood cells and the vessel wall (Wilson and Lerman 2001; Vestweber 2012).

Multiprotein complexes containing transmembrane proteins (such as claudins, occludins, and junction adhesion molecules) and cytosol proteins that connect membrane proteins to the intracellular cytoskeleton form intercellular junctions between ECs (Chistiakov et al. 2015). The endothelium is also considered as an endocrine organ, while it demonstrates several paracrine functions by producing and secreting vasoactive, inflammatory, vasculoprotective, angiogenic, thrombotic and antithrombotic molecules (Fig. 1). Like the other endocrine organs, endothelium possesses receptors that display various cellular and hormonal events (Table 1).

Table 1 Molecules which are produced and secreted by endothelial cells

Regulation of vascular tonicity	
Vasodilatation	Nitric oxide
	Prostacyclin
	Endothelium-derived hyperpolarizing factors
	Adenosine
Vasoconstriction	Endothelin-1
	Angiotensin II
	Thromboxane A_2
	Reactive oxygen species
Balancing of blood fluidity and thrombosis	
Coagulation	Heparin cofactor 2
	Factor V
	Protein S
	Protein C
	Thrombomodulin
	Tissue factor
	von Willebrand factor
Fibrinolysis	Tissue plasminogen activator
	Prostaglandins
	Plasminogen activator inhibitor type 1
	Urokinase
Vascular inflammatory and immunological process control	
Cytokines	Interleukin -1
	Interleukin-6
	Interleukin-8
	Monocyte chemoattractant protein-1
Adhesion molecules	Transforming growth factor
	Tumor necrosis factor
	Vascular cell adhesion protein 1
	Intercellular adhesion molecule 1
	Selectins
Growth factors	Basic fibroblast growth factor
	Insulin like growth factor
	Platelet derived growth factor
	Transforming growth factor

2.1 Regulation of Vascular Tonicity

Vascular tonicity is regulated by atrial natriuretic peptide, eicosanoids, adrenal steroids, sodium, and water excretion and by the control of neurologic, kallikrein- kinin, reno-medullary endothelial systems. Molecules such as endothelin-1 (ET-1), angiotensin II (AT-II), thromboxane A_2 (TXA_2), and reactive oxygen species (ROS) are known as endothelium-derived relaxing factors, whereas NO and prostacyclin are known as endothelium-derived hyperpolarizing factors (EDHFs) (Dawes et al. 2008). In healthy endothelial tissues, a

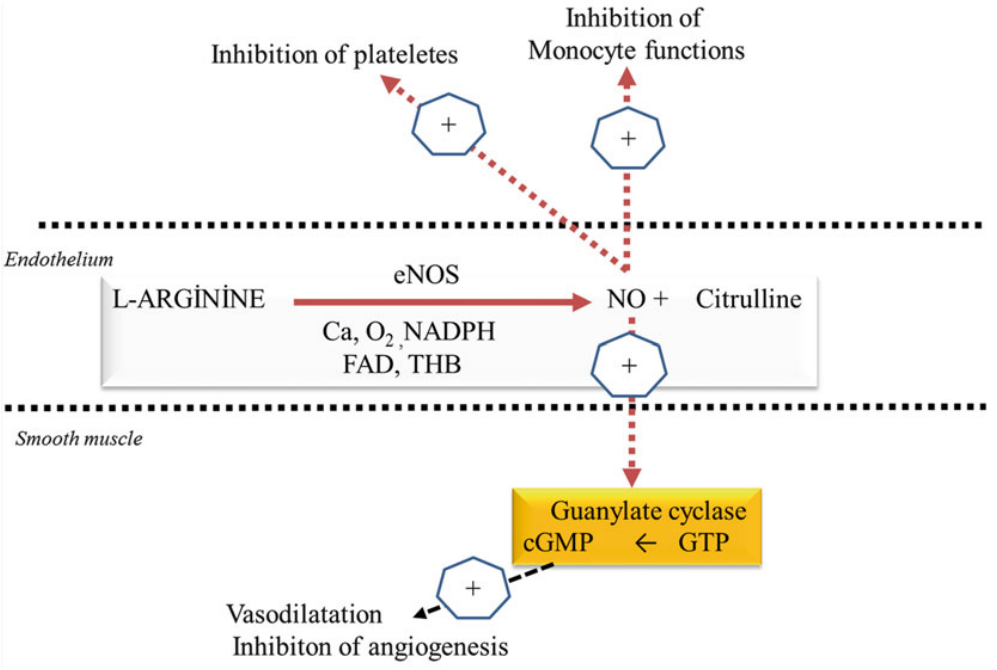

Fig. 2 Nitric oxide (NO) is synthesized by endothelial nitric oxidase synthase (eNOS) can activate soluble guanylate cyclase. cGMP is produced. Vasodilatation occurs, and angiogenesis is inhibited. NO inhibits both platelet and monocyte functions (Şekil Türkçe)

balance between endothelium-derived relaxing factors (EDRFs) and endothelium-derived contracting factors (EDCFs) is maintained. Disturbance of this balance causes endothelial dysfunction (Cahill and Redmond 2016).

Nitric Oxide (NO) Vascular smooth muscle cells release: Endothelium-derived NO, the known most powerful vasodilator which activates the soluble guanylate cyclase. Soluble Guanylate cyclase (sGS) enzyme converts GTP to cyclic GMP (cGMP) which activates protein kinase G that leads decreases in the cytosolic calcium concentrations. NO can also affect cellular activity, independently of sGC activation, by the stimulation of the endoplasmic reticulum calcium ATPase, reducing the intracellular calcium concentration and cause relaxation of the smooth muscle. The release of inflammation, vascular cell proliferation, platelet adhesion, and tissue factor are inhibited by NO (Laher 2014).

NO is synthesized from an L-arginine by the enzyme nitric oxide synthases (NOS) as a free radical (Fig. 2). There are three distinct genes encoding NOS isozymes; neuronal NOS (nNOS or NOS-1), cytokine-inducible NOS (iNOS or NOS-2) and endothelial NOS (eNOS or NOS-3) (Melikian et al. 2009) (Table 2). The production of NO from L-arginine by NOS requires the presence of various co-factors including tetrahydrobiopterin, flavin adenine dinucleotide, flavin mononucleotide, calmodulin (calcium binding protein) and iron protoporphyrin (Palmer et al. 1988). nNOS is expressed in the central and peripheral nervous systems, in cardiac and skeletal myocytes, smooth muscles and ECs. NO produced in the nervous systems by nNOS is associated with the regulation of neuronal excitability and synaptic plasticity, memory and learning processes. It has been suggested that the expression of vascular nNOS is also upregulated by stimulation with

Table 2 The forms of NO synthase

	Gene	Main Localization (s)	Functions	Stimulation
Neuronal NOS (nNOS;NOS-1) (calcium-dependent)	Chromosome 12	Central and peripheral nervous systems	Regulation of neuronal excitability and synaptic plasticity,	Angiotensin II
				Platelet-derived growth factor
		Cardiac and skeletal myocytes Smooth muscle and endothelial cells	Memory and learning processes	
Inducible NOS (iNOS;NOS-2) (calcium-independent)	Chromosome 17	Immune system	Participation in anti-microbial and anti-tumor activities (e.g.oxidative burst of macrophages)	Proinflammatory cytokines (Interleukin-1, Tumor necrosis factor α Interferon γ)
		Cardiovascular system		
		Smooth muscle cells		
Endothelial NOS (eNOS; NOS-3) (calcium–dependent)	Chromosome 7	Endothelium	Regulating vascular function	Shear stress
				Acetylcholine Bradykinin
				Histamine

AT-II and platelet-derived growth factor (Dawson et al. 1991). iNOS is minimal under physiological conditions and is calcium insensitive. When iNOS is stimulated, it continuously produces NO. Induction of iNOS occurs mainly during infection and chronic inflammation. iNOS is expressed in vascular smooth muscle cells following exposure to pro-inflammatory cytokines. It is reported that inflammation-induced iNOS production in the endothelium is related to the vascular dysfunction by limiting the availability of BH_4 for e NOS (Lowenstein and Padalko 2004; Gunnett et al. 2005). eNOS is the major isoform for the regulation of vascular function. The activity of eNOS and the production of NO can be stimulated by shear stress, acetylcholine, bradykinin and histamine by both calcium-dependent and independent ways (Laher 2014). Acetylcholine, bradykinin and histamine bind to specific receptors on the endothelial cell membrane and increase the intracellular concentration of calcium. In a calcium-independent manner, the activation of eNOS is due to the post-translational modification of the enzyme including phosphorylation by NOS kinase and dephosphorylation by phosphatases (Kellogg et al. 2005; Bae et al. 2003). Phosphorylation alters the activity of eNOS, and different sites of phosphorylation can have an opposing effect.The endogenous competitive inhibitor for eNOS is called asymmetric dimethyl arginine (ADMA) (Arora et al. 2013; Zhao et al. 2014). The inhibition of eNOS is correlated with plasma ADMA levels, and plasma ADMA levels are inversely related to endothelium-dependent vasodilation (Vestweber 2012). The acute and chronic rise in the shear stress of blood up-regulates the expression and the activity of eNOS, and thus the release of EDRF/NO (Kolluru et al. 2010; Michel and Vanhoutte 2010). AT-II by binding to its receptor produces bradykinins which stimulate eNOS consequently increases the formation of NO (Yayama et al. 2006).

Additionally, the products of the metabolism of NO are nitrite and nitrate which act as a reservoir of NO. Under certain conditions, several enzymes, such as xanthine oxidoreductase, mitochondrial cytochrome oxidase, aldehyde dehydrogenase 2 and cytochrome P450 reductase, catalyze the reduction of nitrite or nitrate to NO (Weitzberg et al. 2010).

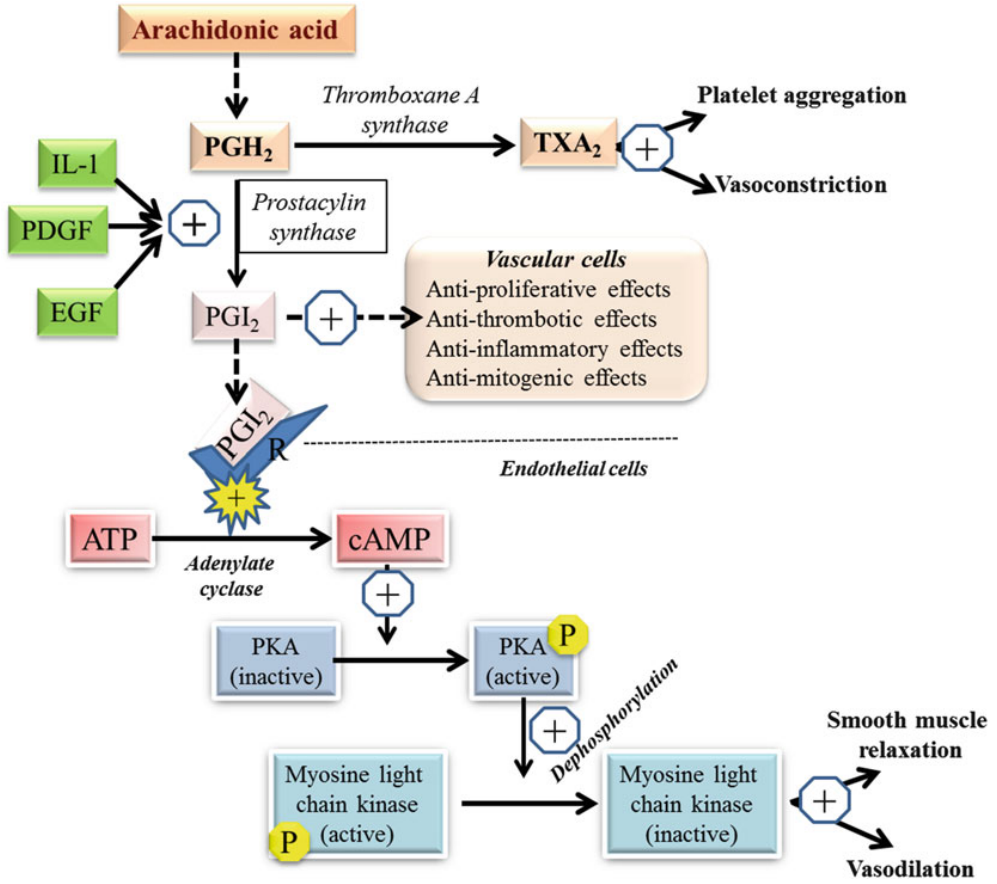

Fig. 3 The synthesis of the prostacyclin from prostaglandin (*PG*) G2 and thromboxane (*TX*) A2. TXA_2 shows interactions in contrast to PGI_2. *IL-1* Interleukin-1, *PDGF* Platelet derived growth factor, *EGF* Epidermal growth factor, *R* PGI_2 receptor

Prostacyclin Another vasodilator molecule is prostacyclin (also called prostaglandin I_2 or PGI_2) which is a prostaglandin that belongs to the eicosanoid family of lipid molecules. Prostacyclin is produced in ECs in response to inflammatory mediators, including interleukin (IL)-1 and platelet-derived and epidermal growth factors from prostaglandin H_2 (PGH_2) by the action of the enzyme prostacyclin synthase (Fig. 3). Like NO, it inhibits platelet activation and act as an effective vasodilator (Cahill and Redmond 2016; Siti et al. 2015). PGI_2 is released by healthy ECs and performs its function via paracrine signaling that involves G protein-coupled receptors on both ECs and platelets. PGI_2 binds to endothelial prostacyclin receptors and raise cAMP levels in the cytosol. cAMP activates protein kinase A (PKA) which promotes the dephosphorylation of the myosin light chain kinase. Dephosphorylation of the enzyme results in the inhibition of myosinlight-chainkinase. This leads relaxation of the smooth muscle relaxation and vasodilation (Francis et al. 2010). Prostacyclin has also antiproliferative, antithrombotic, anti-inflammatory and antimitogenic effects on vascular cells. On the other hand, prostanoids, such as PGD_2 and $PGF_{2,}$ produced in vascular endothelium modulating intracellular Ca^{2+} concentration produce vasoconstriction (Siti et al. 2015).

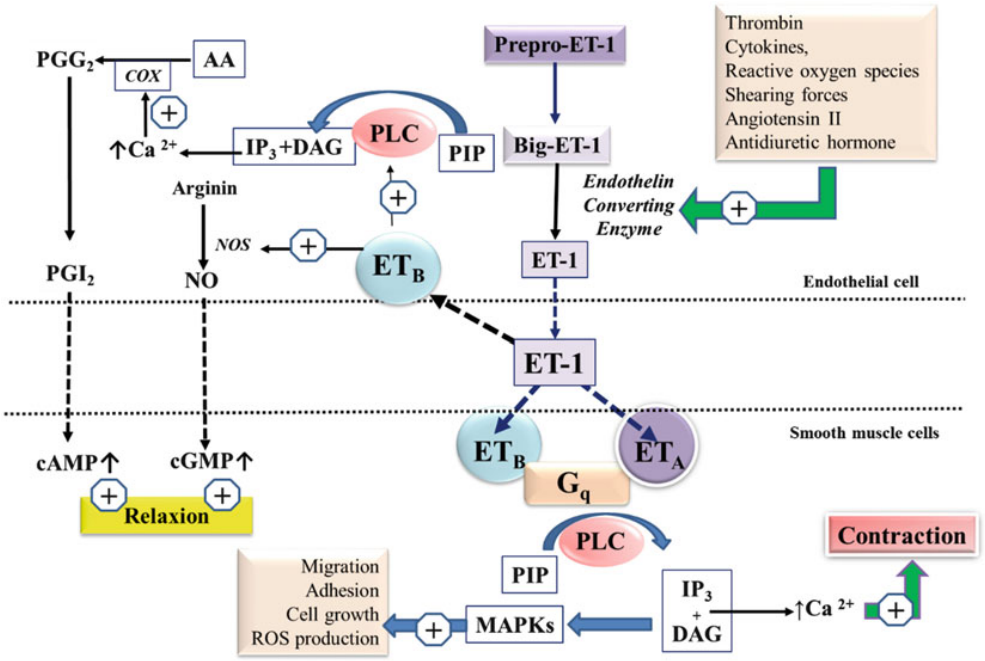

Fig. 4 Endothelin (ET); receptors (ET_A and ET_B), mechanisms and effects. *PLC* Phospholipase C, *PIP* Phosphatidyl inositol diphosphate, *IP_3* Inositol triphosphate, *DAG* Diacylglycerol, *MAPK* Mitogen activated kinase, *AA*Arachidonic acid, *PGG_2* Prostaglandin G_2, *PGI_2* Prostaglandin I_2

Endothelium-Derived Hyperpolarizing Factor The term of EDHF represents a mechanism rather than a specific factor (Luksha et al. 2009). Prostacyclin and NO can be considered as an endothelium-derived hyperpolarizing substance. Because most of the available inhibitors of cyclooxygenase abolish the production of prostaglandins in vascular tissues, any endothelium-dependent hyperpolarization observed in the presence of one of these inhibitors is unlikely to involve prostacyclin. NO can also hyperpolarize, or repolarize, vascular smooth muscle cells by activating, in either a c-GMP dependent or –independent pathways through potassium channels such as K-ATP. NO interacts with other ionic channels of the smooth muscle, including chloride and cationic channels and also influences the membrane potential of the smooth muscle cells indirectly in an autocrine fashion (Félétou and Vanhoutte 2006). Members of a class of arachidonic acid derivatives, the epoxyeicosatrienoic acid, hydrogen peroxide, C-type natriuretic peptide, have been suggested to function as an EDHF in some vascular beds. These molecules are accepted as non-NO–non-PGI_2– EDHFs. EDHF is proposed to be a substance and/or electrical signal that is generated or synthesized in and released from the endothelium. Its function is to hyperpolarize vascular smooth muscle cells, causing these cells to relax. EDHFs are able to activate ion channels, and initiate smooth muscle hyperpolarization and relaxation (Luksha et al. 2009). Calcium-activated K+ channels are opened by EDHFs in vascular smooth muscle cells. The effects of EDHF's are highest on the small arteries, and are very significant for the regulation of organ blood flow, peripheral vascular resistance and blood pressure, particularly when production of NO is depressed (Michel and Vanhoutte 2010; Luksha et al. 2009; Félétou and Vanhoutte 2006; Khazaei et al. 2008).

Endothelins Endothelins (ETs) are potent vasoconstrictor molecules having a key role in vascular homeostasis (Fig. 4). Although there are three

types of ET, vascular ECs produce only ET-1 which has prominent roles (Wang and Zhao 2010). ET-1 is a 21 amino acid peptide that is synthesized from a 39 amino acid precursor named pre-pro endothelin. Active endothelin molecule is generated by the actions of an endothelin converting enzyme (ECE) found on the endothelial cell membranes. There are two basic types of ET-1 receptors: ET_A and ET_B. Both of these receptors are coupled to a G-protein and to the formation of IP_3 (Barton 2011; Kedzierski and Yanagisawa 2001). In blood vessels, the ET_A receptor is dominant under normal conditions. ET-1 produces vasoconstriction through activation of L-type Ca^{+2} channels by binding to ET-A receptors on vascular smooth muscle cells. In addition to the presence of both ET_A and ET_B receptors on the smooth muscle, ET_B receptors are also found on the endothelium, and under the control of vascular tone, considerable cross-talk between ET, NO and prostacyclin occur (Vanhoutte et al. 2009). When ET-1 binds to endothelial ET_B receptors, the formation of NO is stimulated but in the absence of smooth muscle endothelin receptor stimulation, NO causes vasodilation. The other effects of ETs include cell growth, embryonic development, renal functions, neurophysiological functions (such as pain signaling), cardiovascular homeostasis, cancer cell growth, endocrine function, inflammation, pulmonary functions (such as bronchoconstriction) and reproductive system functions (Khazaei et al. 2008). ET-1 production and release are stimulated by AT-II, antidiuretic hormone (ADH), thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. The ET-1 release is inhibited by prostacyclin, atrial natriuretic peptide and NO (Davenport et al. 2016).

Angiotensin I and II Angiotensin II (AT-II) cause structural changes and vasoconstriction in the arterial wall by affecting many cellular and intracellular events in smooth muscle. Two types of AT-II receptors on ECs are determined. AT-II type-1 receptor is particularly involved in the contraction of vascular smooth muscle cells. AT-II-type-1 receptor blockers increase the release of NO and prostaglandins whereas AT II- type-2 receptors provide the activation of the endothelial relaxation (Masuyer et al. 2014; Jiang et al. 2014).

Thromboxane Thromboxane (TX) A_2 is a member of the eicosanoid lipid family. TXA_2 is generated from prostaglandin H_2 by thromboxane-A synthase. TXA_2 acts by binding to the G-protein-coupled thromboxane receptors. Thromboxane is a vasoconstrictor, and it facilitates platelet aggregation (Fig. 3). Therefore, TXA_2 shows interactions in contrast to prostacyclin (Bauer et al. 2014; Korbecki et al. 2014).

Adenosine The vascular ECs releases adenosine to produce vaso-relaxation through activation of purinergic (P_2) receptors. Adenosine release is related to local oxygen tension. Also, adenosine metabolites play roles in local vasoregulation and in the physiological control of blood pressure (Ralevic and Dunn 2015).

2.2 Inflammatory and Immune Response of ECs

Many stimuli associated with inflammatory and immune vascular diseases have been reported to induce endothelial cell apoptosis (Winn and Harlan 2005a). Endothelial cells produce and react to a variety of cytokines (these include chemokines, colony-stimulating factors (CSF), Interleukins (IL), growth factors, and interferons (IFN) and other mediators). Therefore, ECs have important roles in defense and inflammation. The chemokines from ECs affect leukocytes (neutrophils, eosinophils), T lymphocytes, natural killer cells and monocytes. Since ECs are located at the tissue-blood interface, they present several chemokines to circulating leukocytes. When production of chemokines is elevated, Tumor Necrosis Factor (TNF)-α and IL-1 for the receptor (so called as decoy receptor) are released into the circulation (Vanhoutte et al. 2009). IL-1 and TNF-α are synergistically

effective on the expression of pro-inflammatory genes in various cells. Endothelial cells also produce granulocyte macrophage CSF (GM-CSF), granulocyte CSF (G-CSF), macrophage CSF (M-CSF), the stem cell factors, IL-1 and IL-6 and TNF receptors. ECs by themselves are targets of the inflammatory response. TNF-α and TNF-β are produced by activated macrophages and activated T cells, respectively. These activate ECs and neutrophil aggregation, as well as NO synthesis. Inflammatory disease progression depends on the balance between pro-inflammatory and anti-inflammatory cytokines. ECs involve the systemic anti-inflammatory response by producing anti-inflammatory cytokines such as an IL-1 receptor, IL-10, IL-13, and Transforming Growth Factor (TGF)-β. Anti-inflammatory cytokines can either block the process initiated by pro-inflammatory cytokines or suppress the inflammatory cascade. While cytokines such as IL-4, IL-10, IL-13, and TGF-β suppress the production of IL-1, TNF-α, other pro-inflammatory cytokines block the production of these cytokines (Mai et al. 2013). TGF-β is also produced by macrophages, T cells, and endothelium and generally works as a growth inhibitor of ECs. Additionally, IL-8 stimulates proliferation and migration of ECs and have angiogenic properties (Medzhitov 2008; Levesque et al. 1990).

ECs facilitate leukocyte movement into tissues through adhesion molecules such as E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM). Resting ECs are considered not to be adhesive to circulating leukocytes. ICAM-2 is expressed on resting ECs, whereas ICAM-1 and VCAM are minimal on resting state and their expression can be increased by cytokines and endotoxin activation. Lymphocytes, platelets, and other leukocytes can interact with ECs under basal conditions via the L-selectin receptor. When lymphocytes are activated, they express integrins, which interact with ICAM and VCAM. L-selectin, as an adhesion molecule, and β2 integrin are involved in the adherence of leukocytes to ECs. Activated ECs also secrete platelet activating factor (PAF) and stimulate the expression of P-selectin and E-selectin. PAF upregulates integrins on leukocytes. Activated platelets binds to CD40 on ECs (Vanhoutte et al. 2009; Tuttolomondo et al. 2012; Tummala et al. 1999; Szmitko et al. 2003).

The endothelium is also capable of expressing various growth factors including G-CSF, M-CSF, GM-CSF, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factors (FGF). CSFs and growth factors produced by the endothelium are also important for hematopoiesis which increases the number of immune cells in the circulation during inflammation (Croft et al. 2009).

The immune system has important roles in the defense mechanism against infections or in response to tissue injury. Dendritic cells (DC), macrophages, natural killer (NK) T cells, and Toll-like receptors (TLRs) are components of the immune system. ECs actively participate in both innate and adaptive immune responses through producing cytokines and chemokines which recruit phagocytes to the site of infection. Endothelial permeability is also increased, allowing for additional trafficking of immune cells during inflammation. Although ECs at rest do not interact with leukocytes, activated ECs increase the expression of adhesion molecules and chemokines and interact with immune cells during the inflammatory process. ECs also can serve as antigen presenting cells by expressing both MHC I and II molecules and presenting endothelial antigens to T cells during inflammation. Both TLRs (TLR2 and TLR4) and NLRs are expressed in inflamed endothelium. When inflammation is dominated by TH1 cells, ECs express chemokine ligand 10 (CXCL10) and E-selectin, which favors the recruitment of TH1 cells. EC surface molecules such as lymphocyte function-associated antigen (LFA)-3 and ICAM-1 increase the production of IL-2 and IL-4 by T cells. ECs with activated T cells enhance IFN-γ production via OX40 (CD134) signaling (OX40 is a member of the TNFR/TNF superfamily and are expressed on the activated CD4 and CD8 T cells). An anti-angiogenic cytokine derived

from ECs, vascular endothelial growth inhibitor functions to suppress ECs proliferation in a cell cycle-dependent manner lipopolysaccharide, which induce ECs to produce IL-1, IL-8, and monocyte chemotactic protein-1 (MCP-1). Like LPS, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) can induce TLR2 expression via an NF-kB-dependent pathway. ECs also express CD14, a known receptor for LPS and IFN-α, which is an important cytokine in regulating innate immune responses against viruses (Mai et al. 2013; Croft et al. 2009; Rodriguez-Iturbe et al. 2014).

Under healthy conditions, ECs express the lectin-like oxidized low-density lipoprotein (oxLDL) receptor (LOX-1) at low levels. Expression of LOX-1 in ECs is elevated in response to stimulation by oxLDL, pro-inflammatory cytokines, and pro-atherogenic factors such as AT-II. OxLDL also induces cell surface adhesion molecule expression and impair NO production in ECs by increasing superoxide generation. LOX-1 has a role in the mediation of endothelial phagocytosis of aged red blood cells and apoptotic cells. LOX-1-mediated phagocytotic activity can be inhibited by oxLDL. Thus, LOX-1 is important in endothelial-mediated vascular homeostasis and coagulation prevention under physiological conditions (Pirillo et al. 2013; Dunn et al. 2008).

ECs can also induce suppressive immune function in T cells. Mechanistically, after contact with ECs, regulatory T cells upregulate the expression of programmed death-1 receptor and increase the production of anti-inflammatory cytokines IL-10 and TGF-β (Tselios et al. 2014; Pastrana et al. 2012).

Recently, it has been shown that ECs also induce cellular signaling by endothelial microparticles (EMPs). EMPs are small plasma membrane-derived vesicles (0.1–1.5 μm in diameter), are released by various cell types during cell activation or apoptosis (a type of programmed cell death). Microparticle formation induced by various factors, including TNF-α, IL-1β, thrombin, calcium ionophore, and reactive oxygen species. Microparticles express surface antigens from their cells of origin which allow for the identification of their sources. Circulating EMPs are biomarkers of inflammation and contribute to the pathological state. Depending on the nature of the stimulus, EMPs contain endothelial proteins such as ICAM-1, integrin, and cadherin. EMPs also have endothelial nuclear materials such as microRNA, RNA, and DNA, which can induce intracellular signaling via the transfer of these nuclear materials and proteins to target cells. EMPs also have pro-coagulant and pro-adhesive properties, which promote coagulation and vascular inflammation. EMPs were also found to induce the maturation of plasmacytoid dendritic cells. Plasmacytoid dendritic cells matured by EMPs secrete pro-inflammatory cytokines IL-6 and IL-8 (Yuana et al. 2013; Bernal-Mizrachi et al. 2003; Helbing et al. 2014a).

2.3 The Link Between Hemostasis and Coagulation and ECs

The endothelium plays a pivotal role in the regulation of the hemostatic balance, and endothelial and smooth muscle cells express several proteins participating in hemostasis. Hemostasis is a complex event. Multiple interactions between blood cells and the damaged vessel wall, the coagulation proteins, and blood cells and the cell-cell interactions are required in the hemostatic process (Fig. 5). In physiological state, healthy ECs express antiplatelet and anticoagulant molecules that prevent platelet aggregation and fibrin formation, respectively. Injury to endothelium leads to loss of protective molecules and the appearance of adhesive and pro-coagulant activities. When coagulation proteins are activated by their specific receptors on the vascular cell surface, in turn, these cells lead to the expression of genes involved in coagulation, angiogenesis, leukocyte adhesion and regulation of the vascular wall tone (Stenina 2003; Yau et al. 2015).

Tissue factor (TF) is the receptor for factor VII and is a pro-coagulant. It is inhibited by tissue factor pathway inhibitor (TFPI), which is synthesized by ECs and is one of the most important endothelium-derived inhibitors of the blood

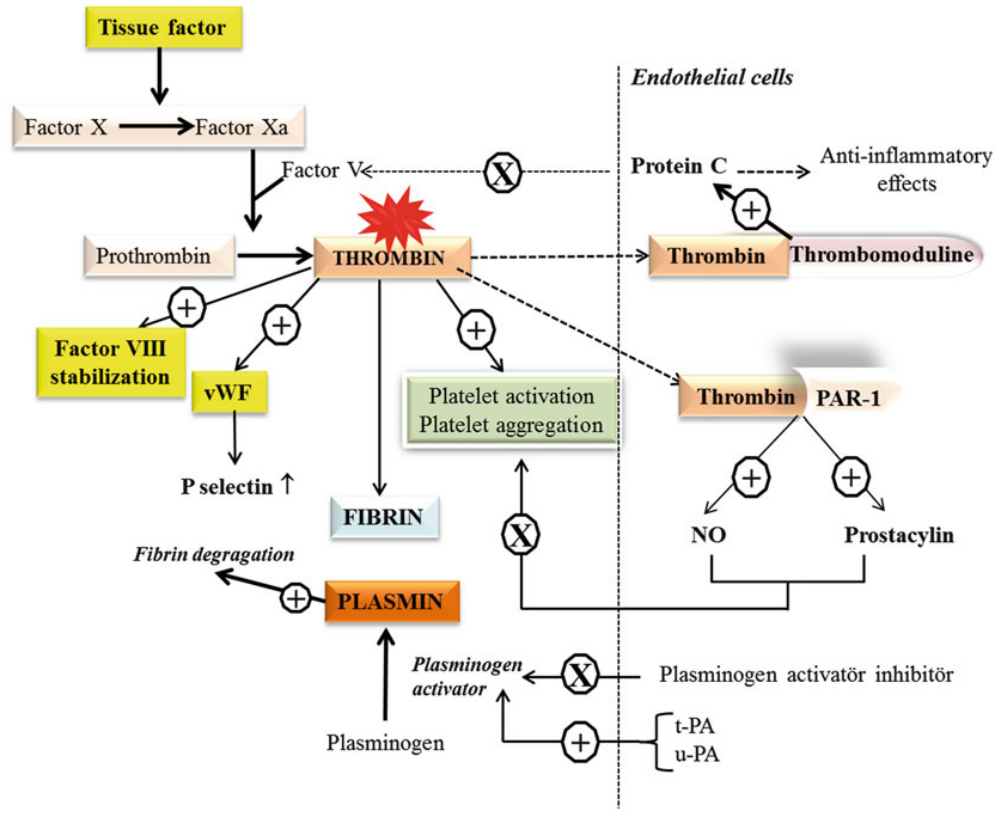

Fig. 5 Endothelium has both anticoagulant and coagulant activities (*see text*); *PAR-1* Protease-activated receptor-1, *t-PA* Tissue type plasminogen activator, *u-PA* urokinase type plasminogen activator, *vWF* von Willebrand factor (Şekilde Türkçe Karakterler mevcut)

coagulation cascade. TF activates factor X, which then combines with factor Va to convert prothrombin to thrombin. Thrombin has pro-coagulant activity. It binds to thrombomodulin which is expressed on the ECs surface. Thrombomodulin requires for the pro-coagulant effects of thrombin as a cofactor in normal vessels. The thrombin-thrombomodulin complex activates protein C. This process is forced by the endothelial protein C receptor (EPCR). Activated protein C (APC) is an effective anticoagulant through the inactivation of factor Va. Thrombin is also chemotactic for polymorphonuclear leukocytes and is a potent inducer of platelet activating factor (PAF) expression in ECs. Thrombin is also involved in the process of inflammation and can up-regulate endothelial cell P-selectin expression through von Willebrand factor (vWF). Endothelium also produces and secretes vWF, mediating platelet adhesion and shear stress-induced aggregation. vWF, which is also synthesized within megakaryocytes and the α-granules of platelets, is a multimeric adhesion glycoprotein. vWF is essential for platelet adhesion to collagen via the platelet receptor glycoprotein Ib-FV-FIX at sites of vascular injury. The vWF binds and stabilizes factor VIII and is a cofactor for platelet binding to exposed extracellular matrix in injured vessel walls (Vanhoutte et al. 2009; Stenina 2003; Yau et al. 2015; Steffel et al. 2006; Esmon 2006).

Under physiological conditions, the endothelium prevents thrombosis. Endothelial protease-activated receptors (PARs) serve as sensors for proteases and initiate a cascade of cell signals upon activation by thrombin, APC, FXa, the

TF/FVIIa/FXa complex, high concentrations of plasmin, and matrix metalloproteases. Thrombin-mediated activation of PAR-1 is responsible for the production of NO and prostacyclin, which limits platelet activation, induces the activation of Weibel-Palade bodies, releasing VWF and t-PA, and mediates the surface exposure of TF. Thus, PARs (especially PAR-2) play an important role in the pro-coagulant response upon stimulation, and this induces pro-inflammatory responses (Lacave et al. 1989; Lijnen and Collen 1997).

Platelets play a fundamental role in preventing blood loss by forming the platelet hemostatic plug and to serve as a platform for coagulation factors. Platelet-endothelium interactions play an important role in the activation and regulation of platelets. While an intact endothelium inhibits the adhesion of platelets, through the release of NO and PGI_2, activated ECs express a variety of molecules and receptors that increase platelet adhesion to the site of injury. In ECs, Weibel-Palade bodies store, vWF, P-selectin, angiopoietin-2, t-PA, and ET-1, which are active participants of platelet adhesion, leukocyte recruitment, inflammation modulation, fibrinolysis, and vasoconstriction, respectively. Following vascular insult or in the presence of vasoactive agents such as histamine, bradykinin, and thrombin, endothelial Weibel-Palade bodies fuse with the plasma membrane and release these products into the space wherein they perform their specific functions (Francis et al. 2010). Normal ECs also produce enzymes called ectonucleotidases, which dephosphorylates ADP to AMP and then to adenosine and inhibit platelet aggregation, and release matrix metalloproteases (MMPs) to cleave platelet aggregates. TXA_2 produced by activated platelets, has prothrombotic properties, stimulating activation of new platelets as well as increasing platelet aggregation. Platelet aggregation is achieved by mediating expression of the glycoprotein complex GP IIb/IIIa in the cell membrane of platelets. Circulating fibrinogen binds to these receptors on adjacent platelets, further strengthening the clot (Yau et al. 2015; Steffel et al. 2006; Esmon 2006; Perutelli et al. 1992; Lacave et al. 1989; Lijnen and Collen 1997).

ECs synthesize and secrete plasminogen activator (PA) to degrade the clot and plasminogen activator inhibitor (PAI), and thus provide anticoagulant and pro-coagulant regulatory mechanisms, respectively. Additionally, MMPs are released from ECs to cleave platelet aggregates. Fibrin degradation is trigged by some fibrinolytic molecules, such as tissue –type PA (t-PA) and urokinase-type PA (u-PA). t-PA is predominantly found in ECs while u-PA is expressed in ECs, macrophages, renal epithelial cells and some tumor cells. T-PA convert plasminogen to plasmin. Both plasminogen and plasminogen activators (t-PA and u-PA) bind to specific cellular receptors; assembly of components of the fibrinolytic system at the endothelial cell surface results in stimulation of fibrinolytic activity. Thus, t-PA provides an essential method for removal of blood clots (Salame et al. 2000; Shih and Hajjar 1993; Barnathan et al. 1990).

2.4 Hemodynamic Factors and Endothelial Cell

Flow rate and pressure in the blood vessels also affect the smooth muscle tone. The increase in flow velocity (shear stress), via ion channels (calcium, potassium and sodium) stimulates eNOS activity and the synthesis of NO from ECs. The increase in pressure reduces both the stress and release of endothelin from NO; vascular shear stress can also influence the coagulant potential of ECs. Arterial shear stress can induce the transcription factors. Likewise, reduced venous shear stress can induce hypoxia and stimulate the release of P-selectin and von Willebrand factor from ECs. The nature of the shear stress also has a significant influence on the type of thrombi that forms. Arterial clots form under high shear stress after atherosclerotic plaque rupture and are rich in platelets (called as white clot). In contrast, venous thrombi develop under low shear stress and are rich in fibrin and red blood cells (called as red clot). It has been indicated that plasma viscosity is a major determinant of capillary blood flow, and alteration in plasma viscosity contributes to impaired blood flow and to increased cardiovascular risk

(Reneman et al. 2006; Ballermann et al. 1998; Li et al. 2005b; Ercan et al. 2003).

2.5 Angiogenesis

Since ECs are an important component of blood vessels, they can be triggered to induce angiogenesis upon stimulation (Francis et al. 2010). VEGF is an angiogenic factor produced by ECs, with specific receptors on the endothelium. The formation of new blood vessels from pre-existing endothelium is mediated by VEGF. VEGF also contributes to the inflammatory response through stimulation of the release of adhesion molecules, MMPs and NO, via the transcription factor activator protein-1 (AP-1) (Kim and Byzova 2014; Jaipersad et al. 2014).

The coagulation system plays a major role in the development of angiogenesis. Activated protein C stimulates angiogenesis in brain endothelium, and cross-linked fibrin serves as a scaffold for ECs to synthesize new blood vessels. Platelets contain a rich source of vasoactive agents and chemokines, such as serotonin, TA_2, PAF and pro-angiogenic growth factors, such as vascular VEGF. VEGF can stimulate/upregulate eNOS and has physiological role for the normal endothelial control of vasomotor tone (Jaipersad et al. 2014).

An anti-angiogenic cytokine derived from ECs, vascular endothelial growth inhibitor functions to suppress EC proliferation in a cell cycle-dependent manner. These compounds stimulate ECs proliferation and promote the growth of new blood vessels. The expression of TF has been shown to induce tumor angiogenesis through TF-FVIIa-dependent PAR-2 activation which induces the expression of VEGF, IL-8, and MMP-7. It has been suggested that TF isoform may play a prominent role in promoting the angiogenesis (Mai et al. 2013; Yau et al. 2015).

Laminar shear stress is also a potent antiapoptotic stimulus in ECs. Some postulated mechanisms of protection include up-regulation of NOS, as well (Ercan et al. 2014).

3 Endothelial Dysfunction

Healthy endothelium has some athero-protective role including promotion of vasodilation, antioxidant and anti-inflammatory effects, inhibition of both leukocyte adhesion and migration and smooth muscle cell proliferation and migration. Healthy endothelium has anticoagulant and profibrinolytic effects, as well as the inhibitory effects on platelet aggregation and adhesion. Impaired endothelium-dependent vasodilation is also associated with the state of endothelial activation which is characterized by elevated pro-inflammatory and pro-coagulatory events (Fig. 6). The major factors for endothelial dysfunction are a reduction of the NO bioavailability, impairment in the response of vascular smooth muscle to the vasodilators, the elevated sensitivity of ECs against

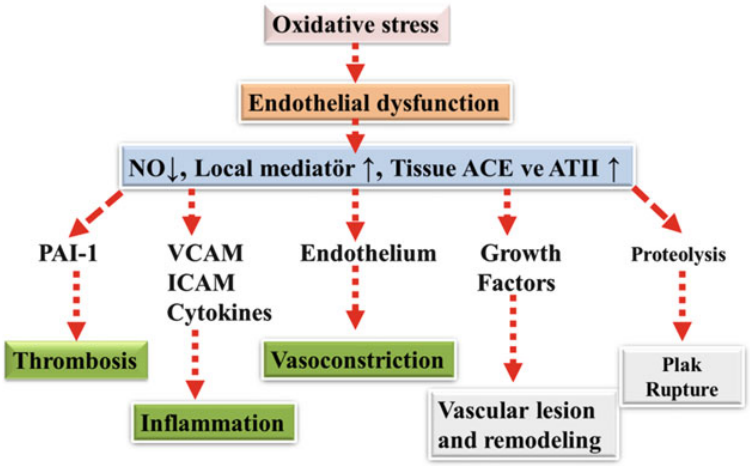

Fig. 6 Oxidative stress induced endothelial dysfunction

vasoconstrictors, increased production of the vasoconstrictor substances, or elevated shear stress (Fig. 7). Traditional and nontraditional risk factors for cardiovascular events, diabetes mellitus, atherosclerosis and hypertension are associated with enhanced ROS or increased oxidative stress. Increased oxidative stress is considered as a major mechanism involved in the pathogenesis of endothelial dysfunction. Disturbance of NO metabolism (elevated degradation of NO, inactivation of NO, or presence of NO inhibitors; Fig. 8) may be due to the elevation in oxidative stress (González et al. 2014; Bonetti et al. 2003).

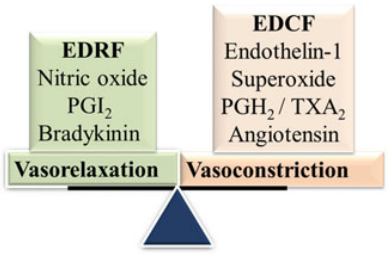

Fig. 7 A balance between endothelium-derived relaxing factors (EDRFs) and endothelium-derived contracting factors (EDCFs)

3.1 NO and Endothelial Dysfunction: The Link with Oxidative Stress

Oxidative stress has been implicated in the pathophysiology of many cardiovascular conditions, including hypertension. ROS significantly increase the influence of stimulants such as inflammation, radiation, high partial oxygen pressure, advanced age, obesity, and chemical substances. Oxidative stress that increases on a cellular level results in oxidative damage by altering the structure of molecules such as deoxyribonucleic acid, amino acid, protein, lipid, and carbohydrate (Fig. 9). A particularly important radical for

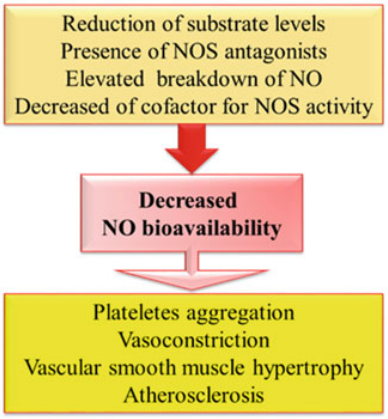

Fig. 8 Nitric oxide (NO) bioavailability

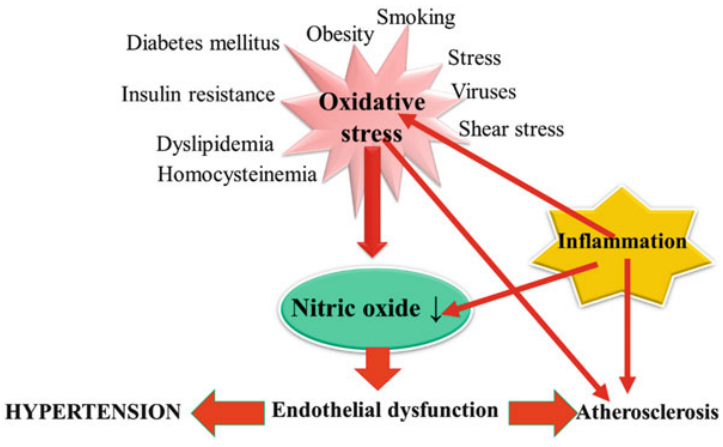

Fig. 9 Oxidative stress has been implicated in the pathophysiology of many cardiovascular conditions, including hypertension. ROS significantly increase the influence of stimulants such as inflammation, insulin resistance, dyslipidemia, advanced age and obesity which are related to decreased nitric oxide bioavailability

cardiovascular biology is superoxide, which is formed by the one-electron reduction of oxygen. Superoxide can serve as both an oxidant and as a reductant and is a progenitor for other ROS. Other radicals include the hydroxyl radical, lipid peroxyl radical, and alkoxyl radicals. Other molecules, including peroxynitrite, hypochlorous acid, and hydrogen peroxide are not radicals but have strong oxidant properties and are, therefore, included as ROS. Another a group of molecules is the reactive nitrogen species (RNS) including NO, the nitrogen dioxide radical, and the nitro sodium cation. The main sources for oxidative excess in the vasculature are adenine dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase, the mitochondrial and uncoupled NOS (Zhao et al. 2014; Bonetti et al. 2003; Ferroni et al. 2006).

NOX catalyzes the reduction of molecular oxygen by NADPH as an electron donor, thus generating superoxide. Superoxide anion is a major determinant of NO synthesis and availability, and can act as a vasoconstrictor. Superoxide combines with NO, which is synthesized by eNOS, to form peroxynitrite, in turn, peroxynitrite oxidizes and destabilizes eNOS to produce more superoxide. Superoxide also leads to BH4 oxidation, which is a cofactor for NO synthesis. Vascular superoxide is derived primarily from NOX when stimulated by hormones such as AT-II and ET-1. Xanthine oxidase is also an important source for oxygen free radical present in the vascular endothelium. It involves purine metabolism. During this process oxygen is reduced to superoxide (González et al. 2014).

eNOS is an important source of superoxide and peroxynitrite. In addition AT-II, acting through the AT1 receptor stimulates NOX causing the accumulation of superoxide, hydrogen peroxide, and peroxynitrite. Peroxynitrite is generated from NO in the increased oxidative stress conditions. It plays proatherogenic roles by leading to oxidation of LDL and degradation of the eNOS cofactor. ROS upregulate VCAM-1, ICAM-1 and MCP-1. Oxidative excess is also linked to a pro-inflammatory state of the vessel wall. Inflammation decreases NO bioavailability. On the other hand, under pathological conditions, EDHF can compensate for the loss of NO in arteries. The effects of EDHF are greatest at the level of small arteries. The changes in the EDHF action are of critical importance for the regulation of organ blood flow, peripheral vascular resistance, and blood pressure (Luksha et al. 2009; Ceriello 2008).

3.2 Asymmetric Dimethylarginine and Endothelial Dysfunction

Asymmetric dimethylarginine (ADMA) is endogenous competitive inhibitor of eNOS. It is created in protein methylation, a common mechanism of post-translational protein modification, which is catalyzed by N-methyltransferases. ADMA is eliminated by excretion through the kidneys or metabolism to citrulline by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). ADMA is one of the molecules associated with oxidative stress. Oxidative stress increases the plasma ADMA levels by increasing the activity of enzymes that take part in the production of ADMA and by decreasing the activity of enzymes that take part in metabolizing ADMA. The increased ADMA levels decrease the release of NO by inhibiting NOS. As NO decreases, hemodynamic changes and endothelial dysfunction occurs. Overexpression of DDAH also decreases ADMA levels and increase eNOS activity. Protein arginine methyltransferases, which produce methylated arginines, were shown to be upregulated by shear stress, and this upregulation was associated with enhanced ADMA generation (Endemann and Schiffrin 2004; Papageorgiou et al. 2015; Siervo et al. 2011).

3.3 LDL Oxidation and Endothelial Dysfunction

Oxidation plays a role in the pathogenesis of atherosclerosis. The oxidation of LDL triggers the uptake of the uptake of oxLDL by macrophages and the formation of foam cell. Also, oxidation processes may result in oxidized

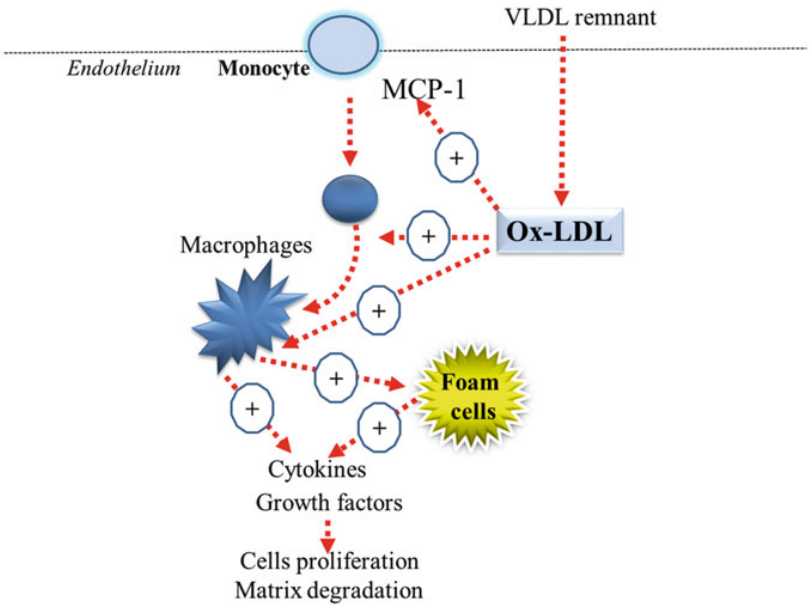

Fig. 10 oxLDL activates macrophages and generation of foam cells. Foam cells trigger the both production and secretion of growth factors and cytokines which stimulate cells proliferation and matrix degradation. *MCP-1* Monocytechemotactic factor-1

lipids with pro-inflammatory effect (Fig. 10). The other lipids which present in the blood vessel wall lead to inflammation and atherosclerosis (Stancel et al. 2016; Ouweneel and Van Eck 2016).

3.4 Homocysteinemia and Endothelial Dysfunction

Homocysteine (Hcy) is a sulfhydryl-containing amino acid. It is synthesized from the demethylation of methionine. The presentation of either methyl tetrahydrofolate or betaine, Hcy may be converted into methionine by methylation reaction or may be metabolized to cysteine by the sulfuration reaction. It has been shown that hyperhomocysteinemia is a major and independent risk factor for cardiovascular disease. Hcy cause arteriosclerosis by damaging the endothelium either directly or by altering oxidative status. In presence of hyperhomocysteinemia, Hcy autoxidation occurs, which may stimulate the production of hydroxyl radicals, as known as oxidative stress initiators. Also, Hcy mediates LDL-autoxidation and changes the redox thiol status in mitochondrial gene expression. Homocysteine and/or adenosine exposure of ECs cause apoptosis (McCully 2015; Pushpakumar et al. 2014).

3.5 Coagulation and Inflammation Pathways and Endothelial Dysfunction

Endothelial dysfunction is responsible for inflammation and blood coagulation. During endothelial dysfunction, ECs become activated and contribute to the pathogenesis of thrombosis. Hypoxic conditions often lead to endothelial dysfunction and promote the release of VWF from ECs. Inflammation can be accompanied by thrombosis. Proinflammatory cytokines, such as TNF-α and IL-1, upregulate the production of TF and VWF, while attenuating the expression of thrombomodulin, NO and prostacyclin. Patients with systemic inflammation show an impaired

protein C system due to impaired protein C synthesis and impaired protein C activation. While protein C is synthesized by hepatocytes, ECs can regulate protein C activation through the expression of thrombomodulin. As such, thrombomodulin levels are significantly down-regulated by the presence of pro-inflammatory cytokines, such as TNF-α and IL-1, resulting in diminished protein C activation. These events result in a shift from anti-thrombotic to pro-thrombotic conditions (Yau et al. 2015; Goldenberg and Kuebler 2015; Kleinegris et al. 2012).

3.6 Shear Stress and Endothelial Dysfunction

Normally high shear stress is beneficial as it promotes adaptive dilatation or structural remodeling of the artery wall through endothelium-mediated mechanisms In addition, growth status of ECs can be regulated by shear stress. It has been shown that shear stress suppresses the EC apoptosis, and can be attenuated by the inhibition of NO production. Anti-apoptotic effect of shear stress is mediated by the up-regulation of eNOS. Although the inter-normal endothelium does not allow the passage of macromolecules such as oxLDL, shear stress, by a variety of mechano-sensors effects, activate intracellular signaling pathways, thus modulating gene expression and cellular functions such as proliferation, apoptosis, migration, permeability, and alignment (Li et al. 2005a). It has been demonstrated that the rheological impairment of dyslipidemic patients was related with endothelial dysfunction and this was a possible cause of both micro and macrovascular complications. Plasma viscosity, ADMA and oxLDL values were significantly higher in subjects with dyslipidemia. Plasma NO concentration was decreased in dyslipidemic subjects compared to the normo-lipidemic subjects (Ercan et al. 2014). Additionally, plasma viscosity, an early atherosclerotic risk factor, might be helpful in the assessment of cardiovascular risk in obese subjects along with classical cardiovascular risk factors such as plasma cholesterol and atherogenic index (Konukoglu et al. 2009).

3.7 Insulin Resistance and Endothelial Dysfunction

Endothelial dysfunction may also favor insulin resistance. It has been reported that the insulin resistance syndrome can be involved as the diverse consequences of endothelial dysfunction in different vascular beds. Insulin resistance is frequently associated with other abnormalities that can affect endothelial function, such as hyperglycemia, hypertension, dyslipidemia, and altered coagulation/fibrinolysis. Insulin resistance leads to endothelial dysfunction and may contribute to obesity (Fig. 11). Obesity leads to insulin resistance and endothelial dysfunction, mainly through fat-derived metabolic products, hormones, and adipocytokines. Obesity, insulin resistance, and endothelial dysfunction closely coexist in type 2 diabetes. The mechanisms are numerous and complex. Non-pharmacological and pharmacological interventions targeting obesity and/or insulin resistance demonstrate an amelioration of endothelial dysfunction and low-grade inflammation (Muniyappa and Sowers 2013; Rao et al. 2015; Prieto et al. 2014).

4 The Links Between Endothelial Dysfunction and Sustained Hypertension

Endothelial dysfunction was initially identified as impaired vasodilation to specific stimulus of acetylcholine or bradykinin. Endothelium dysfunction leads to functional changes in the microvasculature with a predominant and deleterious constrictive tone. Endothelial dysfunction, as a risk factor involves several pathological conditions. Hypertension is also an important risk factor for atherosclerosis and endothelial dysfunction. In hypertension, sustained elevation of systemic pressure in the microvasculature leads to premature aging and increased turnover

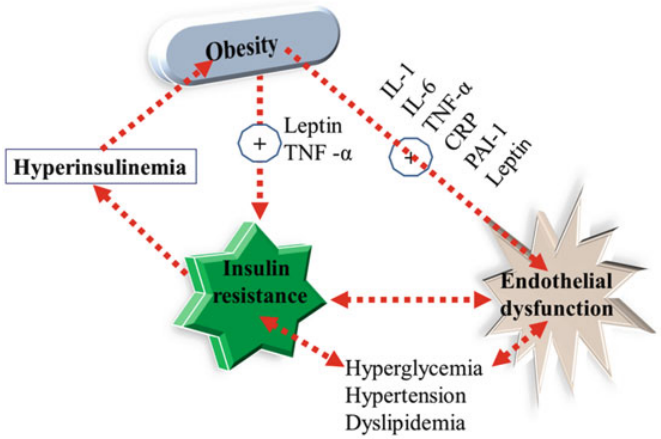

Fig. 11 Insulin resistance and endothelial dysfunction. *IL* Interleukin, *TNF* Tumor necrosis factor, *CRP* C-reactive protein, *PAI-I* Plasminogen activator inhibitor –I

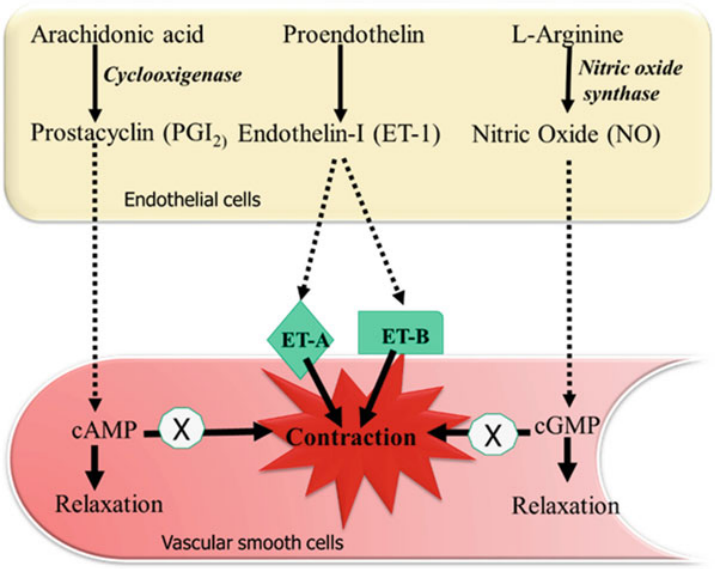

Fig. 12 Impaired response of endothelium to vasoconstriction in hypertension

of ECs. The endothelium has an impaired ability to release EDRFs, resulting in vasoconstriction (Fig. 12). Hypertension has been linked to deficient levels of NO and increased vascular production of ROS. There are some structural changes in the vascular wall in hypertension. Hypertension results in structural alterations in microcirculatory beds such as remodeling and rarefaction. It is remodeling that is responsible for the majority of the chronic elevation in systemic vascular resistance seen in hypertension (Kiowski 1999; McIntyre et al. 1999; Jacobsen et al. 2011)

Reduction in NO synthesis leads to arterial vasoconstriction and hypertension. Chronic administration of NOS inhibitors causes sustained hypertension. NO plays a role in facilitating sodium excretion so that systemic inhibition of NOS promotes salt and water retention (Melikian et al. 2009). Together these findings suggest that a reduction in NO-mediated dilatation will increase arterial

resistance and enhance the susceptibility of the cardiovascular system to pressor stimuli. The role of the endothelium and NO in systemic hypertension is very controversial. Although an impaired release of relaxing factors may partly be associated with the pathogenesis of hypertension (Michel and Vanhoutte 2010; Lüscher et al. 1989), it now appears that endothelium-dependent relaxation is heterogeneously affected in this condition. In some vascular beds of hypertensive rats such as the aorta, mesenteric, carotid and cerebral vessels, endothelium-dependent relaxation is impaired (Calver et al. 1993; Luscher and Vanhoutte 1986; Dohi et al. 1990). In contrast, in coronary and renal arteries of spontaneously hypertensive rats, endothelial function does not seem to be affected by high blood pressure (Luscher 1991; Tschudi et al. 1991).

Despite the fact that mechanisms underlying hypertension are not yet fully elucidated, the evidence shows that oxidative stress plays a central role in its pathophysiology. In general, oxidative stress is defined as excess formation and/or insufficient removal of highly reactive molecules such as ROS and reactive nitrogen species (RNS). ROS promote vasoconstriction and vascular remodeling, increasing systemic vascular resistance, a common finding in most cases of human hypertension. ROS promote vasoconstriction and vascular hypertrophy. NOX is up-regulated by humoral and mechanical signals in hypertension. In hypertension, both endothelial xanthine oxidase and ROS are increased, which is associated with increased arteriolar tone. Xanthine oxidase may play a role in end-organ damage in hypertension (Gimenez et al. 2016; Santilli et al. 2015; Montezano et al. 2015a; Virdis et al. 2011).

Hypertension is associated with lipid peroxidation due to an impaired oxidant/antioxidant status (Armas-Padilla et al. 2007). Increased lipid peroxidation and decreased antioxidants with aging indicate that per oxidative damage further increases with higher blood pressure and the aging process. It has been shown that, there was a significant relationship between acetylcholine-dependent vasodilation and plasma levels of selectins, MCP-1 and thiobarbituric acid-reactive substances (TBARS; as a marker of lipid peroxidation) (Lee et al. 2012; Ahmad et al. 2013; Rodrigo et al. 2013). Previously reported study was to evaluate the influence of aging on the levels of TBARS, lipid hydroperoxide (LOOH), and 8-iso-prostaglandin F2α (8-iso-PGF2α) in elderly hypertensives (Yavuzer et al. 2016a). The results of this study demonstrated that serum TBARS, LOOH and 8-iso-PGF2α levels were significantly high in the elderly hypertensive patients. The relationship between miRNA, NO and eNOS with subclinical atherosclerosis in patients with hypertension has been evaluated (Cengiz et al. 2015). Decreased levels of NO and eNOS and increased miRNA expression were found in this study. This report suggests that miRNA might be involved in the early stages of atherosclerotic process in hypertensive patients. Population-based observational studies have reported an inverse relationship between various plasma antioxidants and blood pressure. Decreased antioxidant activity (SOD, catalase) and reduced levels of ROS scavengers (vitamin E, glutathione) might contribute to oxidative stress in human hypertension (Rodrigo et al. 2007; Loukogeorgakis et al. 2010). Plasma vitamin C levels are inversely related to blood pressure in normotensive and hypertensive cohorts (Block et al. 2008). Amelioration of impaired endothelial function and protection against vascular damage by reducing oxidative stress through exercise, healthy diet, and smoking cessation, but not through antioxidant supplementation, should provide additional therapeutic benefit in the management of patients with hypertension. Until more is known about the molecular mechanisms, whereby ROS cause vascular damage and hypertension in humans, therapies targeting oxidative stress should focus on promoting vascular health through lifestyle and healthy behavioral modifications, such as exercise, nutrition, and smoking cessation (Michalsen and Li 2013).

On the other hand, oxidative stress and endothelial dysfunction are known to be associated with inflammation and can contribute to

hypertension; however, whether inflammation is a cause or effect of hypertension is not clear. Inflammation is a protective response to injury or infection. The acute phase protein, C-reactive protein (CRP), is considered as inflammatory marker showing the strongest association with hypertension. It has been demonstrated that hypertensive patients commonly have higher plasma CRP levels. Hypertensive patients have been reported to have higher plasma concentrations of pro-inflammatory cytokines. Inflammation has been shown to down regulate NOS activity. Chronic inflammation can also trigger oxidative stress, which has been associated with hypertension (Crowley 2014; Yasunari et al. 2002).

There is also evidence for involvement of immune cells in human hypertension. Hypertensive patients with nephrosclerosis have higher renal infiltration of CD4+ and CD8+ T cells than normotensives (Youn et al. 2013). Circulating levels of CXC chemokine receptor type 3 (CXCR3), which is well-known tissue-homing chemokine for T cells, have been reported to be elevated in hypertensive patients (Youn et al. 2013). On the other hand, HT induces vascular wall injury and remodeling. The immune system is a sensitive sensor of tissue injury and is involved in the repair (Winn and Harlan 2005b). Hypertensive factors such as AT II, salt, or aldosterone directly activate the innate immune system (De Ciuceis et al. 2014; De Miguel et al. 2015). This process also leads complement activation and toll-like receptors (TLR) as well as ROS production. Autoimmunity can also be directed against vascular wall antigen. Due to the autoantibodies against AT receptor develop in some hypertensives, it is considered that innate immunity can be a secondary cause of hypertension and adaptive immunity can cause or aggravate hypertension. Therefore immunity may be a potential therapeutic target in hypertension in the future (Wenzel et al. 2016; Anders et al. 2015; Idris-Khodja et al. 2014).

Hypertensive individuals are also at increased risk for type 2 diabetes. They are often overweight, insulin resistant, and have endothelial dysfunction. Interestingly, it has been reported that even non-obese hypertensive individuals have abnormalities in endothelial function and findings that suggest that hypertension might impair endothelial function independently from the effects of weight (Ferri et al. 1998). Insulin has both pro- and anti-atherogenic actions, and endothelin-1-dependent vasoconstrictor actions on the vasculature. Endothelin is secreted by ECs, causes vasoconstriction and elevates blood pressure. Endothelin receptor antagonists reduce blood pressure and peripheral vascular resistance in both normotensive controls and patients with mild to moderate essential hypertension, supporting the interpretation that endothelin plays a role in the pathogenesis of hypertension (Lin et al. 2015; Kobayashi et al. 2008). Leptin is a hormone which is secreted by adipocytes and related with obesity. Leptin regulates energy balance and has also sympathetic, vascular and renal actions that can influence blood pressure (Vaněčková et al. 2014). Recent evidence suggests that hyperleptinemia may induce the systemic oxidative stress and decrease the amount of bioactive NO levels possibly due to its degradation by reactive oxygen species. This may be one of the most important mechanisms in the generation of hypertension in obesity (Bełtowski 2012). It has been reported that that plasma leptin and TBARS levels were increased in obesity, and obese hypertensives have significantly higher plasma leptin levels, TBARS levels and lower NO levels than obese normotensives (Konukoglu et al. 2006). Therefore, hyperleptinemia may be an important contributor to the generation of hypertension in obesity.

Hypertension may be associated with impaired fibrinolysis. Fibrinolytic markers such as PAI-1, tPA, and tPA/PAI-1 complex are independently associated with the development of hypertension (Tabak et al. 2009). In a previous study, it has been suggested that, plasma Hcy, which have thrombotic effects, does not have predictive values for indication of cardiovascular disease. However, in the presence of other risk factors (e.g. hyperlipidemia, hypertension, obesity, and/or hyperinsulinemia), Hcy may have a permissive role on the endothelium damage even

in the normohomocysteinemic range. The effects of Hcy seemed to be related with free radical generating systems in hypertensives (Konukoglu et al. 2003).

Microparticles (MPs) consist of the EMPs, leukocyte microparticles (LMs) and platelet microparticles (PMPs). MPs are assayed by flow cytometry. Recent data indicate that altered, activated ECs release EMPs into circulation. MPs are furthermore involved in the progression of impaired endothelial function as well as in angiogenesis (Helbing et al. 2014b). There are only few study to show the relationship between MPs and arterial hypertension (Preston et al. 2003; Marques et al. 2013). It has been found that both EMPs and PMPs were significantly increased in hypertensives and that EMPs were correlated with the level of blood pressures. EMPs can be found in several conditions which are associated with arterial hypertension, such as preeclampsia (Marques et al. 2013). It has been found that, EMPs reduce NO in patients with myocardial infarction [135] (Burada EMPler MI'lı hastalarda NO seviyelerini azaltır demek mi istedik?). At the present time, it is considered that circulating MPs might be novel therapeutic targets in microparticle mediated diseases (Helbing et al. 2014b).

5 Antihypertensive Therapy and Endothelial Dysfunction

Current therapies for human hypertension include AT-II type 1 receptor blockers (ARB), Angiotensin-converting enzyme inhibitors (ACEIs), diuretics, calcium channel antagonists, and β-blockers. Treatment with commonly used antihypertensive drugs reduce the risk of total major cardiovascular events, and more importantly, it appears that the higher the reduction in blood pressure, the larger the reduction in cardiovascular risk (James et al. 2014). It has been well documented that endothelium dysfunction can be improved by the use of a statin drug and aspirin, Mediterranean diet, aerobic exercise and weight loss (Montezano et al. 2015b).

Hypertension management guidelines categorize ACEIs and ARB interchangeably as first-line treatments in uncomplicated hypertension (Hirata et al. 2010). These medications have different mechanisms of action and quite different evidence bases (Sindone et al. 2016). The AT-IR leads to vasoconstriction, cell growth, and cell proliferation; the AT-IIR has the opposite effect. The AT-IR is antinatriuretic; the AT-IIR is natriuretic. The AT-IR stimulation results in free radicals; AT-II R stimulation produces *NO* which can neutralize free radicals. The AT-IR induces plasminogen activator inhibitor-1 (*PAI-1*) and other growth family pathways; the AT-II R does not. The ARB binds to and blocks selectively at the AT-IR, promoting stimulation of the receptor by AT-II (Chappell 2016; Matavelli and Siragy 2015). ACEIs prevent the breakdown of bradykinin, a mediator that stimulates the endothelium to generate NO. ACEIs increase NO bioavailability by decreasing the synthesis of AT-II and by enhancing serum levels of NO-releasing bradykinin via inhibition of its degradation. Moreover, ACEIs may also enhance the activity of endothelium-derived hyperpolarizing factor under certain conditions (Mendoza-Torres et al. 2015; Su 2015). On the other hand, it has been reported that treated hypertensive patients with ACEIs had lower plasma sPLA and oxLDL levels and higher Paraoxonase-1 activities than hypertensive patients without therapy (Rao et al. 2015). Therefore, ACEI treatment may also help reduce inflammation and oxidative stress in hypertensives. Short and long-term ACEI administration may be lead an improvement in both coronary and peripheral endothelial function in patients with CAD and/or its risk factors, but the magnitude of this effect may vary depending on the compound used, the presence of risk factors, and genetic variables (Ferroni et al. 2006; Mullen et al. 1998). Additionally, in contrast to ACEIs, controversial results have been reported regarding the effect of AT receptor antagonists on endothelial function (Chappell 2016; Prasad et al. 2001; Li et al. 2014). Recently published data results have been shown that ARBs improve peripheral endothelial function, however, the effect couldn't be maintained for a long time (Prasad et al. 2000).

Some β-blockers have endothelial protective effects. It can improve the endothelium-dependent vasodilator responses by increasing NO release and reducing prothrombotic blood levels of fibrinogen, homocysteine and plasminogen activator inhibitor-1 (e.g. nebivolol, as a β_1-antagonist) (Tzemos et al. 2001), or by its antioxidant capacity (e.g.carvedilol, a non-selective β_1- and β_2 antagonist with α-antagonist property) in patients with essential hypertension (Zepeda et al. 2012). It has been also suggested that the combination of a beta blocker with an ACE inhibitor have more beneficial effect on endothelial function than monotherapy in hypertensive patients with obesity (Vyssoulis et al. 2004). Therefore this combination can be used for the treatment of endothelial dysfunction associated with hypertension, as well as diabetes or atherosclerosis.

Dihydropyridine calcium channel blockers protect against ROS-induced endothelial cell death They have an endothelial protective effect against oxLDL induced ROS, antioxidant activity related to reduction in lipid peroxidation and associated ROS generation (Kelly et al. 2012) or an anti-inflammatory effect as indicated by decreased CRP and IL-6 levels as well as leukocyte activation (Napoli et al. 1999). Combination of calcium channel blockers (e.g. amlodipine) with a renin inhibitor improves endothelial dysfunction in hypertensive patients linked to its NO-releasing action and anti-inflammatory effect (Yasu et al. 2013; Celźk et al. 2015).

Angiotensin-(1-7) is a metabolite of AT-I under the action of various enzymes. It can also be generated from AT-II (He et al. 2014). In ECs, AT-(1-7) activates eNOS and inhibits AT II-induced NAD (P) H oxidase activation (Trask and Ferrario 2007). Chronic treatment with AT-(1-7) improves renal endothelial dysfunction by increasing NO release (Arora et al. 2013) and eNOS expression (Costa et al. 2010). Otherwise, AT-(1-7) restores NO/cGMP by production and migration, decreases NOX activity, and enhances survival and proliferation of endothelial progenitor cells isolated from the blood of diabetics (Jarajapu et al. 2013).

ETB receptor on both ECs and vascular smooth muscle cells mediates vasodilatation and constriction, respectively. Although it has been demonstrated that the long term treatment with mixed ETA-receptor and ETB-receptor antagonists (as endothelin receptor antagonist, ERA, bosentan) decreases blood pressure in the patients with mild-to-moderate essential hypertension, suggesting that endothelin may be used in such patients (Krum et al. 1998), development of endothelin drug class for the indication of systemic hypertension has been discontinued because of toxicity (teratogenicity, testicular atrophy, and hepatotoxicity) (Spence et al. 1999; Thaete et al. 2001). Nowadays, ERAs were only used for the treatment of pulmonary arterial hypertension (Chaumais et al. 2015).

It has been indicated that aggressive treatment of dyslipidemia and hypertension was very important by decreasing the development of the atherosclerosis (Hsueh and Quiñones 2003). The thiazolidinediones which are peroxisome proliferator-activated receptor–γ agonists improve glucose and lipid metabolism. These drugs have recently been shown to improve endothelial function in the early stages of insulin resistance (Salomone and Drago 2012).

As a result of this, it is currently difficult to precisely define the possible links between endothelial dysfunction and hypertension or its effects on target organs such as the heart, brain or kidneys. Despite the difficulty of distinguishing the possible direct effects of antihypertensive drugs on endothelial function from indirect protection secondary to the decreased blood pressure, the effects of various antihypertensive drugs on endothelial dysfunction have been tested (Mancia et al. 2013).

6 The Links Between Endothelial Dysfunction and White Coat Hypertension

White coat hypertension (WCH) is a term used for people not receiving antihypertensive medication who have a persistently high office blood

pressure (≥ 140/90 mmHg) together with a normal; ambulatory blood pressure (<135/85 mmHg) or home blood pressure (Soma et al. 1996). Subjects with WCH are characterized by elevated arterial pressure in the physician's office, but "normal" pressure at other times. Many studies reported that white coat effect can be seen mostly in women, children and elderly. In order not to cause possible risks of inaccurate treatment in these patients, ambulatory blood pressure measurements should be done regularly and treatment decision should be given accordingly.

The prognosis in the patients with WCH remains uncertain. Several studies indicate a good prognosis of this condition by demonstrating a low-degree of end organ damage (Pickering et al. 1988; White et al. 1989). Other authors report WCH exhibits end-organ damage (Cardillo et al. 1993; Hoegholm et al. 1994) and metabolic abnormalities such as hyperlipidemia, impaired insulin sensitivity, elevated blood glucose, and increased serum insulin levels (Bjorklund et al. 2002; Julius et al. 1990; Weber et al. 1994). Sustained hypertension causes atherosclerotic changes and it is one of the main risk factors of coronary artery disease. It is not clear, if WCH also causes atherosclerosis as it is associated with other target organ changes similar to those associated with sustained hypertension. Clinical surveys on endothelial dysfunction in WCH are controversial (Hlubocka et al. 2002; Vaindirlis et al. 2000a; Gomez-Cerezo et al. 2002). In meta-analyses, the patients with WCH were not significantly different from true normotensive individuals when adjusted for age, gender and other covariates (Fagard and Cornelissen 2007; Pierdomenico and Cuccurullo 2011; Franklin et al. 2012). On the other hand, other meta-analyses state that common carotid intima-media thickness is greater in WCH patients than in true normotensive individuals and is not different from sustained hypertensive patients (Cuspidi et al. 2015a). In few meta-analyses indicate that WCH is not an entirely benign condition (Briasoulis et al. 2016; Cuspidi et al. 2015b; Stergiou et al. 2014). WCH might not be considered as an innocent trait. It seems to be an important clinical situation requiring a close follow-up.

Various studies also observed the presence of endothelial dysfunction and abnormal angiogenesis with increased values of ET-1, homocysteine and vascular VEGF accompanying with a decrease in NO in WCH (Tabak et al. 2009; Uzun et al. 2004; Karter et al. 2004; Curgunlu et al. 2005a; Curgunlu et al. 2005b; Caner et al. 2006; Marchi-Alves and Carnio 2009; Lengyel et al. 2012; Yavuzer et al. 2015). The relationship of oxidative stress and NO is well known. Increased NO levels in WCH patients may be the result of enhanced oxidative stress. It indicates the increased oxidative stress which was probably the leading cause of endothelial dysfunction. The elevated oxidative status is a strong risk factor for coronary artery disease. Procalcitonin (PCT) levels in WCH patients are significantly and consistently higher than normotensives (Yavuzer et al. 2016b). Systemic inflammation moderately occurs in the WCH. PCT monitoring may be a useful biomarker in inflammation related to atherosclerosis and early stage hypertension.

Even though several studies described WCH as a benign entity and showed no difference in cardiovascular events and deaths between WCH and normotensive patients, other studies have indicated similar or at least close rates of death or cardiovascular events in patients with WCH and clinical hypertensive patients (Verdecchia et al. 1996; Strandherg and Salomaa 2000). The early detection of these patients by ambulatory blood pressure monitorization might prevent future mortality and morbidity. To sum up, white coat effect is not an innocent phenomenon like normal blood pressure nor as hazardous as clinical hypertension. WCH may thus be a transition state between normotension and hypertension. It may be concluded that vascular changes in WCH were not structural but functional. Further studies are needed to assess the increased cardiovascular risk in WCH conferred by endothelial dysfunction.

Conclusion Endothelial dysfunction is a common mechanism involved in many cardiovascular diseases, and plays a critical role in the development of diseases or contributes to the development and progression of organ damages. Multiple mechanisms such as inflammation, increased ROS and RNS, cellular apoptosis, increased vasoconstrictor production, decreased vasodilator production and vascular remodeling are involved in endothelial dysfunction. In endothelial dysfunction, NO bioavailability seems to play a central role in the development and progress of hypertension, as well as diabetes or atherosclerosis. It appears that a drug with endothelium-protective property may yield therapeutic benefits. Endothelial dysfunction is more prevalent in WCH than in true normotensive individuals, but it is either equal or better in WCH as compared to sustained hypertension. Therefore, the evaluation of endothelium-improving action may be helpful for the hypertension related cardiovascular events.

References

Ahmad A, Singhal U, Hossain MM, Islam N, Rizvi I (2013) The role of the endogenous antioxidant enzymes and malondialdehyde in essential hypertension. J Clin Diagn Res 7:987–990

Anders HJ, Baumann M, Tripepi G, Mallamaci F (2015) Immunity in arterial hypertension: associations or causalities. Nephrol Dial Transplant 30:1959–1964

Armas-Padilla MC, Armas-Hernández MJ, Sosa-Canache B, Cammarata R, Pacheco B, Guerrero J, Carvajal AR, Hernández-Hernández R, Israili ZH, Valasco M (2007) Nitric oxide and malondialdehyde in human hypertension. Am J Ther 14:172–176

Arora P, Arora A, Sharma S (2013) Vascular endothelium dysfunction and hypertension: insight on molecular basics. Innov Pharm Pharmacother 1:199–219

Bae SW, Kim HS, Cha YN, Park YS, Jo SA, Jo I (2003) Rapid increase in endothelial nitric oxide production by bradykinin is mediated by protein kinase A signaling pathway. Biochem Biophys Res Commun 306:981–987

Ballermann BJ, Dardik A, Eng E, Liu A (1998) Shear stress and the endothelium. Kidney Int Suppl 67: S100–S108

Barnathan ES, Kuo A, Karikó K, Rosenfeld L, Murray SC, Behrendt N, Rønne E, Weiner D, Henkin J, Cines DB (1990) Characterization of human endothelial cell urokinase-type plasminogen activator receptor protein and mRNA. Blood 76:1795–1806

Barton M (2011) The discovery of endothelium-dependent contraction: the legacy of Paul M. Vanhoutte Pharmacol Res 63:455–462

Bauer J, Ripperger A, Frantz S, Ergün S, Schwedhelm E, Benndorf RA (2014) Pathophysiology of isoprostanes in the cardiovascular system: implications of isoprostane-mediated thromboxane A2 receptor activation. Br J Pharmacol 171:3115–3131

Bełtowski J (2012) Leptin and the regulation of endothelial function in physiological and pathological conditions. Clin Exp Pharmacol Physiol 39:168–178

Bernal-Mizrachi L, Jy W, Jimenez JJ, Pastor J, Mauro LM, Horstman LL, de Marchena E, Ahn YS (2003) High levels of circulating endothelial microparticles in patients with acute coronary syndromes. Am Heart J 145:962–970

Bjorklund K, Lind L, Vessby B, Andren B, Lithell H (2002) Different metobolic predictors of white-coat and sustained hypertension over a 20-year follow up. Circulation 106:63–68

Block G, Jensen CD, Norkus EP, Hudes M, Crawford PB (2008) Vitamin C in plasma is inversely related to blood pressure and change in blood pressure during the previous year in young Black and White women. Nutr J 7:35.1–9

Bonetti PO, Lerman LO, Lerman A (2003) Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 23:168–175

Boulanger CM, Scoazec A, Ebrahimian T, Henry P, Mathieu E, Tedgui A, Mallat Z (2001) Circulating microparticles from patients with myocardial infarction cause endothelial dysfunction. Circulation 104:2649–2652

Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D (2016) White-coat hypertension and cardiovascular events: a meta-analysis. J Hypertens 34:593–599

Cahill PA, Redmond EM (2016) Vascular endothelium – gatekeeper of vessel health. Atherosclerosis 248:97–109

Calver A, Collier J, Vallance P (1993) Nitric oxide and cardiovascular control. Exp Physiol l78:303–326

Caner M, Karter Y, Uzun H, Curgunlu A, Vehid S, Balci H, Yucel R, Güner I, Kutlu A, Yaldiran A, Oztürk E (2006) Oxidative stress in human in sustained and white coat hypertension. Int J Clin Pract 60:1565–1571

Cardillo C, Felice FD, Campia U, Folli G (1993) Psychological reactivity and cardiac end organ changes in white coat hypertension. Hypertension 21:836–844

Celık T, Balta S, Karaman M, Ahmet Ay S, Demırkol S, Ozturk C, Dınc M, Unal HU, Yılmaz MI, Kılıc S, Kurt G, Tas A, Iyısoy A, Quartı-Trevano F, Fıcı F, Grassı G (2015) Endocan, a novel marker of endothelial dysfunction in patients with essential hypertension: comparative effects of amlodipine and valsartan. Blood Press 24:55–60

Cengiz M, Yavuzer S, Kılıçkıran Avcı B, Yürüyen M, Yavuzer H, Dikici SA, Karataş ÖF, Özen M, Uzun H, Öngen Z (2015) Circulating miR-21 and eNOS in subclinical atherosclerosis in patients with hypertension. Clin Exp Hypertens 37:643–649

Ceriello A (2008) Possible role of oxidative stress in the pathogenesis of hypertension. Diabetes Care Am Diabetes Assoc 31(Supl 2):S181–S184

Chappell MC (2016) Biochemical evaluation of the renin-angiotensin system: the good, bad, and absolute? Am J Physiol Heart Circ Physiol 310:H137–H152

Chaumais MC, Guignabert C, Savale L, Jaïs X, Boucly A, Montani D, Simonneau G, Humbert M, Sitbon O (2015) Clinical pharmacology of endothelin receptor antagonists used in the treatment of pulmonary arterial hypertension. Am J Cardiovasc Drug 15:13–26

Chistiakov DA, Orekhov AN, Bobryshev YV (2015) Endothelial barrier and its abnormalities in cardiovascular disease. Front Physiol 6:1–11

Coban E, Ozdoğan M, Ermiş C (2004) Plasma levels of homocysteine in patients with white-coat hypertension. Int J Clin Pract 58:997–999

Costa MA, Lopez Verrilli MA, Gomez KA, Nakagawa P, Peña C, Arranz C, Gironacci MM (2010) Angiotensin-(1-7) upregulates cardiac nitric oxide synthase in spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol 299:H1205–H1211

Croft M, So T, Duan W, Soroosh P (2009) The significance of OX40 and OX40L to T cell biology and immune disease. Immunol Rev 229:173–191

Crowley SD (2014) The cooperative roles of inflammation and oxidative stress in the pathogenesis of hypertension. Antioxid Redox Signal 20:102–120

Curgunlu A, Uzun H, Bavunoğlu I, Karter Y, Genç H, Vehid S (2005a) Increased circulating concentrations of asymmetric dimethylarginine (ADMA) in white coat hypertension. J Hum Hypertens 19:629–633

Curgunlu A, Karter Y, Uzun H, Aydin S, Ertürk N, Vehid S, Simsek G, Kutlu A, Oztürk E, Erdine S (2005b) Hyperhomocysteinemia: an additional risk factor in white coat hypertension. Int Heart J 46:245–254

Cuspidi C, Sala C, Tadic M, Rescaldani M, Grassi G, Mancia G (2015a) Is white-coat hypertension a risk factor for carotid atherosclerosis? A review and meta-analysis. Blood Press Monit 20:57–63

Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G, Mancia G (2015b) White-coat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: a meta-analysis. J Hypertens 33:24–32

Davenport AP, Hyndman KA, Dhaun N, Southan C, Kohan DE, Pollock JS, Pollock DM, Webb DJ, Maguire JJ (2016) Endothelin. Pharmacol Rev 68:357–418

Dawes MG, Bartlett G, Coats AJ, Juszczak E (2008) Comparing the effects of white coat hypertension and sustained hypertension on mortality in a UK primary care setting. Ann Fam Med 6:390–396

Dawson TM, Bredt DS, Fotuhi M, Hwang PM, Snyder SH (1991) Nitric oxide synthase and neuronal NADPH diaphorase are identical in brain and peripheral tissues. Proc Natl Acad Sci 88:7797–7801

De Ciuceis C, Rossini C, La Boria E, Porteri E, Petroboni B, Gavazzi A, Sarkar A, Rosei EA, Rizzoni D (2014) Immune mechanisms in hypertension. High Blood Press Cardiovasc Prev 21:227–234

De Miguel C, Rudemiller NP, Abais JM, Mattson DL (2015) Inflammation and hypertension: new understandings and potential therapeutic targets. Curr Hypertens Rep 17:507

Dohi Y, Thiel MA, Buhler FR, Luscher TF (1990) Activation of the endothelial L-arginine pathway in pressurized mesenteric resistance arteries: effect of age and hypertension. Hypertension 15:170–179

Dunn S, Vohra RS, Murphy JE, Homer-Vanniasinkam S, Walker JH, Ponnambalam S (2008) The lectin-like oxidized low-density-lipoprotein receptor: a pro-inflammatory factor in vascular disease. Biochem J 409:349–355

Endemann DH, Schiffrin EL (2004) Endothelial dysfunction. J Am Soc Nephrol 15:1983–1992

Ercan M, Konukoglu D, Onen S (2003) Plasma viscosity as a cardiovascular risk marker in patients with proteinuria. Clin Hemorheol Microcirc 29:111–116

Ercan M, Firtina S, Konukoglu D (2014) Comparison of plasma viscosity as a marker of endothelial dysfunction with nitric oxide and asymmetric dimethylarginine in subjects with dyslipidemia. Clin Hemorheol Microcirc 57:315–323

Esmon CT (2006) Inflammation and the activated protein C anticoagulant pathway. Semin Thromb Hemost 32 (Suppl 1):49–60

Fagard RH, Cornelissen VA (2007) Incidence of cardiovascular events in white-coat, masked and sustained hypertension vs. true normotension: a meta-analysis. J Hypertens 25:2193–2198

Félétou M, Vanhoutte PM (2006) Endothelium-derived hyperpolarizing factor: where are we now? Arterioscler Thromb Vasc Biol 26:1215–1225

Ferri C, Desideri G, Baldoncini R, Bellini C, De Angelis C, Mazzocchi C, Santucci A (1998) Early activation of vascular endothelium in nonobese, non-diabetic essential hypertensive patients with multiple metabolic abnormalities. Diabetes 47:660–667

Ferroni P, Basili S, Paoletti V, Davì G, Psaty BM (2006) Endothelial dysfunction and oxidative stress in arterial hypertension. Nutr Metab Cardiovasc Dis 16:222–233

Francis SH, Busch JL, Corbin JD, Sibley D (2010) cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. Pharmacol Rev 62:525–563

Franklin SS, Thijs L, Hansen TW, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Wang J,

Ibsen H, O'Brien E, Staessen JA, International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators (2012) Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. Hypertension 59:564–571

Gimenez M, Schickling BM, Lopes LR, Miller FJ Jr (2016) Nox1 in cardiovascular diseases: regulation and pathophysiology. Clin Sci 130:151–165

Goldenberg NM, Kuebler WM (2015) Endothelial cell regulation of pulmonary vascular tone, inflammation, and coagulation. Comp Physiol 5:531–559

Gomez-Cerezo J, Ríos Blanco JJ, Suárez García I, Moreno Anaya P, García Raya P, Vázquez-Muñoz E, Barbado Hernández FJ (2002) Noninvasive study of endothelial function in white coat hypertension. Hypertension 40:304–309

González J, Valls N, Brito R, Rodrigo R (2014) Essential hypertension and oxidative stress: new insights. World J Cardiol 6:353–366

Gunnett C, Lund D, McDowell A, Faraci F, Heistad D (2005) Mechanisms of inducible nitric oxide synthaseemediated vascular dysfunction. Arterioscler Thromb Vasc Biol 25:1617–1622

He Y, Si D, Yang C, Ni L, Li B, Ding M, Yang P (2014) The effects of amlodipine and S(-)-amlodipine on vascular endothelial function in patients with hypertension. Am J Hypertens 27:27–31

Helbing T, Olivier C, Bode C, Moser M, Diehl P (2014) Role of microparticles in endothelial dysfunction and arterial hypertension. World J Cardiol 6:1135–1139

Hirata Y, Nagata D, Suzuki E, Nishimatsu H, Suzuki J, Nagai R (2010) Diagnosis and treatment of endothelial dysfunction in cardiovascular disease. Int Heart J 51:1–6

Hlubocka Z, Umnevora V, Heller S et al (2002) Circulating intercellular cell adhesion molecule-1, endothelin-1and von willebrand factor-markers of endothelial dysfunction in uncomplicated essensial hypertension: the effect of treatment with ACE inhibitors. J Hum Hypertens 16:557–562

Hoegholm A, Bang LE, Kristensen KS, Nielsen JW, Holm J (1994) Microalbuminuria in 411 untreated individuals with established hypertension, white coat hypertension and normotension. Hypertension 24:101–105

Hsueh WA, Quiñones MJ (2003) Role of endothelial dysfunction in insulin resistance. Am J Cardiol 92:10J–17J

Idris-Khodja N, Mian MO, Paradis P, Schiffrin EL (2014) Dual opposing roles of adaptive immunity in hypertension. Eur Heart J 35:1238–1244

Jacobsen JC, Hornbech MS, Holstein-Rathlou NH (2011) Significance of microvascular remodelling for the vascular flow reserve in hypertension. Interface Focus 1:117–131

Jaipersad AS, Lip GY, Silverman S, Shantsila E (2014) The role of monocytes in angiogenesis and atherosclerosis. J Am Coll Cardiol 63:1–11

James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311:507–520

Jarajapu YP, Bhatwadekar AD, Caballero S, Hazra S, Shenoy V, Medina R, Kent D, Stitt AW, Thut C, Finney EM, Raizada MK, Grant MB (2013) Activation of the ACE2/angiotensin-(1-7)/Mas receptor axis enhances the reparative function of dysfunctional diabetic endothelial progenitors. Diabetes 62:1258–1269

Jiang F, Yang J, Zhang Y, Dong M, Wang S, Zhang Q, Liu FF, Zhang K, Zhang C (2014) Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets. Nat Rev Cardiol 11:413–426

Julius S, Mejia A, Jones K et al (1990) 'White coat' versus 'sustained' borderline hypertension in Tecimseh, Michigan. Hypertension 16:617–623

Karter Y, Ertürk NT, Aydín S, Curgunlu A, Uzun H, Vehid S, Kutlu AO, Yaldiran A, Oztürk E, Erdine S, Sipahioğlu F (2003) Endothelial dysfunction in sustained and white coat hypertension. Am J Hypertens 16:892

Karter Y, Aydin S, Curgunlu A, Uzun H, Ertürk N, Vehid S, Kutlu A, Simsek G, Yücel R, Arat A, Ozturk E, Erdine S (2004) Endothelium and angiogenesis in white coat hypertension. J Hum Hypertens 18:809–814

Kedzierski RM, Yanagisawa M (2001) Endothelin system: the double-edged sword in health and disease. Annu Rev Pharmacol Toxicol 41:851–876

Kellogg D, Zhao J, Coey U, Green J (2005) Acetylcholine-induced vasodilation is mediated by nitric oxide and prostaglandins in human skin. J Appl Physiol 98:629–632

Kelly AS, Gonzalez-Campoy JM, Rudser KD, Katz H, Metzig AM, Thalin M, Bank AJ (2012) Carvedilol-lisinopril combination therapy and endothelial function in obese individuals with hypertension. J Clin Hypertens 14:85–91

Khazaei M, Moien-afshari F, Laher I (2008) Vascular endothelial function in health and diseases. Pathophysiology 15:49–67

Kim YW, Byzova TV (2014) Oxidative stress in angiogenesis and vascular disease. Blood 123:625–631

Kiowski W (1999) Endothelial dysfunction in hypertension. Clin Exp Hypertens 21:635–646

Kleinegris MC, Ten Cate-Hoek AJ, Ten Cate H (2012) Coagulation and the vessel wall in thrombosis and atherosclerosis. Pol Arch Med Wewn 122:557–566

Kobayashi T, Nogami T, Taguchi K, Matsumoto T, Kamata K (2008) Diabetic state, high plasma insulin

and angiotensin II combine to augment endothelin-1-induced vasoconstriction via ETA receptors and ERK. Br J Pharmacol 155:974–983

Kolluru GK, Sinha S, Majumder S, Muley A, Siamwala JH, Gupta R, Chatterjee S (2010) Shear stress promotes nitric oxide production in endothelial cells by sub-cellular delocalization of eNOS: a basis for shear stress mediated angiogenesis. Nitric Oxide 22:304–315

Konukoglu D, Serin O, Ercan M, Turhan M (2003) Plasma homocysteine levels in obese and non-obese subjects with or without hypertension; its relationship with oxidative stress and copper. Clin Biochem 36:405–408

Konukoglu D, Serin O, Turhan MS (2006) Plasma leptin and its relationship with lipid peroxidation and nitric oxide in obese female patients with or without hypertension. Arch Med Res 37:602–606

Konukoglu D, Firtina S, Serin O, Cavusoglu C (2009) Relationship among plasma secretory phospholipase A2, oxidized low density lipoprotein & paraoxonase activities in hypertensive subjects treated with angiotensin converting enzyme inhibitors. Indian J Med Res 129:390–394

Korbecki J, Baranowska-Bosiacka I, Gutowska I, Chlubek D (2014) Cyclooxygenase pathways. Acta Biochim Pol 61:639–649

Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V (1998) The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan Hypertension Investigators. N Engl J Med 338:784–790

Lacave R, Rondeau E, Ochi S, Delarue F, Schleuning WD, Sraer JD (1989) Characterization of a plasminogen activator and its inhibitor in human mesangial cells. Kidney Int 35:806–811

Laher I (ed) (2014) Systems biology of free radicals and antioxidants book. Springer, Berlin/Heidelberg

Lee R, Margaritis M, Channon KM, Antoniades C (2012) Evaluating oxidative stress in human cardiovascular disease: methodological aspects and considerations. Curr Med Chem 19:2504–2520

Lengyel S, Katona E, Zatik J, Molnár C, Paragh G, Fülesdi B, Páll D (2012) The impact of serum homocysteine on intima-media thickness in normotensive, white-coat and sustained hypertensive adolescents. Blood Press 21:39–44

Lerman A, Burnett JC Jr (1992) Intact and altered endothelium in regulation of vasomotion. Circulation 86 (suppl III):III-12–II-19

Levesque MJ, Nerem RM, Sprague EA (1990) Vascular endothelial cell proliferation in culture and the influence of flow. Biomaterials 11:702–707

Li Y, Haga C, Chien S (2005) Molecular basis of the effects of shear stress on vascular endothelial cells. J Biomech 38:1949–1971

Li S, Wu Y, Yu G, Xia Q, Xu Y (2014) Angiotensin II receptor blockers improve peripheral endothelial function: a meta-analysis of randomized controlled trials. PLoS One 9, e90217

Lijnen HR, Collen D (1997) Endothelium in hemostasis and thrombosis. Prog Cardiovasc Dis 39:343–350

Lin YJ, Juan CC, Kwok CF, Hsu YP, Shih KC, Chen CC, Ho LT (2015) Endothelin-1 exacerbates development of hypertension and atherosclerosis in modest insulin resistant syndrome. Biochem Biophys Res Commun 460:497–503

Loukogeorgakis SP, van den Berg MJ, Sofat R, Nitsch D, Charakida M, Haiyee B, de Groot E, MacAllister RJ, Kuijpers TW, Deanfield JE (2010) Role of NADPH oxidase in endothelial ischemia/reperfusion injury in humans. Circulation 121:2310–2316

Lowenstein CJ, Padalko E (2004) iNOS (NOS2) at a glance. J Cell Sci 117:2865–2867

Luksha L, Agewall S, Kublickiene K (2009) Endothelium-derived hyperpolarizing factor in vascular physiology and cardiovascular disease. Atherosclerosis 202:330–344

Luscher TF (1991) Endothelium-derived nitric oxide: the endogenous nitrovasodilator in the human cardiovascular system. Eur Heart J 12(Suppl E):2–11

Luscher TF, Vanhoutte PM (1986) Endothelium-dependent contractions to acetylcholine in the aorta of the spontaneously hypertensive rat. Hypertension 8:344–348

Lüscher TF, Yang ZH, Diederich D, Bühler FR (1989) Endothelium-derived vasoactive substances: potential role in hypertension, atherosclerosis, and vascular occlusion. J Cardiovasc Pharmacol 14(Suppl 6):S63–S69

Mai J, Virtue A, Shen J, Wang H, Yang X-F (2013) An evolving new paradigm: endothelial cells–conditional innate immune cells. J Hematol Oncol 6:61

Mancia G, Fagard R, Narkiewicz K et al (2013) ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 34:2159–2219

Marchi-Alves LM, Carnio EC (2009) Is there any correlation between insulin resistance and nitrate plasma concentration in white coat hypertensive patients? Cardiol Res Pract 2009:376735

Marques FK, Campos FM, Sousa LP, Teixeira-Carvalho-A, Dusse LM, Gomes KB (2013) Association of microparticles and preeclampsia. Mol Biol Rep 40:4553–4559

Masuyer G, Yates CJ, Sturrock ED, Acharya KR (2014) Angiotensin-I converting enzyme (ACE): structure, biological roles, and molecular basis for chloride ion dependence. Biol Chem 395:1135–1149

Matavelli LC, Siragy HM (2015) AT2 receptor activities and pathophysiological implications. J Cardiovasc Pharmacol 65:226–232

McCully KS (2015) Homocysteine and the pathogenesis of atherosclerosis. Expert Rev Clin Pharmacol 8:211–219

McIntyre M, Bohr DF, Dominiczak AF (1999) Endothelial function in hypertension: the role of superoxide anion. Hypertension 34:539–545

Medzhitov R (2008) Origin and physiological roles of inflammation. Nature 454:428–435

Melikian N, Seddon MD, Casadei B, Chowienczyk PJ, Shah AM (2009) Neuronal nitric oxide synthase and human vascular regulation. Trends Cardiovasc Med 19:256–262

Mendoza-Torres E, Oyarzún A, Mondaca-Ruff D, Azocar A, Castro PF, Jalil JE, Chiong M, Lavandero S, Ocaranza MP (2015) ACE2 and vasoactive peptides: novel players in cardiovascular/renal remodeling and hypertension. Ther Adv Cardiovasc Dis 9:217–237

Michalsen A, Li C (2013) Fasting therapy for treating and preventing disease – current state of evidence. Forsch Komplementmed 20:444–453

Michel T, Vanhoutte PM (2010) Cellular signaling and NO production. Pflugers Arch - Eur J Physiol 459:807–816

Montezano AC, Tsiropoulou S, Dulak-Lis M, Harvey A, Camargo Lde L, Touyz RM (2015a) Redox signaling, Nox5 and vascular remodeling in hypertension. Curr Opin Nephrol Hypertens 24:425–433

Montezano AC, Dulak-Lis M, Tsiropoulou S, Harvey A, Briones AM, Touyz RM (2015b) Oxidative stress and human hypertension: vascular mechanisms, biomarkers, and novel therapies. Can J Cardiol 31:631–641

Mullen MJ, Clarkson P, Donald AE, Thomson H, Thorne SA, Powe AJ, Furuno T, Bull T, Deanfield JE (1998) Effect of enalapril on endothelial function in young insulin-dependent diabetic patients: a randomized, double-blind study. J Am Coll Cardiol 31:1330–1335

Muniyappa R, Sowers JR (2013) Role of insulin resistance in endothelial dysfunction. Rev Endocr Metab Disord 14:5–12

Napoli C, Salomone S, Godfraind T, Palinski W, Capuzzi DM, Palumbo G, D'Armiento FP, Donzelli R, de Nigris F, Capizzi RL, Mancini M, Gonnella JS, Bianchi A (1999) 1,4-Dihydropyridin ealcium channel blockers inhibit plasma and LDL oxidation and formation of oxidation-specific epitopes in the arterial wall and prolong survival in stroke-prone spontaneously hypertensive rats. Stroke 30:1907–1915

Oparil S, Zaman MA, Calhoun DA (2003) Pathogenesis of hypertension. Ann Intern Med 139:761–776

Ouweneel AB, Van Eck M (2016) Lipoproteins as modulators of atherothrombosis: from endothelial function to primary and secondary coagulation. Vascul Pharmacol 82:1–10

Palmer RM, Ashton D, Moncada S (1988) Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 333:664–666

Papageorgiou N, Androulakis E, Papaioannou S, Antoniades C, Tousoulis D (2015) Homoarginine in the shadow of asymmetric dimethylarginine: from nitric oxide to cardiovascular disease. Amino Acids 47:1741–1750

Pastrana JL, Sha X, Virtue A, Mai J, Cueto R, Lee IA, Wang H, Yang XF (2012) Regulatory T cells and Atherosclerosis. J Clin Exp Cardiol 2012(Suppl 12):002–019

Perutelli P, Marchese P, Mori PG (1992) The glycoprotein IIb/IIIa complex of the platelets. An activation-dependent integrin. Recenti Prog Med 83:100–104

Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH (1988) How common is white coat hypertension. JAMA 259:225–228

Pierdomenico SD, Cuccurullo F (2011) Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta-analysis. Am J Hypertens 24:52–58

Pierdomenico SD, Bucci A, Lapenna D, Lattanzio FM, Talone L, Cuccurullo F, Mezzetti A (2003) Circulating homocysteine levels in sustained and white coat hypertension. J Hum Hypertens 17:165–170

Pirillo A, Norata GD, Catapano AL (2013) LOX-1, OxLDL, and atherosclerosis. Mediators Inflamm 2013:1–13

Prasad A, Tupas-Habib T, Schenke WH, Mincemoyer R, Panza JA, Waclawiw MA, Ellahham S, Quyyumi AA (2000) Acute and chronic angiotensin-1 receptor antagonism reverses endothelial dysfunction in atherosclerosis. Circulation 101:2349–2354

Prasad A, Halcox JPJ, Waclawiw MA, Quyyumi AA (2001) Angiotensin type 1 receptor antagonism reverses abnormal coronary vasomotion in atherosclerosis. J Am Coll Cardiol 38:1089–1095

Preston RA, Jy W, Jimenez JJ, Mauro LM, Horstman LL, Valle M, Aime G, Ahn YS (2003) Effects of severe hypertension on endothelial and platelet microparticles. Hypertension 41:211–217

Prieto D, Contreras C, Sánchez A (2014) Endothelial dysfunction, obesity and insulin resistance. Curr Vasc Pharmacol 12:412–426

Pushpakumar S, Kundu S, Sen U (2014) Endothelial dysfunction: the link between homocysteine and hydrogen sulfide. Curr Med Chem 21:3662–3672

Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, Nishigaki I (2013) The vascular endothelium and human diseases. Int J Biol Sci 9:1057–1069

Ralevic V, Dunn WR (2015) Purinergic transmission in blood vessels. Auton Neurosci 191:48–66

Rao A, Pandya V, Whaley-Connell A (2015) Obesity and insulin resistance in resistant hypertension: implications for the kidney. Adv Chronic Kidney Dis 22:211–217

Reneman RS, Arts T, Hoeks AP (2006) Wall shear stress–an important determinant of endothelial cell function and structure in the arterial system in vivo. Discrepancies with theory. J Vasc Res 43:251–269

Rodrigo R, Prat H, Passalacqua W, Araya J, Guichard C, Bächler JP (2007) Relationship between oxidative

stress and essential hypertension. Hypertens Res 30:1159–1167
Rodrigo R, Libuy M, Feliú F, Hasson D (2013) Oxidative stress-related biomarkers in essential hypertension and ischemia-reperfusion myocardial damage. Dis Markers 35:773–790
Rodriguez-Iturbe B, Pons H, Quiroz Y, Lanaspa M, Johnson RJ (2014) Autoimmunity in the pathogenesis of hypertension. Nat Rev Nephrol 10:56–62
Salame MY, Samani NJ, Masood I, deBono DP (2000) Expression of the plasminogen activator system in the human vascular wall. Atherosclerosis 152:19–28
Salomone S, Drago F (2012) Effects of PPARγ ligands on vascular tone. Curr Mol Pharmacol 5:282–291
Santilli F, D'Ardes D, Davì G (2015) Oxidative stress in chronic vascular disease: from prediction to prevention. Vasc Pharmacol 74:23–37
Shih GC, Hajjar KA (1993) Plasminogen and plasminogen activator assembly on the human endothelial cell. Proc Soc Exp Biol Med 202:258–264
Siervo M, Corander M, Stranges S, Bluck L (2011) Post-challenge hyperglycaemia, nitric oxide production and endothelial dysfunction: the putative role of asymmetric dimethylarginine (ADMA). Nutr Metab Cardiovasc Dis 21:1–10
Sindone A, Erlich J, Lee C, Newman H, Suranyi M, Roger SD (2016) Cardiovascular risk reduction in hypertension: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers. Where are we up to? Intern Med J 46:364–372
Siti HN, Kamisah Y, Kamsiah J (2015) The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease. Vasc Pharmacol 71:40–56
Soma J, Aakhus S, Dahl K, Slørdahl S, Wiseth R, Widerøe TE, Skjaerpe T (1996) Hemodynamics in white coat hypertension compared to ambulatory hypertension and normotension. Am J Hypertens 9:1090–1098
Spence S, Anderson C, Cukierski M, Patrick D (1999) Teratogenic effects of the endothelin receptor antagonist L-753,037 in the rat. Reprod Toxicol 13:15–29
Stancel N, Chen CC, Ke LY, Chu CS, Lu J, Sawamura T, Chen CH (2016) Interplay between crp, atherogenic ldl, and lox-1 and its potential role in the pathogenesis of atherosclerosis. Clin Chem 62:320–327
Steffel J, Lüscher TF, Tanner FC (2006) Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications. Circulation 113:722–731
Stenina OI (2003) Regulation of gene expression in vascular cells by coagulation proteins. Curr Drug Targets 4:143–158
Stergiou GS, Asayama K, Thijs L, Kollias A, Niiranen TJ, Hozawa A, Boggia J, Johansson JK, Ohkubo T, Tsuji I, Jula AM, Imai Y, Staessen JA, International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) Investigators (2014) Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. Hypertension 63:675–682
Strandherg TE, Salomaa V (2000) White coat effect, blood pressure and mortality in men: prospective cohort study. Eur Heart J 21:1714–1718
Su JB (2015) Vascular endothelial dysfunction and pharmacological treatment. World J Cardiol 7:719–741
Szmitko PE, Wang CH, Weisel RD, de Almeida JR, Anderson TJ, Verma S (2003) New markers of inflammation and endothelial cell activation: part I. Circulation 108:1917–1923
Tabak O, Gelisgen R, Uzun H, Kalender B, Balci H, Curgunlu A, Simsek G, Karter Y (2009) Hypertension and hemostatic/fibrinolytic balance disorders. Clin Invest Med 32:E285–E290
Thaete LG, Neerhof MG, Silver RK (2001) Differential effects of endothelin A and B receptor antagonism on fetal growth in normal and nitric oxide-deficient rats. J Soc Gynecol Investig 8:18–23
Trask AJ, Ferrario CM (2007) Angiotensin-(1-7): pharmacology and new perspectives in cardiovascular treatments. Cardiovasc Drug Rev 25:162–174
Tschudi MR, Criscione L, Luscher TF (1991) Effect of aging and hypertension on endothelial function of rat coronary arteries. J Hypertens 9:164–165
Tselios K, Sarantopoulos A, Gkougkourelas I, Boura P (2014) T regulatory cells: a promising new target in atherosclerosis. Crit Rev Immunol 34:389–397
Tummala PE, Chen XL, Sundell CL, Laursen JB, Hammes CP, Alexander RW, Harrison DG, Medford RM (1999) Angiotensin II induces vascular cell adhesion molecule-1 expression in rat vasculature: potential link between the renin-angiotensin system and atherosclerosis. Circulation 100:1223–1229
Tuttolomondo A, Di Raimondo D, Pecoraro R, Arnao V, Pinto A, Licata G (2012) Atherosclerosis as an inflammatory disease. Curr Pharm Des 18:4266–4288
Tzemos N, Lim PO, MacDonald TM (2001) Nebivolol reverses endothelial dysfunction in essential hypertension: a randomized, double-blind, crossover study. Circulation 104:511–514
Uzun H, Karter Y, Aydin S, Curgunlu A, Simşek G, Yücel R, Vehiyd S, Ertürk N, Kutlu A, Benian A, Yaldiran A, Oztürk E, Erdine S (2004) Oxidative stress in white coat hypertension; role of paraoxonase. J Hum Hypertens 18:523–528
Vaindirlis I, Peppa-Patrikiou M, Dracopoulou M, Manoli I, Voutetakis A, Dacou-Voutetakis C (2000) 'White coat hypertension' in adolescents: increased values of urinary cortisol and endothelin. J Pediatr 136:359–364
Vaněčková I, Maletínská L, Behuliak M, Nagelová V, Zicha J, Kuneš J (2014) Obesity-related hypertension: possible pathophysiological mechanisms. J Endocrinol 223:R63–R78