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Target Organ Damage in Essential Hypertension

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1. Introduction

Epidemiological data suggests that hypertension remains a major modifiable risk factor for cardiovascular disease in Western countries. The prevalence of the disease among adults in Slovenia aged 25–64 years is between 40–50% (CINDI, 2006). The early detection and severity of typical target organ damage and secondary diseases are key determinants of cardiovascular prognosis in patients suffering from arterial hypertension (Mancia et al., 2009). The classic manifestations of hypertensive target organ damage include: damage in the conduit arteries (atherosclerosis), kidney (nephrosclerosis) and heart (left ventricular hypertrophy, diastolic dysfunction, reduction of coronary reserve). The recommendations of medical societies specializing in hypertension do not base risk stratification solely on blood pressure (BP), but rather take into account concomitant cardiovascular diseases as well (Mancia et al., 2009). Early detection and adequate management of hypertensive target organ damage can slow or prevent damage, or even allow disease regression where organ damage is still at reversible stage. Therefore, the diagnosis of hypertensive target organ damage is of decisive importance. The purpose of this review is to summarize current and emerging approaches to the pathophysiology, early detection and treatment of hypertensive disease.

2. Etiopathogenesis of essential hypertension

In spite of intensive investigation, etiology of essential hypertension (EH), which accounts for 90-95% of all cases of arterial hypertension remains poorly understood. Heredity is a predisposing factor (Sagnella & Swift, 2006), but environmental factors (e.g., dietary Na^+, obesity, sedentary lifestyle, stress, alcohol intake) seem to increase the risk of developing hypertension (Kyrou et al., 2006; Lackland & Egan, 2007).

Pathogenesis is also not known. Because BP equals cardiac output (CO) × total peripheral vascular resistance (TPR), pathogenic mechanisms must involve increased CO, increased TPR, or both. Many theories have been proposed to explain this equation; the microcirculation theory is the most attractive among them. In accordance with this theory the primary defect involves small resistance vessels, leading to increased TPR and sustained

elevated BP. Several basic studies support this theory as functional and morphological abnormalities in the microcirculation may appear very early in evolving EH. Functional changes (endothelial dysfunction) could be the first event; later on, morphological changes of the vasculature ensue. The latter include increased media/lumen ratio due to hypertrophy and/or hyperplasia of myocytes in the vessel wall and decreased density (rarefaction) of blood vessels on biopsy (Mark, 1984; Schiffrin, 1992; Sivertsson et al., 1979; Takeshita & Allyn, 1980). Plethysmographic studies suggest that TPR is increased even in normotensive young men with a familial predisposition to hypertension (Takeshita et al., 1982).

Endothelial cells (EC) have a pivotal role in the maintenance of the basal tone and modulation of TPR. In the endothelium releases several biologically active substances, which maintain the homeostasis between circulating blood and arterial wall via autocrine and paracrine mechanisms. Vasoconstricting factors (endothelin-1, thromboxane A_2, angiotensin II) on one side and vasorelaxing factors (prostacyclin, nitric oxide /NO/) on the other are secreted by EC (Lüscher, 1994; Vane et al., 1990) (Figure 1.). In their pioneer work Furchgott and Zawadzki 1980 reported that EC stimulated by a neurotransmitter (acetylcholine) can evoke vasodilation (Furchgott & Zawadzki, 1980). The mediator of these responses is a diffusible substance with a half-life of few seconds, the so-called *endothelium derived relaxing factor* – EDRF, which is chemically identical to NO and is continuously secreted upon shear stress forces (produced by blood flow) from EC (Hutchinson & Palmer, 1987; Ignarro et al., 1987). Basal generation of NO keeps arterial circulation in an actively dilated state (Schiffrin, 1992). The intracellular mechanism by which NO causes dilation in vascular smooth muscle cells involves formation of cyclic 3',5'-guanosine monophosphate (cGMP) via the enzyme soluble guanylyl cyclase, intracellular Ca^{++}-ion depletion and consequently relaxation of myocytes (endothelium-dependent dilation) (Palmer et al., 1987; Rubany et al., 1986; Wennmalm, 1994). Indeed, many experimental studies have shown that NO could contribute to TPR and to modulation of BP (Persson et al., 1990; Rees et al., 1989; Vallance et al., 1989). In addition, NO appears to be an endogenous inhibitor of norepinephrine in animal studies and thus a modulator of the sympathetic nerve system, a mechanism which could also be involved in the pathogenesis of EH (Cohen & Weisbrod, 1988; Greenberg et al., 1990).

3. Target organ damage

3.1 Vascular abnormalities (endothelial dysfunction) in EH

Recently, works related to the association between EH and sustained endothelial damage has gained popularity among hypertension scientists. It remains unclear however whether endothelial changes precede the development of hypertension or whether such changes are mainly due to long standing elevated BP.

The term endothelial dysfunction describes several pathological conditions, including altered anticoagulant and anti-inflammatory properties in the endothelium, impaired modulation of vascular growth, and deregulation of vascular remodeling, decreased production of NO and unbalanced production of other different vasoactive substances (endothelin-1, thromboxane A_2, and angiotensin II) (Moncada et al., 1991). In the literature

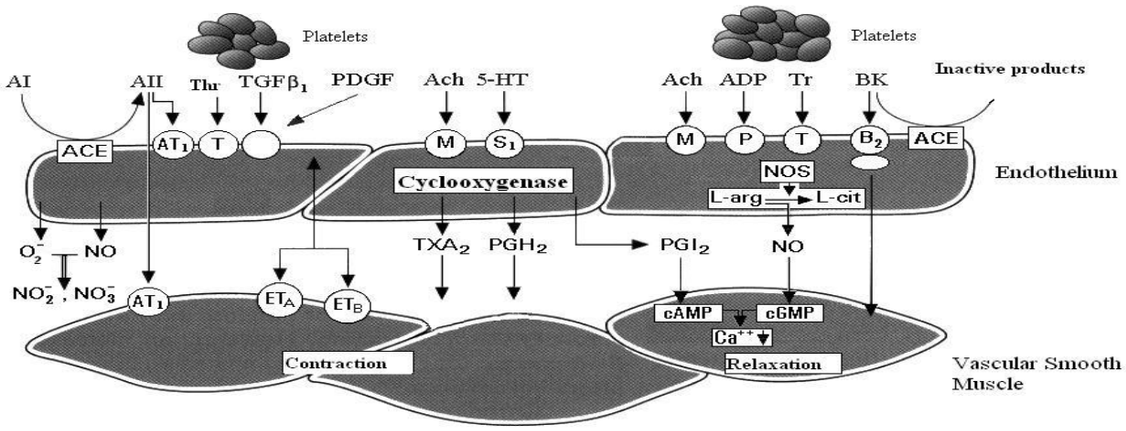

Fig. 1. Endothelium derived vasoactive substances. The endothelium is a source of relaxing (*right*) and contracting factors (*left*). *AT_1*, angiotensin receptor; *A II*, angiotensin II; *ACE*, angiotensin-converting enzyme; *Ach*, acetylcholine; *ADP*, adenosine diphosphate; *BK*, bradykinin; *cAMP/cGMP*, cyclic adenosine/guanosine monophosphate; *5-HT*, 5-hydroxytryptamine (serotonin); *ET-1*, endothelin-1; *L-arg*, L-arginine; *NO*, nitric oxide; *NO_2^-/NO_3^-*, nitrite/nitrate; *O_2^-*, superoxide radical; *PGI_2*, prostacyclin; *$TGF\beta_1$*, transforming growth factor β_1; *Thr*, thrombin; *TXA_2*, thromboxane A_2; *Circles* represent receptors; Modified from Lüscher, 1994.

however, the term specifically refers to an impairment of endothelium-dependent vasodilation caused by decreased NO bioavailability in the vessel wall (Poredoš, 2002). Endothelial dysfunction has been demonstrated in subjects with different risk factors for atherosclerosis including arterial hypertension, and in coronary atherosclerotic disease (Egashira et al., 1995; Zeiher et al., 1993). We shall now focus on evidences which indicate that endothelial dysfunction is a characteristic finding in patients with EH (Taddei & Salvetti, 2002).

Under basal conditions, whole-body NO bioavailability is diminished in hypertension (Moncada et al., 1991). With few exceptions (Cockcroft et al., 1994), hypertensive patients have shown to have impaired endothelium-dependent vasodilative response of the peripheral resistance arteries (usually measured by forearm blood flow using venous occlusion plethysmography) to NO stimulants (acetylcholine) (Panza et al., 1993; Panza et al., 1990; Taddei et al., 1993), but not to endothelium-independent vasodilators such as nitroprusside (Panza et al., 1993). Using B-mode ultrasound the impairment of dilation capability of systemic conduit arteries during reactive hyperemia was demonstrated, as was reduced vasodilative response to acetylcholine in coronary vessels of patients with EH (Treasure et al., 1993; Zeiher et al., 1993; Žižek et al., 2001a; Žižek & Poredoš 2001b). Authors postulate that EH like other risk factors for atherosclerosis (hypercholesterolemia, diabetes and smoking) damage and change the function of EC (Drexler et al., 1991; Zeiher et al., 1991). The evidence for a role of defective NO-mediated vasodilation in the etiopathogenesis of arterial hypertension has been further strengthened by its recognition in still normotensive children of hypertensive parents (Žižek et al., 2001a, Žižek & Poredoš, 2001b). As impaired endothelium-dependent vasodilation precedes and predicts the future development of hypertension, one could reasonably speculate that endothelial dysfunction

is causally related to EH (Rossi et al., 2004). Moreover, it seems that endothelial dysfunction is partly inherited but deteriorates further in evolving hypertension – thus suggesting that endothelial dysfunction in established hypertension could be the cause and the consequence of hypertensive disease (Calver et al., 1992; Žižek et al., 2001a).

There are relatively few data, albeit controversial, on mechanisms leading to decreased production of NO in EH. The majority of investigators attach weight to inherited or acquired decreased activity of a key enzyme, NO synthase (Bogle et al., 1995; Mehta et al., 1994). Recent reports have shown that reduced NO bioactivity may be linked to increased circulating level of the endogenous NO synthase inhibitor, asymmetric dimethyl L-arginine (Achan et al., 2003). In sustained EH decreased vasodilation was explained by a deficiency of L-arginine, the precursor of NO (Panza et al., 1993), inactivation of NO due to free radicals formation (Mechta et al., 1994), impeding diffusion to smooth muscle cells (Van de Voorde & Leusen, 1986), blunted response of the smooth muscle to pharmacological and physiological stimuli (Robinson et al., 1982), and increased production of vasoconstricting factors (endothelin-1, angiotensin II) (Lüscher, 1994).

In addition to NO, prostacyclin (PGI_2) is released by EC in response to shear stress, hypoxia and to several substances (acetylcholine, substance P, serotonin) which are also released by NO (Figure 1.). PGI_2 is synthesized by cyclo-oxygenase from arachidonic acid (Vane et al., 1990). Prostacyclin increases cyclic 3′,5′-adenosine monophosphate (cAMP) in smooth muscle cells and platelets. Its platelet inhibitory effects are probably more important than its contribution to endothelium-dependent relaxation (Vane et al., 1990). The synergistic effect of both PGI_2 and NO enhances the antiplatelet and anticoagulant activity of the EC (Pearson & Wheeler-Yones 1997; Yang et al., 1994).

The family of endothelins consists of three closely related peptides: endothelin-1 (ET-1), endothelin-2, and endothelin-3 (Figure 1.). EC produce exclusively endothelin-1, which is the strongest vasoconstricting factor (Rossi et al., 1999). The release of the peptide is modulated by shear stress, epinephrine, angiotensin II, thrombin, inflammatory cytokines (tumor necrosis factor-α, interleukin-1, -2) and hypoxia (Moncada et al., 1991). There are well known interactions between ET-1 and other vasoactive substances. After inhibition of the endothelial L-arginine pathway, thrombin and angiotensin II induced ET-1 production is augmented (Moncada et al., 1991). ET-1 can release NO and PGI_2 from EC, which as a negative feedback mechanism reduces peptide production in endothelium and its vasoconstrictor action in smooth muscle (Moncada et al., 1991; Rossi et al., 1999). Infusion of an ET-1 receptor antagonist in healthy humans leads to vasodilation, indicating a role of ET-1 in the maintenance of basal vascular tone (Haynes et al., 1996). In some severe hypertensive patients ET-1 gene expression and vascular hypertrophy in small resistance arteries were reported (Schiffrin et al., 1997).

Oxidative stress plays an important role in the development of endothelium injury found in EH. It is defined as imbalance between production of reactive oxygen species (ROS) and antioxidants that neutralize them (Landmesser & Drexler, 2007; Spieker et al., 2000). Formation of ROS, resulting in scavenging of NO and reduced NO bioavailability, has been suggested as a hallmark of endothelial dysfunction and a pathogenetic mechanism in several cardiovascular diseases, including hypertension (Figure 1.) (Schulz et al., 2011). Indeed, increased production of ROS has been observed in human hypertension (Higashi et al., 2002;

Redon et al., 2003) as well as evidenced in animal models, such as in angiotensin II (Landmesser et al., 2002) or in genetically defined hypertension (Nishiyama et al., 2004).

Increased production of vascular ROS, especially superoxide anion (O_2^-) contributes significantly to functional and morphological alterations in hypertension (Touyz et al., 2004). Exaggerated superoxide production and low NO bioavailability lead to endothelial dysfunction and hypertrophy of vascular cells promoting atherosclerosis (Figure 1.). It has been reported that the enzyme NAD(P)H oxydase plays a major role as the most important source of superoxide anion in vascular cells (Zalba et al., 2001). Experimental observations indicated an enhanced superoxide generation as a result of the activation of vascular NAD(P)H oxydase in hypertension (Griendling et al., 2000). During pulsatile stretch of the arterial wall expression of the enzyme is increased, thus enabling a positive feedback mechanism between oxidative stress and hypertension (Hishikawa et al., 1997). Although NAD(P)H oxydase responds to stimuli such as vasoactive factors, growth factors, and cytokines, some recent data suggest a genetic background modulating its expression (Landmesser & Drexler, 2007). Oxidative excess is also linked to a pro-inflammatory state of the vessel wall. Adhesion and chemotactic molecules upregulated by ROS seem to play a key pathophysiological role in the process of atherogenesis (Touyz, 2004). In particular, increased O_2^- production is associated with NO bioinactivation, which influences afferent arteriolar tone, tubuloglomerular feedback responses, and sodium reabsorption – all of which is paramount in long-term BP regulation (Wilcox, 2002). Moreover, ROS are known to quench NO with formation of peroxynitrite, which is a cytotoxic oxidant. Peroxynitrite leads to degradation of NO synthase cofactor of tetrahydrobiopterin leading to uncoupling of endothelium NO synthase in hypertension and secretion of ROS rather than NO (Landmesser et al., 2003).

The best known regulator of BP and determinant of target organ damage in hypertension is the renin-angiotensin-aldosterone system (RAAS). The basic scheme of function has been known for a long time; however, recent evidence shows that apart from circulating RAAS, tissue RAAS also exists and may well be of greater importance (Hsueh & Wyne, 2011). Tissue RAAS is most important in the vessel wall, the heart and the kidney. Constituents of RAAS could enter the endothelium or could originate from it (Hsueh & Wyne, 2011). The role of angiotensin II in neurohumoral modulation is very well investigated. Angiotensin II modifies the vascular tone either directly by activation angiotensin 1 (AT_1) receptors in vessel wall myocytes or indirectly by stimulation of norepinephrine secretion from the nerve endings (Kim & Iwao, 2000; Williams, 2001). Although acute hemodynamic effects of angiotensin II are useful, its chronic elevation could have deleterious non-hemodynamic consequences. Angiotensin II can cause endothelial dysfunction, vascular stiffness and accelerated atherogenesis independently from BP (Williams, 2001). It is proposed that in the condition of low plasma renin level for its non-hemodynamic effects an increased expression of AT_1 receptors could play a role (Figure 1.). Namely, in hypertension expression is increased due to pulsatile stretch of arterial wall leading to increased local effects of AT_1 receptors. This inaugurates increased angiotensin II effects and other constituents of RAAS, especially aldosterone (Kim & Iwao, 2000; McMahon, 2001). Harmful effects of the latter extend from endothelial dysfunction, fibrosis and inflammation of arterial wall to systemic electrolytes and hemodynamic imbalance (Brasier et al., 2002; Duprez, 2006). In particular, convincing evidence exist that overactivation of RAAS, or at least part of it, may induce ET-1 production and increase angiotensin-converting enzyme

(ACE) activity, which splits bradykinin, an important endothelium-derived relaxing factor (Watanabe et al., 2005). Angiotensin II has been shown to increase secretion of vascular NAD(P)H oxydase and formation of ROS (Hitomi et al., 2007). Indeed, increased production of ROS has been observed in human hypertension (Higashi et al., 2002; Redon et al., 2003).

Endothelial dysfunction is the earliest measurable disturbance in arterial wall function, which could be measured *in vivo*. Early detection of endothelial dysfunction in EH can be achieved by the abovementioned methods – namely, measurement of hemodynamic changes by ultrasound, measurement of hemodynamic changes by occlusive plethysmography, and measurement of circulating markers of defective EC function (ET-1, adhesion molecules, tumor necrosis factor–TNF-α, von Willebrand's factor, plasminogen activator inhibitor-1, asymmetric dimethyl L-arginine) (Achan et al., 2003; Devaraj et al., 2003; Treasure et al., 1993; Yang et al., 2010; Žižek et al., 2001a). Detailed description of these methods exceeds the purpose of this paper.

Endothelial dysfunction could be improved or even restored with preventive measures. Different studies showed that elimination or management of risk factors (for example treating hypercholesterolemia with statins) results in improvement of endothelial dysfunction (Wassmann et al., 2001). Considerably less interventional data, albeit controversial, are available concerning treatment of EH and endothelial dysfunction of the large conduit arteries. Studies on animal models and in humans have shown that normalization of BP can restore impaired endothelium-dependent vascular responses (Iwatsubo et al., 1997; Lüscher & Vanhoutte, 1987). Conversely, another group of investigators failed to show normalization of endothelial dysfunction in conduit arteries treated with the same drug (ACE inhibitor) (Eržen et al., 2006). Thus, several questions still remain unanswered – it is not clear whether endothelial dysfunction can be completely normalized, whether normalization of endothelial function is related to adequacy of antihypertensive treatment, and whether antihypertensive drugs importantly differ in their ability to improve endothelial dysfunction. In this regard, ACE inhibitors seem to be the most appropriate class of antihypertonic agents (Virdis & Ghiadoni, 2011). Endothelial dysfunction could also be improved by substances with protective function on endothelium such as L-arginine, low-cholesterol diet, exercise and antioxidants (vitamin C) (Kabat & Dhein, 2006). Significance of the measures taken in the improvement of endothelial function is of greater importance when we consider the results from studies showing that cardiovascular morbidity and mortality very much depends on the severity of endothelium dysfunction (Kitta et al., 2005).

3.2 Morphological changes of the large arteries – atherosclerosis

EH is an important risk factor for atherosclerosis. As the cellular and molecular pathogenetic mechanisms of atherosclerosis and the effects of hypertension are being more clearly defined, it becomes apparent that the two processes have certain common mechanisms. The endothelium is a likely source of interaction between both diseases. NO acts as a vasodilator and inhibits platelet adherence and aggregation, smooth muscle proliferation, and endothelial cell-leukocyte interaction. Furthermore, a decrease in NO activity may contribute importantly to the initiation and progression of atherosclerotic lesions. It is proposed that several interrelated cellular and molecular processes such as inflammation are a likely consequence of mechanical and chemical damage of the endothelium by

different risk factors, including hypertension (Badimon & Fuster, 1993; Bondjers et al., 1991; Fuster et al., 1992; Landmesser & Drexler, 2007). However, recent observations favour the hypothesis that endothelial dysfunction in EH could be a primary defect and as such directly inherited (Bondjers et al., 1991; Vane et al., 1990; Žižek et al., 2001a; Žižek & Poredoš 2001b). Irrespective of the sequence of events, endothelial dysfunction promotes atherogenesis through different mechanisms: expression of adhesions molecules, increased adherence of monocytes and platelets, enhanced permeability of the endothelium layer to monocytes/macrophages and lipoproteins, which then accumulate in the vessel wall. As the atherosclerotic process progresses to plaque formation growth factors secreted by macrophages stimulate smooth muscle cells migration, proliferation and interstitial collagen synthesis. In the late stages of disease, the event that initiates the development of the majority of myocardial infarctions is the rupture of the fibrous cap of the plaque inducing thrombus formation. (Fuster et al., 1998; Ross, 1993).

It must be emphasized that risk factors for atherosclerosis tend to cluster, and therefore EH is rarely the only risk factor found in an individual patient. Hypertension is often accompanied by the metabolic syndrome, which encompasses a cluster of risk factors: obesity, dyslipidemia, glucose intolerance, a pro-thrombotic (high levels of fibrinogen and plasminogen activator inhibitor-1) and a pro-inflammatory state (high levels of tumor necrosis factor-α, interleukin-1, -2, C-reactive protein) (Devaraj et al., 2003; DeFronzo & Ferrannini, 1991; Tamakoshi et al., 2003). It is proposed that these heterogeneous groups of clinical conditions favor atherogenesis. People with the metabolic syndrome are at increased risk of coronary heart disease and other diseases related to plaque buildups in the arterial wall (e.g., stroke and peripheral vascular disease) (Olijhoek et al., 2004).

Assessment of the earliest morphological abnormalities in the arterial wall by B-mode ultrasound has been reported two decades ago. Diffuse thickening of the inner layer of arterial wall could be measured and followed by this non-invasive method (Pignoli et al., 2006). However, the method does not differentiate intima from media. Therefore both entities are measured together as the intima-media thickness (IMT) (Salonen et al., 1993). IMT of large peripheral arteries, especially carotid arteries, can be assessed by B-mode ultrasound in a relatively simple way. Due to tight associations between atherosclerotic changes in the carotid arteries and in other parts of the circulation, especially coronary arteries, carotid arteries could be regarded as a gateway enabling us to estimate the progression of arterial disease (Poredoš, 2004). Carotid arterial IMT is used in studies as a surrogate endpoint to measure progression of atherosclerosis. Several studies have shown a significant relationship between IMT and cardiovascular risk factors, such as age, male gender, cholesterol levels, BP, diabetes mellitus and smoking habits (Poredoš et al., 1999; Salonen et al., 1993; Žižek & Poredoš, 2002). Thicker IMT could be detected in healthy normotensive offspring of parents with EH, thus implying that morphological changes could be directly inherited (Žižek & Poredoš, 2002).

The relation between IMT and EH was confirmed in interventional studies. One of the largest studies, ELSA (European Lacidipine Study on Atherosclerosis) assessed IMT in EH patients. It showed that slowing of progression of the thickening could be achieved only by some drugs irrespective of the comparable lowering of the BP (Tang et al., 2000). This finding is important because in recent years we got strong evidence that IMT is an independent risk factor for cardiovascular events and is a better predictor of events than all

other known single conventional risk factors. In a Finnish study, ultrasonographic assessment of 1,257 men was compared with diagnostic information obtained from a prospective registry for acute myocardial infarction; it concluded that for each 0.1 mm of the common carotid IMT, the risk for a myocardial infarction increased by 11% (Salonen et al., 1993).

Recently, ample interest has been devoted to the relationship between arterial stiffness and cardiovascular disease. Pulse pressure and pulse wave velocity, surrogate measurements of arterial stiffness, indicate that arterial stiffness increases both with age and in certain disease states that are themselves associated with increased cardiovascular risk, including hypertension, diabetes mellitus and hypercholesterolemia (Glasser et al., 1997). Arterial stiffness may be measured using a variety of different techniques, mainly ultrasound based. Applanation tonometry pulse wave velocity is the most commonly used parameter in detecting central arterial stiffness (Nichols, 2005). Arterial stiffening has been particularly implicated in the development of isolated systolic hypertension and heart diseases leading to increased cardiovascular morbidity and mortality (Laurent et al., 2001).

3.3 Hypertensive nephropathy

EH is the main cause of the chronic kidney disease; however, morphologic evidence on the subject remains poorly understood (Fournier et al., 1994). A perennial problem in understanding the interaction between kidney and hypertension is the poor correlation between hypertension, and vascular and glomerular lesion. This is in part due to these lesions being present to a greater or lesser degree in the normotensive, aging kidney, with racial differences in severity further confounding the problem. Recent experimental and clinical data suggest that functional impairment and vasoconstriction in afferent arterioles (renal autoregulation) precede morphologic lesions. Progression of the endothelial dysfunction and consequent alterations in autoregulation of renal blood flow at higher pressures enable to dilate afferent arterioles transferring elevated BP to the glomeruli. The latter mechanism finally leads to glomerulosclerosis. Histological changes in the arterioles (stiffness) are present as intimal thickening, afferent arteriolar hyalinosis and smooth muscle atrophy. Loss of renal autoregulation with glomerular hypertrophy, hyperfiltration, and focal segmental glomerulosclerosis is now recognized to contribute significantly to nephrosclerosis, particularly in the black population. However, ischemic glomerulosclerosis may ultimately be the most important lesion, with consequent hypoxia in the parenchyma leading to tubular atrophy and interstitial fibrosis. Pathomorphological changes contribute variably to renal failure according to the level of hypertension (Freedman et al., 1995; Hill, 2008)

Recent studies provided convincing evidence that overactivation of RAAS, or part of it, may play a key role in functional and morphological abnormalities found in hypertensive nephrosclerosis (Volpe et al., 2002). In line with this statement, interventional studies showed that ACE inhibitors, AT_1 receptor blockers (ARBs) and direct renin inhibitors such aliskiren may slow down or stop progression of chronic kidney disease (Momback & Toto, 2009; Riccioni, 2011).

Hypertensive nephropathy often results in chronic renal failure, which mostly occurs unnoticed and without clinical symptoms. It has been shown that even a minimal reduction

of renal function could be regarded as an independent risk factor for cardiovascular mortality and morbidity (Ruilope & Bakris, 2011; Segura et al., 2004). Hypertensive nephropathy can be detected by means of early signs such as the occurrence of mild albuminuria and reduced glomerular filtration rate, both of which are easily measured parameters. Albuminuria can be traced to functional and morphological transformational processes in the glomeruli that are associated with increased permeability (Hill, 2008). A recent study demonstrated that increasing albuminuria is associated with an exponential increase in the risk of developing chronic renal failure and cardiovascular complications (Levey et al., 2009).

Rigorous, mostly multidrug antihypertensive therapy can prevent the progression of chronic renal failure and albuminuria/proteinuria and thereby improve both, renal and cardiovascular prognosis (Ruilope & Bakris, 2011). Hence, treatment with ARB (losartan) as shown in the LIFE study reduction of albuminuria in hypertensive patients with left ventricular (LV) hypertrophy is associated with fewer cardiovascular complications (Ibsen et al., 2005).

3.4 Hypertensive heart disease

The heart in EH is affected very often and sometimes very early. LV hypertrophy, diastolic dysfunction and reduced coronary vasodilation reserve are direct manifestations of cardiovascular target organ damage in patients with arterial hypertension and signify hypertensive heart disease. Coronary artery disease, afflicted by atherosclerotic processes is another indirect consequence of hypertension. All these pathophysiological conditions are interrelated and may end in myocardial infarction, heart failure and arrhythmia (Schmieder, 2010).

3.4.1 Abnormalities in left ventricular diastolic function

The term diastolic dysfunction is used to describe abnormalities of ventricular filling, including decreased diastolic distensibility and impaired relaxation. LV is not able to accept adequate blood volume without compensatory increase of the filling pressure (Zile & Brutsaert, 2002). Diastolic dysfunction is thought to represent an important pathophysiological intermediate between hypertension and heart failure, especially in heart failure with normal ejection fraction (Sanderson, 2007). Up to 50% of patients with history of hypertension have evidence of diastolic dysfunction, which represents an attractive target for heart failure prevention (Fischer et al., 2003). However, to date no specific treatments have been definitively shown to improve diastolic function and clinical outcome (Solomon et al., 2007).

Diastolic dysfunction is considered the earliest functional change in evolving hypertension and could be measured before morphological abnormalities (hypertrophy) ensue. We reported that LV filling abnormalities were detected in normotensive offspring of hypertensive families suggesting that diastolic dysfunction is affected by factors other than BP (Žižek et al., 2008). Diastolic filling abnormalities in hypertensive heart disease result from a delayed LV relaxation and in the later stages from a reduced LV compliance due to increased myocardial fibrosis (Zile & Brutsaert, 2002). Systemic/local RAAS or parts of it and ET-1 have been reported as factors influencing fibrosis (Böhm et al., 2011; Hart et al.,

2001). The mechanisms involved in delayed relaxation are not completely understood, but altered myocardial metabolism of energy-rich phosphates has been proposed (Lamb et al., 1999). In hypertensive patients decreased concentration of ATP and increased concentration of other phosphates leading to disturbances in Ca^{++} homeostasis have been reported (Lamb et al., 1999). Decreased levels of Ca^{++} in sarcoplasmic reticulum not only impair LV systolic function but also delay relaxation, which may ultimately end in abnormalities in LV filling properties and heart failure (Piacentino et al., 2003).

Recent experimental studies have firmly established that NO released from coronary endothelial cells and from myocytes exerts several specific effects on myocardial function, analogous to endothelial regulation of vascular wall function (Paulus & Shah, 1999). In particular, these include selective enhancements of myocardial relaxation (Cotton et al., 2001) and reduction in myocardial oxygen consumption (Xie et al., 1996). Several other paracrine and autocrine effects of NO on myocardial function have been described, e.g. modulating inotropic state (Cotton et al., 2001), modulating sarcolemmal Ca^{++} homeostasis (Piacentino et al., 2003) and inhibiting growth-promoting effects of norepinephrine in myocites and fibroblasts (Calderone et al., 1998; Ruetten et al., 2005).

Echocardiography is now the most commonly used noninvasive tool for assessment of cardiac function. Detailed information can be obtained by standard pulsed Doppler echocardiography and from recent developed tissue Doppler-, strain rate- and speckle tracking imaging (Wang & Nagueh, 2009).

3.4.2 Left ventricular hypertrophy

An increase in peripheral vascular resistance is the hallmark of established hypertension. Following sustained hypertension the heart develops concentric hypertrophy that is characterized by thickening of LV walls. Hypertrophic process is initially adaptive and enables the heart to neutralize wall stress associated with increased impedance to ventricular emptying (afterload) (Grossman, 1980). Moreover, this thickening process is accompanied by a series of maladaptive changes that occur in the extracellular matrix as well as in cardiac myocytes. The presence of LV hypertrophy is clinically important because it is associated with an increased incidence of myocardial infarction, heart failure, ventricular arrhythmias and sudden cardiac death (Muiesan et al., 1996).

Pathogenetic mechanisms leading to LV hypertrophy and dysfunction in EH are not completely understood. It seems that they are results of various interrelated hemodynamic and non-hemodynamic factors. Sometimes hypertrophy can be detected in the prehypertensive period of evolving hypertension implying that a genetic background could also play a role (Žižek & Poredoš, 2008). One fundamental component of cardiomyocyte response to pressure overload of the LV is a slowing of maximum shortening velocity (V_{max}). Diminution of V_{max} is beneficial at the cardiomyocyte level, allowing the cardiac fiber to contract at a normal energy cost. However, at the LV level the diminution of V_{max} is the first step that will finally lead to heart failure (Swynghedauw et al., 2010). Another component of the response of the myocyte to pressure overload includes increased cell size, caused by multiplication of contractile units and, according to the law of Laplace this will normalize wall stress and preserve LV chamber function (Frohlich et al., 2011). An additional component of the cardiomyocyte response involves a shift in substrate oxidation

from fatty acids (FAs) toward carbohydrates (Akki & Seymour, 2008). Although in terms of oxygen cost, the oxidation of glucose is more efficient than that of FAs, in absolute terms the oxidation of one molecule FAs yields far more ATP than glucose. Accordingly, the hypertrophied heart is an energy-compromised organ with a diminished ATP production. On the other hand, a sustained decline in FAs oxidation may cause inappropriate accumulation of lipids in the hypertrophied cardiomyocyte resulting in contractile dysfunction (Neubauer, 2007).

The re-expression of the cardiomyocyte fetal gene program is essential for the abovementioned pathophysiological responses to sustained hypertension (Barry et al., 2008). Activation of the fetal gene program allows coordinated synthesis of proteins necessary to bring about increased cardiomyocyte size and adjustment to the altered energy demands of these larger cells. Recent studies have revealed that in conditions of pressure overload both neurohumoral factors and physical stretch stimulate protein G and phospholipase C leading to activation of several signaling molecules including Ca^{++}-dependent proteins (i.e., Ca^{++}/calmodulin and calcineurin), protein kinases (i.e., protein kinase C and mitogen-activated protein kinases ERK, JNK and p38), and intracrine growth factors (i.e., angiotensin II) that result in altered gene expression associated with pathological cardiomyocyte hypertrophy (Baker et al., 2004; Dorn & Force, 2005).

Systemic/local RAAS is an important pathogenetic mechanism in development of hypertensive heart disease (Agabiti-Rosei & Muiesan, 2001, Schunkert et al., 1997). Experimental studies on hypertensive rat hearts and cell culture media confirm cardiotropic effects of angiotensin-II (Brilla et al., 1994). The angiotensin II has direct influences on various pathophysiological abnormalities in intracellular Ca^{++} handling, metabolism of contractile proteins and myocardial remodeling (Agabiti-Rosei & Muiesan, 2001). Studies performed during the last two decades have provided evidence that complex changes in myocardial composition are responsible for the morphological remodeling of the myocardium in hypertensive heart disease beyond cardiomyocyte hypertrophy (Frohlich et al., 2011). Exaggerated deposition of collagen fibers types I and III promoting interstitial and perivascular fibrosis, which is a well recognized lesion in hypertrophied myocardium (Weber, 2000). The interstitial fibrosis increases myocardial stiffness, thus facilitating LV diastolic dysfunction and diastolic heart failure (Neubauer, 2007). Mounting evidence shows that fibrosis may be a reparative response of fibroblasts induced by pro-inflammatory and pro-fibrotic factors, such as aldosterone (Böhm et al., 2011; Young, 2008). In alignment with the latter statement, epidemiologic studies show that aldosterone is a predictor of future EH and cardiovascular complications (Blacher et al., 1997; Vasan et al., 2004).

Beyond hemodynamic and humoral factors, the genetic background may also influence myocardial composition in hypertensive heart disease. Up to 60% of the variance of LV mass may be due to genetic factors independent of BP. An increasing number of genes have been described, including members of the RAAS system, the type A human natriuretic peptide receptor gene, protein G gene affecting the Na^+/H^+ exchanger, as well as genes related to contractility and function such as the myosin-binding protein C and genes involved in the β-adrenergic system (Deschepper et al., 2002). Among them, the most strongly associated with LV hypertrophy is the polymorphism of genes that encode components of the RAAS system (Kuznetsova et al., 2004). These non-hemodynamic factors may be involved in the development of inappropriate LV mass, which is defined as the growth of the LV exceeding

the individual needs to compensate hemodynamic load imposed by increased BP (Agabiti-Rosei & Muiesan, 2001). Moreover, increased LV mass may be associated with cardiac dysfunction and adverse cardiovascular prognosis (Muiesan et al., 1996).

Echocardiography is the gold standard test for LV hypertrophy. It can precisely estimate a patient's left ventricular mass and assess for other morphological cardiac abnormalities. Electrocardiography is more commonly used in everyday practice; it is more cost-effective and has high specificity, but lower sensitivity (Schmieder, 2010).

In recent years, many papers dealing with antihypertensive therapy have been published. Treatment of hypertension accompanied with LV hypertrophy has shown that each and every class of available antihypertensive drugs could diminish LV mass but with different efficacy. ACE inhibitors and ARBs seem to be superior to other classes of antihypertonic agents (Dahlöf et al., 1992; Oren et al., 1996). Later on the investigators demonstrated that reduction of the LV mass is associated with reduced cardiovascular risk (Verdecchia et al., 2003) and that observed clinical benefit with ACE inhibitors and ARBs tended to be greater than that expected from a decrease in BP. These potential effects "beyond BP control" are perhaps responsible for the protective properties of these drugs interfering with RAAS system-mediated myocardial remodeling (Devereux et al., 2004). However, data from the large ONTARGET/TRASCEND study has shown that treatment with an ARB (telmisartan) alone or in combination with an ACE inhibitor (ramipril) was associated with a lower prevalence of LV hypertrophy, but this was ultimately not translated into a prognostic benefit (Verdecchia et al., 2009). Whatever the causes of these unsatisfactory results, the unacceptably high residual risk still persisted in treated hypertensive patients in whom LV mass decreased with the treatment (Zanchetti, 2009).

Increasing evidence suggests that aldosterone receptor blockade (spirinolactone, eplerenone) may prevent myocardial fibrosis in patients with hypertensive heart disease independent of its effects on BP (Böhm et al., 2011; Jansen et al., 2009). In patients with EH, addition of low-dose spirinolactone to an ACE inhibitor (enalapril/trandolapril) or ARB (candesartan) resulted in a greater decrease in LV mass and fibrosis than any of these drugs alone (Sato et al., 2002; Taniguchi et al., 2006). The failure of ACE inhibition to achieve regression of LV hypertrophy might in part be caused by the phenomenon of aldosterone escape, which means the inability of ACE inhibitor therapy to reliably suppress aldosterone release (Sato & Saruta, 2001).

3.4.3 Reduced coronary reserve

Reduced coronary vasodilation reserve is a typical complication in patients with established hypertension and may be presented in the absence of angiographically demonstrable atherosclerotic disease (Antony et al., 1993). Reduced coronary microcirculatory reserve could be even detected in hypertensive patients without LV hypertrophy (Brush et al., 1988). Authors have reported that functional and morphological abnormalities in microcirculation may appear very early in evolving EH. Functional (endothelial dysfunction) changes could be the first event, with morphological changes of vessels ensuing later on (Schiffrin, 1992). Functional abnormalities of the vessels are evidenced by blunted response to pharmacological and physiological stimuli (Drexler & Zeiher, 1991). An interrelationship between endothelial dysfunction and microvascular angina (syndrome X) has been

proposed. This clinical setting is characterized by angina-like pain and abnormal exercise electrocardiography changes in the presence of a normal coronary angiogram (Scheler et al., 1994). The role of endothelial dysfunction in this setting is controversial. It has been shown that patients with microvascular angina have endothelial dysfunction in the resistance vessels, possibly as result of diminished formation of NO. However, other studies on coronary arteries in patients with syndrome X were unable to find signs of endothelial dysfunction (Bøtker & Ingerslev, 2000).

Morphological changes in small arteries in hypertrophied LV and unbalance between increased LV mass and blood supply are the another pathophysiological mechanisms underlying a reduced coronary reserve in small arteries (Agabiti-Rosei & Muiesan, 2001). It has been suggested that morphological abnormalities (such as increased media/lumen ratio due to hypertrophy and/or hyperplasia of myocites in the vessel wall, and the rarefaction of blood vessels in the myocardium) represent adaptations to an increased hemodynamic load imposed by increased BP (Kozakova et al., 1997).

Some controversy in the literature exists whether endothelial dysfunction in small resistance vessels could be influenced by drugs. In experimental animal models, improvement or even normalization by ACE inhibitor (captopril) and ARB (losartan) were reported (Rodrigo et al., 1997). In human studies, improvement was only noticed after a single application of captopril (Hirooka et al., 1992). Conversely, months of therapy with ACE inhibitors and ARBs resulted in only a slight or no effect on endothelial function in resistance arteries (Ghiadoni et al., 2000; Kiowski et al., 1996).

4. Conclusions

The results of recent studies emphasize the key role of endothelial function in the pathogenesis of essential hypertension. In accordance with the microcirculation theory, functional and morphological changes in small resistance vessels are thought to be the cause and consequence of hypertensive disease. This condition is predisposed by abnormal endothelial cell function, which is characterized by decreased production of nitric oxide and unbalanced production of other vasoactive substances (angiotensin II, endothelin-1, prostacyclin, and aldosterone) and reactive oxygen species. The target organ damage in conduit arteries (atherosclerosis), kidney (nephrosclerosis) and heart (diastolic dysfunction, left ventricular hypertrophy, reduction of coronary reserve) are the consequence of elevated blood pressure. There is currently no effective treatment known for hypertension. It is important to treat hypertension in the early stages, when preventive measures and antihypertensive therapy (preferably angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) are most effective. Nowadays, non-invasive ultrasound based methods can detect abnormalities in different organs, which predict the unfavorable course of hypertensive disease resulting in a worse cardiovascular prognosis.

5. References

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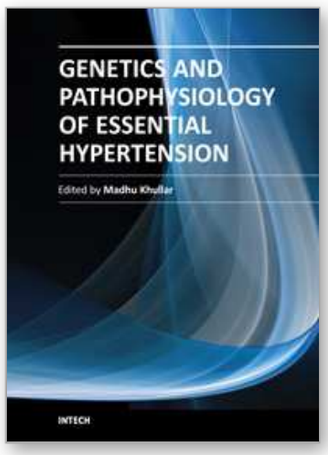

Genetics and Pathophysiology of Essential Hypertension

Edited by Prof. Madhu Khullar

ISBN 978-953-51-0282-3
Hard cover, 236 pages
Publisher InTech
Published online 09, March, 2012
Published in print edition March, 2012

This book, authored by renowned researchers in the field of Hypertension Research, details the state of the art knowledge in genetics, genomics and pathophysiology of Essential hypertension, specifically the genetic determinants of hypertension and role of gene variants in response to anti-hypertensive therapy. Two chapters describe mitochondrial mutations in Essential hypertension and in hypertension associated Left ventricular hypertrophy, one chapter reviews in detail the global gene expression in hypertension, and an up to date treatise on pathophysiology of resistant hypertension is detailed in another chapter. Other topics included in the book are end organ damage, baroreceptor sensitivity and role of music therapy in essential hypertension.

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