

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Role Erectile Dysfunction Plays in Cardiovascular Diseases

Sandra Crestani^{1,2}, Kenia Pedrosa Nunes², Maria Consuelo Andrade Marques¹, José Eduardo Da Silva Santos³ and R. Clinton Webb²

¹*Federal University of Parana*

²*Georgia Health Sciences University, Augusta, Georgia*

³*Federal University of Santa Catarina*

^{1,3}*Brazil*

²*USA*

1. Introduction

Erectile dysfunction (ED) is defined as the persistent inability to maintain or achieve a penile erection sufficient for satisfactory sexual performance (1-2). ED is a very common condition in middle-aged men (3). According to the National Institute of Health (NIH) this physiological disorder affects 30 million men in the United States (US) (2). The outlook for 2025 is scary because this number is expected to grow to approximately 322 million (4). Although ED is directly associated with aging (5), its etiology is considered multifactorial. Both conditions, ED and aging, share a variety of risk factors such as atherosclerosis, sedentary lifestyle, abnormal lipids, diabetes, smoking, metabolic syndrome and hypertension (2, 6-7). In addition, ED is considered an important marker of cardiovascular disease (CVD) (8). Studies over the last decade suggest vascular changes as a common factor between ED and CVD (1, 7, 9). Also, the most important vascular alteration mentioned in these pathologies cited above is endothelial dysfunction. According to several authors, endothelial and smooth muscle dysfunction are crucial factors involved in systemic and peripheral vascular diseases, especially ED (10). In this chapter we will discuss the association between the main CVD and ED.

2. ED and atherosclerosis

Atherosclerosis begins with oxidation of Low Density Lipoproteins (LDL) particles in the arterial wall (11). Oxidatively modified LDL (oxLDL) damages the endothelial layer in the artery (8, 11), and then the elasticity of the arteries deteriorates. Impaired arterial elasticity and increased levels of circulating oxLDL, as well as elevated fibrinogen and resting heart rate associated with subclinical atherosclerosis have increased CVD risk (12-17). The decrease and/or loss of elasticity impair the blood flow because the cholesterol builds up in the blood vessel walls and forms plaque. When plaque becomes very advanced, it can completely stop blood from passing through the wall, characterizing a heart attack (18).

Diseases due to atherosclerosis are common and are becoming a growing health problem in industrialized and developing countries, evoking a huge impact on quality of life and life expectancy (2, 19). Atherosclerosis affects not only the blood vessels supplying the heart (coronary arteries), but also blood vessels throughout the entire body. In addition, various alterations disturbing normal body function can occur when atherosclerosis develops leading to more complex pathologies such as angina, heart attacks, strokes, and ED (18).

The artery size hypothesis is a pathophysiologic mechanism proposed in recent years to explain the relationship between ED and coronary artery diseases (CAD) (20). It is based on the fact that atherosclerosis, a systemic disorder, should theoretically affect all major vascular beds at the same time and extent. However, symptoms at different points in the system rarely become evident at the same time. This is probably the result of larger vessels being able to better tolerate equivalent amount of plaque compared with smaller ones. The diameter of these vessels confirms this idea: penile artery has an arterial diameter of 1-2 millimeters (mm), coronary artery is 3-4 mm, internal carotid artery is 5-7 mm and femoral artery is 6-8 mm. Results from patients with 50% obstruction in the penile artery with no coronary circulation critically affected could be explained because larger systemic arteries would be impacted later than the smaller penile artery. Thus, it suggests a mechanism for the absence of concomitant CAD in early stage ED (20-21).

The initial step in the development of atherosclerosis is endothelial dysfunction. Since the normal penile erection requires an intact endothelium, it has been proposed that patients with ED show a higher probability of developing atherosclerosis (2, 19). Regarding penile erection, nitric oxide (NO) plays an important role in physiological conditions. The sexual stimulus makes the parasympathetic nerves in the penis produce NO, triggering a cascade of events that culminate with increased dilatation of the corpora cavernosum sinusoids to induce penile erection. Many other agents are involved in this process that requires a perfect balance between vasodilators and vasoconstrictors. Thus, the physiological complexity makes it difficult to identify the etiology of ED. As a result, this condition is considered multifactorial and includes arterial, neurogenic, hormonal, cavernosal, iatrogenic, and psychogenic causes. However, it is now accepted that organic ED, in a substantial majority of men, is due to underlying vascular causes (22-23). Endothelial dysfunction is thought to be the main etiologic factor in systemic and peripheral vascular diseases, including ED (24). It has been associated with impaired vasodilatation, preceding the development of atherosclerotic lesions through the impaired release of NO, which is modulated by parasympathetic nonadrenergic, noncholinergic nerves (NANC) and by vascular endothelial cells (7). Moreover NO production is also influenced by oxidative stress, which is deleterious to the endothelium.

Reactive oxygen species (ROS) are very important in the pathophysiology of vascular disease, especially atherosclerosis. Under normal physiological conditions, ROS destruction by antioxidant enzymes is sufficient to maintain a controlled activation of signaling cascades. In contrast, in vascular diseases, the production of ROS in excess of endogenous antioxidant capacity leads to oxidative stress, which in turn results in abnormal physiological responses. Interaction between ROS and NO is implicated in many vascular diseases such as atherogenesis and play an important role in ED (25). One of the most detrimental ROS is superoxide (O_2^-), which interacts with NO decreasing NO bioavailability and resulting in formation of peroxynitrite ($ONOO^-$). All types of vascular cells produce O_2^-

and H_2O_2 , two of the most significant ROS in the vessel wall. H_2O_2 can also be metabolized by myeloperoxidase, a heme enzyme produced by macrophages that converts H_2O_2 into reactive nitrogen and reactive chlorine. These reactive species can attack both LDL and HDL, enhancing cholesterol intake, reducing cholesterol efflux and contributing to plaque formation (26). In pathological situations homeostasis disruption by oxidative stress contributes to activation of proinflammatory, profibrotic and mitogenic signaling pathways leading to oxidative damage in the vasculature which in turn results in increased vasoreactivity, endothelial dysfunction, vascular remodeling, reduced vascular compliance and elevated blood pressure (BP)(26-28). All these factors also contribute to an increased adhesion and aggregation of platelets and neutrophils, and release of vasoconstrictor substances (29-30).

3. Stroke and ED

Stroke is a neuroendovascular event resulting in death of brain cells due to an ischemic lesion. According to the World Health Organization (WHO), stroke can be classified based on the size and site of lesion and its clinical consequences. Most cases of subarachnoid hemorrhage, intracranial hemorrhage and cerebral infarction are examples of stroke (31-33). Cerebrovascular diseases are the third leading cause of death in the United States, affecting 5.5 million people a year. When analyzing diseases that cause long-term consequences, the frequency of stroke is largest compared with others (34). Stroke has been responsible for 50 million deaths worldwide. In adults, cerebrovascular disease is the most frequent pathology that induces severe damage (35). It is predicted that over the next 20 years, stroke will rise from 7th in the DALY league table to 4th, principally influenced by the aging of populations especially in less economically developed countries (31, 36).

It has been hypothesized that ED represents “the tip of the iceberg” of a systemic vascular disorder. Thus, ED would potentially precede larger damage in the body, working as a sentinel event (5). Additionally, ED could be an indicator of potentially life-threatening coronary heart disease (CHD), hypertension, hyperlipidemia and stroke (37-42), which are diseases that have been the cause of morbidity and mortality among adults in industrialized societies (43).

In most studies about stroke, only the cognitive and emotional ability of the patient after the stroke has been discussed. (34). However, the sexual function of these men has recently been investigated deeper. Since 1998 Koperlainen et al, showed that stroke patients and their wives have some level of dissatisfaction with sexual function (44). Also, ED in stroke patients has been linked with psychological causes (45). In this case, it has been speculated that impairment of cerebral erectile control functions, physical limitations after the stroke, and emotional changes, generate psychogenic and neurogenic ED (34, 46). Studies compared unilateral stroke patients compared with those showing stroke lesions in the right cerebral hemisphere. The results reported that both patients experienced ejaculation disorders besides a significant decrease in sexual desire and intercourse frequency (34, 47).

Until recently, it was believed that ED was a health problem in patients after stroke. However, increasing evidence supports an idea that men with ED have more comorbidities than men who do not. More importantly, men with ED were more likely to have strokes than those without. In the others words, ED has been cited as a strong indicator of stroke, as well as a clinical marker for cerebrovascular diseases (22, 48-49). Ponholzer et al, reported

that 2,561 men with moderate to severe ED had an increased risk of stroke over 10 years (24.7% and 43.6%) (50). Furthermore, it has been suggested that ED is an independent risk factor for stroke. In this study, 1,209 men from the Massachusetts Male Aging Study were evaluated over a 15 year period and it was reported that those men who have had ED were approximately three times more likely to have a stroke if compared to those without ED (5).

The penile arteries have a smaller diameter than internal carotid, coronary and others major arteries. Thus lumen obstruction may lead to the development of ED prior to cardiac signs or stroke (22). Corroborating with this idea Lojanapiwat et al performed studies showing that patients who developed ED had endothelial dysfunction prior to the clinical symptoms. Also laboratory results for this patients indicated cardiovascular risks (51). In addition, Vincenzini et al suggested that cerebrovascular reactivity was reduced in patients with ED without other signs of clinical atherosclerosis (52). Finally Chung et al, suggested that men with ED have a significant increased risk for stroke 5 years after ED symptoms first began (22).

4. Hypertension and ED

Arterial hypertension is a systemic disorder characterized by altered regulation of cardiovascular hemodynamic, including arterial vascular resistance and cardiac index, leading to an increase in arterial blood pressure (53). It is accompanied by proliferation, migration of VSMCs, and varying levels of inflammation of the arterial wall, processes that together constitute vascular remodeling (54). Hypertension is associated with increased vasoconstrictor and reduced vasodilator responses (55-57). The pathological changes resulting from altered vascular function include injury to the brain, kidney and heart (55). Several studies have established a clinical correlation between incidence of hypertension and ED (58). According to Buccchardt et al, 30% of hypertensive patients have ED and the severity of this sexual disorder is directly proportional to the severity of hypertension. Nowadays, this fact has been well accepted because both pathologies are an unbalance between endogenous contractile and relaxing substances. In addition, since both are pathological vascular disorders, it is supposed that ED in hypertensive patients is highly prevalent and more severe than in the other people (3).

Deficiency of NO has been hypothesized to be a major cause of ED in patients with hypertension. Another substance that is important in hypertension and ED is endothelin (ET-1). ET-1 is considered a physiological antagonist of NO. ET-1 induces vasoconstriction and activates transcriptional factors that coordinate an increase of cytokines and enzymes, thus enhancing inflammation, oxidative stress and tissue damage. All these factors are very important in hypertension associated vascular dysfunction (59). Several studies have underlined the potential importance of ET-1 in the modulation of corpus cavernosum (CC) smooth muscle tone (60), since these cells can synthesize ET-1. The fetal human and adult penile cells, and several animal species, also express endothelin converting enzyme 1, the endothelin receptors A (ETA) and B (ETB) subtypes (61-63). Furthermore, Melegy et al showed that ET-1 levels were significantly greater in patients with ED than the normal group (64).

Even though NO is well known as the major vasodilator involved in ED, other mediators are also involved. Activation of B1 or B2 kinin receptors by bradykinin (BK) induce NO and/or prostacyclin release from endothelial cells (65-66). Teixeira et al reported the

existence of functional B2 kinin receptors in human erectile tissues and demonstrated that activation of it resulted in NO release. These findings were supported by results from Becker et al. They demonstrated that BK is able to promote relaxation in CC. This effect appear to involve more cAMP than cGMP (67). However, both cGMP and cAMP are associated with relaxation in systemic or penile vessel circulation.

O-GlcNAcylation is an important regulatory mechanism that also modulates stress responses in the cardiovascular system and may have significant influence on vascular blood pressure (68). Glucosamine (GlcN) is an amino sugar that can stimulate O-linked-N-acetylglucosamine (O-GlcNAc) modification of proteins by increasing flux through the hexosamine biosynthesis pathway, thus increasing production of UDP-GlcNAc. UDP-GlcNAc is a substrate for O-GlcNAc transferase (OGT), which catalyzes the O-linked addition of GlcNAc to serine and threonine residues of nucleocytoplasmic proteins in higher eukaryotes (68). GlcN has anti-inflammatory effects in a variety of inflammatory models and cell types. Recently, it has been demonstrated that systemic treatment with glucosamine and PUGNAc, which increases O-GlcNAc modification of proteins by inhibiting O-GlcNAcase, can inhibit acute inflammatory and neointimal responses to endoluminal arterial injury in rat's carotid artery (69). ET-1-induced changes in vascular contractile responses are mediated by O-GlcNAc modification of proteins. Aortas from Doca-salt rats, which exhibit ET-1 augment, displayed increased contractions to phenylephrine and enhanced levels of O-GlcNAc proteins. Treatment of Doca-salt rats with an endothelin A antagonist abrogated augmented vascular levels of O-GlcNAc and prevented the increase in phenylephrine vasoconstriction, suggesting that ET-1 indeed augments O-GlcNAc levels and this modification contributes to the vascular changes induced by this peptide (70). On the other hand, O-GlcNAcylation is also involved in ED. A new line of investigation has pointed to the significance of hyperglycemia-induced O-GlcNAc associated with modification of eNOS, as well as inactivation of the enzyme. It has been demonstrated that O-GlcNAc inactivates eNOS in diabetes-associated ED (71). However, the exact mechanism through O-GlcNAcylation is correlated with hypertension or ED is still not well understood. In the last decade, another mechanism involved in the regulation of ED has been the renin-angiotensin system (RAS). Evidence has shown that there is a RAS inside of the corpus cavernosum. According Becker et al human CC is able to produce and secrete physiologically relevant amounts of angiotensin II (Ang II) (67). Ang II is the main active metabolite of the renin-angiotensin cascade. The most important physiologic effect of Angio II is induction of vascular smooth muscle contraction. This action contributes to the maintenance of systemic blood pressure through various mechanisms in the cardiovascular and renal systems. Ang II is also an important modulator of erectile function (72). Reinforcing the association of RAS and ED, angiotensin-converting enzyme (ACE) has been found in the endothelial cells of dog CC (73), and ACE mRNA expression is up-regulated in a rat model of arteriogenic ED, although it is expressed at very low levels in the penis of control rats (74).

Arginase pathway has been cited as another mechanism that may be involved in both, hypertension and ED. Growing evidence suggests that arginase misregulation plays a key role in the pathophysiology of essential hypertension and that the involvement of arginase in ED has been apparent in recent years. Arginase exists in two isoforms, the hepatic type, arginase I and the extrahepatic type, arginase II (75). Both isoforms are expressed in human CC tissue (76). Surprisingly, the role of arginase in hypertension is poorly documented. Augmented arginase activity (AA)/expression were reported in different vascular beds in

models of essential or secondary hypertension (77-78). Recent studies reported that arginase inhibitor improved aortic endothelial function via a NO-dependent mechanism in pre-hypertensive or young adult SHR, and also prevented the development of hypertension (79-80).

During hypertension or ED, elevated levels of arginase can compete with NOS for available L-arginine, reducing NO and increasing superoxide production via NOS uncoupling (81). Considering this, arginase pathway can regulate overall NO production. Additionally, elevated superoxide combines with NO to form peroxynitrite further reducing NO, and also oxidative species increase arginase activity (82). ED mechanisms involve oxidative stress and vascular inflammation (83), both of which have been associated with enhanced arginase activity and expression in the vasculature (84). Furthermore, up-regulated arginase is mechanistically linked to the pathogenesis of vascular dysfunction with hypertension through increases in the polyamine and proline precursor L-ornithine, which contributes to VSM cell proliferation and intimal thickening (81, 85). There is evidence of a biological role of arginase in regulating erectile function in the aged penile vascular bed, at both the molecular and functional level (83). Also, endothelial arginase II has been proposed as a novel target for the treatment of atherosclerosis (80). Taking into account that in pathological conditions arginase can influence NO availability and consequently disrupt the perfect balance necessary to keep the VSM tone, arginase can be considered involved in both hypertension and ED. However, a more complete understanding about the exact mechanism leading to disruption of vascular dynamics by arginase in ED and hypertension is needed.

Regarding hypertension and ED, another important factor is the unwanted side effects from anti-hypertensive drugs. The treatment for hypertension can be associated with ED because some medicines affect erectile function, for example, diuretics. Several studies suggest that about 10% to 20% of patients taking thiazide can have ED (86), as well as patients that use an aldosterone antagonist (87). Fortunately, the effect of diuretics on ED is completely reversible after cessation of administration. β -adrenergic receptor blockers have also been suggested by several studies to be associated with ED, specially propranolol (88). However, the new generation of β -blockers appears to have less effect on erectile function, such as nebivolol. This drug enhances erectile response and reverses ED in diabetic rats, as well as potentiates NO/cGMP-mediated relaxation of human penile tissues (89). Interestingly, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) appear to favorably affect sexual function (90). Patients treated with captopril showed improved sexual function by 40% to 80% compared to non-treated patients (91). The same has been observed for hypertensive patients treated with valsartan; reduced ED and improved orgasmic function and sexual satisfaction (92). Also, it was found that losartan helps preserve erectile function in male rats after bilateral cavernous nerve injury by counter-acting fibrotic activator factors (93). However, recent study showed no change in ED progression in humans with ACEI or angiotensin-receptor blocker (ARB) therapy (94).

Regarding the α -adrenoceptor agents to treat hypertension, has been showed that direct cavernosal injection of α 1-antagonists cause erection in both, experimental and humans, although this effect is not observed with α 2-selective drugs. Notably, it has been observed that patients treated with α 1-blockers of the adrenergic receptors exhibited improvement of their sexual activity. On the other hand, especial attention is necessary for hypertensive patients treated with vasodilators such as α -blockers because if those patients have ED, they should not take PDE5 inhibitors, otherwise, combining these drugs will result in

hypotension. The treatment with calcium channel blockers, which dilate arteries by reducing calcium influx into cells also effectively lower blood pressure. The currently available ones inhibit L -type channels in humans and seem to have a neutral effect on erection (95). Possibly this is because this channel is linked with nNOS activation from cholinergic nerve endings into the penis, which is important for NO release and consequently erection. However, although this channel is inhibited, nNOS from nitrergic nerves will be activated, allowing the erectile process to begin. Finally, direct vasodilators such as hydralazine and minoxidil have rarely been reported to cause ED.

5. Heart failure and ED

Heart failure (HF) is a syndrome manifesting as the inability of the heart to fill with or eject blood due to structural or functional cardiac conditions (96). Some authors believe that HF can be considered as the last stage of heart disease and a significant cause of mortality and morbidity worldwide (97). According to the American Heart Association (AHA), HF is a condition that affects nearly 5.7 million Americans of all ages (98). Nevertheless, in the last decade improvement in survival of myocardial infarction and HF has been observed, concurrent with consequences from these diseases. It is believed that the prevalence of these diseases will continue to increase in the population, with an estimated number of more than 10 million patients by the year 2037. Coronary artery disease, with or without myocardial infarctions, with a subsequent development of ischemic cardiomyopathy or loss of contractile proteins, remains the major cause of chronic HF progression, especially among the elderly population (99). Looking at chronic heart failure (CHF) the numbers are equally alarming. The AHA has estimated more than 4.9 million people in the US have CHF (98). As this pathophysiology progresses, patients experience an increase in fatigue, shortness of breath, palpitations, or angina, decreasing their quality of life and potentially interfering with their sexual performance (90).

While HF per se can have many effects on a patient's lifestyle, ED can further aggravate these effects and contribute to poor quality of life and depression. Studies showed the prevalence of ED is around 67% in men 65 or older, and 68% in men older than 79 (100). The prevalence of ED in patients with HF appears to be significantly higher. Baraghoush et al, found a prevalence of 84% general sexual dysfunction in the male population with an average of 59 years of age and chronic compensated HF (99, 101).

It is common sense that the physiology behind an erection is a primarily vascular phenomenon. In patients with HF, several factors that come into play at the microvascular level, such as reduced arterial compliance, endothelial dysfunction, and generalized focal atherosclerosis (99). There are few theories that explain the mechanism of endothelial dysfunction in patients with HF. Impaired relaxation mediated by L-arginine-NO was found in smooth muscle cells (SMC) and in the penis from animals and humans with atherosclerotic coronary arteries (102). However, systemic endothelium-dependent vasodilatation has been shown to decrease ED in men with and without clinical CVD (103). In addition, decreased NO production via downregulation of endothelial NO synthase (eNOS) and cyclooxygenase (COX) was observed after the onset of pacing-induced HF in dogs (104). Rho-kinase signaling is very important in erectile function because in the absence of arousal, the penis remains in the non-erect state by cavernosal vasoconstriction induced mainly by norepinephrine and endothelin 1 (ET-1), which are Rho-kinase mediated responses. Thus, its upregulation leads to

ED (105). Also, this pathway is involved in the regulation of myofibrillar Ca^{+2} sensitivity in cardiac muscle and contributes to irreversible myocardial damage. Rho-kinase is involved also in the pathogenesis of cardiovascular remodeling and its inhibition plays a significant role in treatment of the failing heart by limiting infarct size, which is the major contributor to the development of heart failure. The cardioprotective effect of Rho-kinase inhibition involves PI3K/AKT and NOS activation. However, Rho-kinase inhibitor compounds need to be evaluated for their efficacy during varying index ischemia periods, a wide dose range, and *in vivo* animal models mimicking the clinical setting more closely (105).

Becker et al reported that patients with HF have vasomodulators, systemic levels unbalanced and this change can lead to increased SMC tone and vasoconstriction in the penile vessels through a variety of mechanisms (106). According to Pedersen et al, the ET-1, RhoA/Rho-kinase and ROS are not the only mechanism that can be modified, vasopressin also is elevated in patients with HF (107). Compared to patients with CHF, the situation is very similar. In 2005 Rastogi et al suggested that multiple factors may be involved in the onset of ED in patients with CHF. These patients have arterial compliance abnormalities and often atherosclerosis, which reduce blood flow into the CC (108). In addition, endothelial dysfunction decreased the production or increases the breakdown of NO. Other vasoconstrictors are also increased in patients with CHF and can be interfering with their ability to achieve and maintain an erection (109). Finally, several medicines commonly used to treat HF have been shown to either cause or worsen ED (99). Digoxin for example, is a drug that can cause ED even though the mechanism by which this happen is not really clear, but it has been speculated that this drug creates a sexual hormonal unbalance (110) and the inhibition of cavernosal sodium/potassium-adenosine triphosphate activity, consequently impairing NO relaxation (111).

End Points	No. of Events		
	Total	No ED During Study	ED prior to Cardiovascular event ED after to Cardiovascular event
Angina	297	12	241
Miocardial infarction	571	57	57
Miocardial infarction or angina	801	68	649
Stroke	181	16	157
Congestive Heart failure	33	7	25
Transient ischemic attack	113	7	96
Arrhythmia	193	21	149
First cardiovascular event	1186	113	955
Death due to any cause	457	75	382

Table 1. **Relationship between the first report of ED and subsequent cardiovascular disease.** Incident ED was statistically significant associated with subsequent angina, myocardial infarction and stroke (red circles). Also, number of patients who showed ED prior the cardiovascular event was extremely higher compared to those who shoed ED after cardiovascular event (red circle). Men with incident ED had a significantly increased risk of myocardial infarctation or angina relative to men without a report of ED. Adapted from Thompson et al, 2005 (112).

6. The link between ED and CVD

An emerging basic science and clinical database provides a strong argument for endothelial and smooth muscle dysfunction as a central etiologic factor in systemic and peripheral diseases, including ED (113). The endothelium is the single layer of cells that line the luminal surface of blood vessels. It is far more than just a structural lining; it has a range of important physiological functions. It acts as a direct interface between the components of circulating blood and local tissue, and regulates numerous local blood vessel functions, including vascular tone, cell adhesiveness, coagulation, inflammation and permeability. The endothelium produces and responds to several potent, locally and active mediators. The most important of these is NO, which is a nonadrenergic-noncholinergic (NANC) vasodilator neurotransmitter involved in the regulation of vascular wall function (113). This highly reactive gas presents potent anti-atherogenic properties, in addition to inhibiting platelet aggregation and regulating vascular tone (114). Moreover, in the atherosclerosis installation process there are leucocytes adhesion and inflammatory agents that contribute to plaque instability and rupture, and this event can be inhibited by NO.

The vasodilatation induced by NO is initiated with the synthesis from L-arginine by nitric oxide synthases (NOS) (115). Physiological amounts of NO can be produced by endothelium (eNOS) or neuronal (nNOS) enzymes and both are involved in penile erection. Down regulation of eNOS in pathological conditions results in reduced bioavailability of NO and consequently endothelial dysfunction (8). Inhibition of nNOS attenuated erectile responses (116). Erectile function was also found to be preserved in mice lacking eNOS. However, intracavernosal pressure during erection was significantly decrease in eNOS-deficient mice and over all, NOS activity was only 60% of the activity observed in wild type mice. Thus, physiologic penile erection is mediated by both nNOS and eNOS (7, 117).

NO activates a soluble guanylyl cyclase that forms cyclic guanosine monophosphate (cGMP) (118) in vascular smooth muscle cells, resulting in penile relaxation (8, 23). Reports of ED in cGMP-dependent kinase-I (cGKI)-deficient mice suggest that cGMP is indeed the main second messenger in ED (119). These findings are supported by clinical data showing that phosphodiesterase type 5 inhibitor (PDE5, e.g. sildenafil) prevents the degradation of cGMP (120). In cGKI-deficient mice cAMP-mediated pathway cannot compensate deficient cGMP-dependent signaling *in vivo* (119). However, in humans prostaglandin E1 and its derivative alprostadil, which induce relaxation predominantly via cAMP pathway, were found to be highly effective in the treatment of ED (121-122).

Dysfunction of the endothelium may be interpreted as homeostasis disturbance due to breakdown. Also, endothelial dysfunction can be caused by vascular insults, such as diabetes, smoking, hyperlipidemia and hypertension (123). At the cellular level, endothelial dysfunction outcomes in impaired release of NO, which may be considered a key pathomechanism in both endothelial (124-125) and erectile dysfunction (115, 126). Oxidative stress, which is directly toxic to the endothelium and also interferes with the NO pathway, is a causal factor in clinically evident occlusive CVD and vascular damage associated with preclinical disease. Free radical damage, impaired function and availability of NO can also result in increased adhesion, aggregation of platelets and neutrophils, besides the release of vasoconstrictor substances (29-30, 113). In addition NOS depends on tetrahydrobiopterin as a co-factor. Endothelial dysfunction associated with tetrahydrobiopterin depletion could be

reversed by supplementation of this substance (127-129). Indeed the treatment with tetrahydrobiopterin increased NOS activity by 30% in rabbit CC (130).

Over the past years studies have showed that many men will realize the onset of ED occurs before they are diagnosed with CVD. The anatomic structure of the penis and the physiology of getting and maintaining an erection provide clues as to the reason the penile vascular bed has some unique properties that facilitate early detection of systemic vascular disease (113). Nowadays, it is well known that ED can result from any number of structural or functional abnormalities in the penile vascular bed. For instance, ED may be a consequence of the cavernosal arteries occlusion by atherosclerosis, impairment of endothelial-dependent and/or independent smooth muscle relaxation, or a combination of these two factors. It is believed that ED caused by functional vascular factors occurs early and is likely associated with oxidative stress and decreased NO availability. Initially these factors result in poor relaxation of penile endothelium and in smooth muscle that presents clinically as ED, with difficulty to maintain a firm erection. This early clinical symptom probably occurs before the development of structural, occlusive penile arterial disease and may be among the earliest signs of systemic CVD. Thus, it has been accepted that endothelial dysfunction is the etiologic connection between ED and systemic cardiovascular diseases (9, 30).

Corroborating this idea, Lojanapiwat et al examined 41 ED patients and 30 age-matched normal control, subjects were investigated for cardiovascular risks and endothelial function. Changes in brachial arterial diameter after its occlusion were compared between the groups. Results did not show differences in baseline characteristics for cardiovascular risks and lipid levels. However, a significant difference regarding endothelial dysfunction in ED patients without clinical cardiovascular risks versus control patients was observed. They concluded that patients who developed ED showed endothelial dysfunction and cardiovascular risk markers prior to the clinical symptoms. In addition, a study evaluating systemic vascular structure and function in 30 patients with ED and 27 age-matched normal controls, investigated whether patients with vascular ED and no other clinical CVD have structural and functional abnormalities of other vascular beds. Systemic endothelial function using flow mediated brachial artery vasodilatation showed that men with ED exhibited significantly lower brachial artery flow-mediated, vascular defect in endothelium-dependent and independent vasodilatation, which happen before the development of structural or functional systemic vascular disease, when compared to controls. According to the authors these data suggest the presence of peripheral vascular abnormality in the NO pathway (131). In another study, biochemical markers of endothelial cell activation were used to compare 45 men with ED and no clinical CVD with 25 age-matched healthy. The results showed that the carotid intima-media thickness (IMT) was similar between the groups. However, soluble P-selectin (intracellular adhesion molecule-1) and endothelin-1 levels were significantly higher in men with ED and no CVD (132).

Alterations in the several signalling pathways, mainly in Rho-kinase signaling, are common in ED as well as CDV, contributing to a further increase in endothelial dysfunction. Rho-kinase, is involved in the sequence of events that stimulates vascular smooth muscle contraction, stress fiber formation, cell migration, and, indirectly, blood pressure regulation. In this way, RhoA/Rho-kinase activation has significant effects on various cardiovascular diseases, such as arterial hypertension (133), atherosclerosis (134), heart attack (135), stroke

(136), coronary vasospasm (137), myocardial hypertrophy (138), myocardial ischemia-reperfusion injury (139), vascular remodeling (140) and ED. Since the main function of Rho-kinase is the regulation of smooth muscle tone (141), the upregulation of the Rho-kinase pathway increases cavernosal smooth muscle contraction, leading to ED (142-143). Furthermore, studies indicate that Rho-kinase isoforms are activated in patients with a cardiovascular disorder or associated risk factors (144-145). Also, RhoA mRNA expression and activity is increased in aortas from aged rats, suggesting a role of RhoA in the development of age-related cardiovascular disease (146).

7. Conclusion

Although the link between ED and CVD has been previously documented, convincing evidence of the direction and magnitude of the effect has not been available. However, several studies support the idea that ED precedes overt structural occlusion of larger blood vessels, and ED is often an early manifestation of systemic vascular disease. The evaluation of ED in the medical history as an early symptom of endothelial dysfunction and atherosclerosis may be a predictor of future cardiovascular events, including death. This might be relevant to identifying patients with a particularly high risk of experiencing cardiovascular events even though is not clear yet what kind evaluation or parameters should be prompted in ED condition.

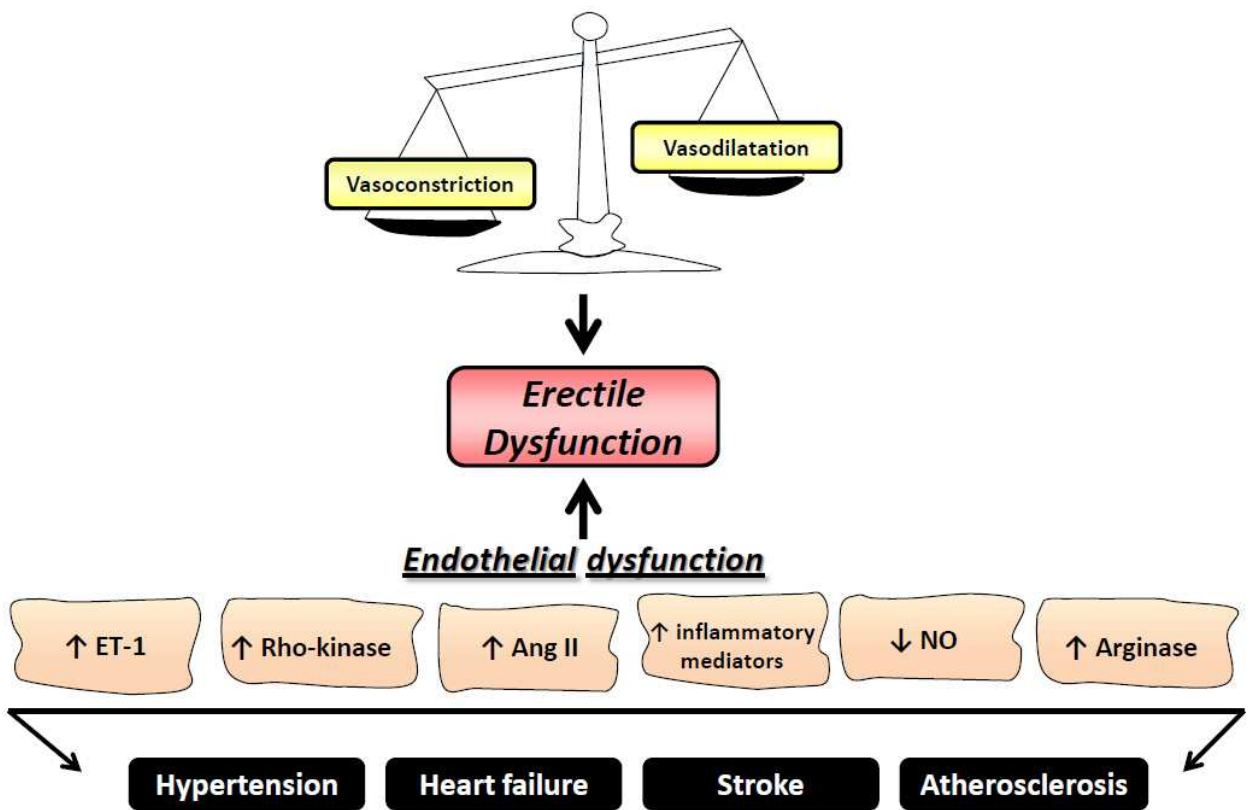


Fig. 1. Endothelial dysfunction is a common situation in both CVD and ED. Generally ED is caused by unbalance between vasoconstrictors (Ang II, ET-1, Rho-kinase, arginase) and vasodilators (NO) endogenous agents. Endothelial dysfunction leads to ED development and later to onset of CVD.

8. References

- [1] Fung MM, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. *J Am Coll Cardiol*. 2004 Apr 21;43(8):1405-11.
- [2] NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA*. 1993 Jul 7;270(1):83-90.
- [3] Burchardt M, Burchardt T, Baer L, Kiss AJ, Pawar RV, Shabsigh A, et al. Hypertension is associated with severe erectile dysfunction. *J Urol*. 2000 Oct;164(4):1188-91.
- [4] Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int*. 1999 Jul;84(1):50-6.
- [5] Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*. 1994 Jan;151(1):54-61.
- [6] Derby CA, Mohr BA, Goldstein I, Feldman HA, Johannes CB, McKinlay JB. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology*. 2000 Aug 1;56(2):302-6.
- [7] Maas R, Schwedhelm E, Albsmeier J, Boger RH. The pathophysiology of erectile dysfunction related to endothelial dysfunction and mediators of vascular function. *Vasc Med*. 2002 Aug;7(3):213-25.
- [8] Kirby M, Jackson G, Simonsen U. Endothelial dysfunction links erectile dysfunction to heart disease. *Int J Clin Pract*. 2005 Feb;59(2):225-9.
- [9] Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart*. 2003 Mar;89(3):251-3.
- [10] Billups KL. Erectile dysfunction as an early sign of cardiovascular disease. *Int J Impot Res*. 2005 Dec;17 Suppl 1:S19-24.
- [11] Stocker R, Keaney JF, Jr. Role of oxidative modifications in atherosclerosis. *Physiol Rev*. 2004 Oct;84(4):1381-478.
- [12] Cohn JN, Finkelstein S, McVeigh G, Morgan D, LeMay L, Robinson J, et al. Noninvasive pulse wave analysis for the early detection of vascular disease. *Hypertension*. 1995 Sep;26(3):503-8.
- [13] Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension*. 2002 Jan;39(1):10-5.
- [14] van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*. 2001 Feb;32(2):454-60.
- [15] Holvoet P, Mertens A, Verhamme P, Bogaerts K, Beyens G, Verhaeghe R, et al. Circulating oxidized LDL is a useful marker for identifying patients with coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2001 May;21(5):844-8.
- [16] Danesh J, Lewington S, Thompson SG, Lowe GD, Collins R, Kostis JB, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA*. 2005 Oct 12;294(14):1799-809.
- [17] Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J*. 2010 Apr;159(4):612-9 e3.

- [18] Schwartz BG, Kloner RA. Cardiology patient page: cardiovascular implications of erectile dysfunction. *Circulation*. 2011 May 31;123(21):e609-11.
- [19] Vlachopoulos C, Aznaouridis K, Ioakeimidis N, Rokkas K, Vasiliadou C, Alexopoulos N, et al. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *Eur Heart J*. 2006 Nov;27(22):2640-8.
- [20] Montorsi P, Montorsi F, Schulman CC. Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder? *Eur Urol*. 2003 Sep;44(3):352-4.
- [21] Montorsi P, Ravagnani PM, Galli S, Rotatori F, Briganti A, Salonia A, et al. The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. *Am J Cardiol*. 2005 Dec 26;96(12B):19M-23M.
- [22] Chung SD, Chen YK, Lin HC. Increased risk of stroke among men with erectile dysfunction: a nationwide population-based study. *J Sex Med*. 2011 Jan;8(1):240-6.
- [23] Lue TF. Erectile dysfunction. *N Engl J Med*. 2000 Jun 15;342(24):1802-13.
- [24] Costa C, Virag R. The endothelial-erectile dysfunction connection: an essential update. *J Sex Med*. 2009 Sep;6(9):2390-404.
- [25] Agarwal A, Nandipati KC, Sharma RK, Zippe CD, Raina R. Role of oxidative stress in the pathophysiological mechanism of erectile dysfunction. *J Androl*. 2006 May-Jun;27(3):335-47.
- [26] Lyle AN, Griendling KK. Modulation of vascular smooth muscle signaling by reactive oxygen species. *Physiology (Bethesda)*. 2006 Aug;21:269-80.
- [27] Berk BC. Redox signals that regulate the vascular response to injury. *Thromb Haemost*. 1999 Aug;82(2):810-7.
- [28] Cave AC, Brewer AC, Narayanapanicker A, Ray R, Grieve DJ, Walker S, et al. NADPH oxidases in cardiovascular health and disease. *Antioxid Redox Signal*. 2006 May-Jun;8(5-6):691-728.
- [29] Jeremy JY, Angelini GD, Khan M, Mikhailidis DP, Morgan RJ, Thompson CS, et al. Platelets, oxidant stress and erectile dysfunction: an hypothesis. *Cardiovasc Res*. 2000 Apr;46(1):50-4.
- [30] Jones RW, Rees RW, Minhas S, Ralph D, Persad RA, Jeremy JY. Oxygen free radicals and the penis. *Expert Opin Pharmacother*. 2002 Jul;3(7):889-97.
- [31] Bener A, Al-Ansari A, Al-Hamaq AO, Elbagi IE, Afifi M. Prevalence of erectile dysfunction among hypertensive and nonhypertensive Qatari men. *Medicina (Kaunas)*. 2007;43(11):870-8.
- [32] Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. 1980;58(1):113-30.
- [33] Asplund K, Bonita R, Kuulasmaa K, Rajakangas AM, Schaedlich H, Suzuki K, et al. Multinational comparisons of stroke epidemiology. Evaluation of case ascertainment in the WHO MONICA Stroke Study. *World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke*. 1995 Mar;26(3):355-60.
- [34] Jung JH, Kam SC, Choi SM, Jae SU, Lee SH, Hyun JS. Sexual dysfunction in male stroke patients: correlation between brain lesions and sexual function. *Urology*. 2008 Jan;71(1):99-103.
- [35] Werner RA, Kessler S. Effectiveness of an intensive outpatient rehabilitation program for postacute stroke patients. *Am J Phys Med Rehabil*. 1996 Mar-Apr;75(2):114-20.

- [36] Ebrahim S. Conference report. World Stroke Congress, 25-29 November 2000, Melbourne, Australia. *Int J Epidemiol*. 2001 Feb;30(1):189.
- [37] Ma RC, So WY, Yang X, Yu LW, Kong AP, Ko GT, et al. Erectile dysfunction predicts coronary heart disease in type 2 diabetes. *J Am Coll Cardiol*. 2008 May 27;51(21):2045-50.
- [38] Chew KK, Finn J, Stuckey B, Gibson N, Sanfilippo F, Bremner A, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. *J Sex Med*. 2010 Jan;7(1 Pt 1):192-202.
- [39] Miner MM. Erectile dysfunction and the "window of curability": a harbinger of cardiovascular events. *Mayo Clin Proc*. 2009 Feb;84(2):102-4.
- [40] Chew KK, Bremner A, Jamrozik K, Earle C, Stuckey B. Male erectile dysfunction and cardiovascular disease: is there an intimate nexus? *J Sex Med*. 2008 Apr;5(4):928-34.
- [41] Salem S, Abdi S, Mehraei A, Saboury B, Saraji A, Shokohideh V, et al. Erectile dysfunction severity as a risk predictor for coronary artery disease. *J Sex Med*. 2009 Dec;6(12):3425-32.
- [42] Araujo AB, Travison TG, Ganz P, Chiu GR, Kupelian V, Rosen RC, et al. Erectile dysfunction and mortality. *J Sex Med*. 2009 Sep;6(9):2445-54.
- [43] Seftel AD, Sun P, Swindle R. The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *J Urol*. 2004 Jun;171(6 Pt 1):2341-5.
- [44] Korpelainen JT, Kauhanen ML, Kemola H, Malinen U, Myllyla VV. Sexual dysfunction in stroke patients. *Acta Neurol Scand*. 1998 Dec;98(6):400-5.
- [45] Monga TN, Lawson JS, Inglis J. Sexual dysfunction in stroke patients. *Arch Phys Med Rehabil*. 1986 Jan;67(1):19-22.
- [46] Pistoia F, Govoni S, Boselli C. Sex after stroke: a CNS only dysfunction? *Pharmacol Res*. 2006 Jul;54(1):11-8.
- [47] Coslett HB, Heilman KM. Male sexual function. Impairment after right hemisphere stroke. *Arch Neurol*. 1986 Oct;43(10):1036-9.
- [48] Schouten BW, Bohnen AM, Bosch JL, Bernsen RM, Deckers JW, Dohle GR, et al. Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: results from the Krimpen Study. *Int J Impot Res*. 2008 Jan-Feb;20(1):92-9.
- [49] Araujo AB, Hall SA, Ganz P, Chiu GR, Rosen RC, Kupelian V, et al. Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? *J Am Coll Cardiol*. 2010 Jan 26;55(4):350-6.
- [50] Ponholzer A, Temml C, Obermayr R, Wehrberger C, Madersbacher S. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? *Eur Urol*. 2005 Sep;48(3):512-8; discussion 7-8.
- [51] Lojanapiwat B, Weerusawin T, Kuanprasert S. Erectile dysfunction as a sentinel marker of endothelial dysfunction disease. *Singapore Med J*. 2009 Jul;50(7):698-701.
- [52] Vicenzini E, Altieri M, Michetti PM, Ricciardi MC, Ciccariello M, Shahabadi H, et al. Cerebral vasomotor reactivity is reduced in patients with erectile dysfunction. *Eur Neurol*. 2008;60(2):85-8.
- [53] Reffellmann T, Kloner RA. Sexual function in hypertensive patients receiving treatment. *Vasc Health Risk Manag*. 2006;2(4):447-55.

- [54] Kai H, Kudo H, Takayama N, Yasuoka S, Kajimoto H, Imaizumi T. Large blood pressure variability and hypertensive cardiac remodeling--role of cardiac inflammation. *Circ J*. 2009 Dec;73(12):2198-203.
- [55] Chitaley K, Weber D, Webb RC. RhoA/Rho-kinase, vascular changes, and hypertension. *Curr Hypertens Rep*. 2001 Apr;3(2):139-44.
- [56] Mombouli JV, Vanhoutte PM. Endothelial dysfunction: from physiology to therapy. *J Mol Cell Cardiol*. 1999 Jan;31(1):61-74.
- [57] Rudic RD, Sessa WC. Nitric oxide in endothelial dysfunction and vascular remodeling: clinical correlates and experimental links. *Am J Hum Genet*. 1999 Mar;64(3):673-7.
- [58] Chitaley K, Webb RC, Dorrance AM, Mills TM. Decreased penile erection in DOCA-salt and stroke prone-spontaneously hypertensive rats. *Int J Impot Res*. 2001 Dec;13 Suppl 5:S16-20.
- [59] Lima VV, Giachini FR, Hardy DM, Webb RC, Tostes RC. O-GlcNAcylation: a novel pathway contributing to the effects of endothelin in the vasculature. *Am J Physiol Regul Integr Comp Physiol*. 2011 Feb;300(2):R236-50.
- [60] Sullivan ME, Thompson CS, Dashwood MR, Khan MA, Jeremy JY, Morgan RJ, et al. Nitric oxide and penile erection: is erectile dysfunction another manifestation of vascular disease? *Cardiovasc Res*. 1999 Aug 15;43(3):658-65.
- [61] Granchi S, Vannelli GB, Vignozzi L, Crescioli C, Ferruzzi P, Mancina R, et al. Expression and regulation of endothelin-1 and its receptors in human penile smooth muscle cells. *Mol Hum Reprod*. 2002 Dec;8(12):1053-64.
- [62] Dai Y, Pollock DM, Lewis RL, Wingard CJ, Stopper VS, Mills TM. Receptor-specific influence of endothelin-1 in the erectile response of the rat. *Am J Physiol Regul Integr Comp Physiol*. 2000 Jul;279(1):R25-30.
- [63] Carneiro FS, Nunes KP, Giachini FR, Lima VV, Carneiro ZN, Nogueira EF, et al. Activation of the ET-1/ETA pathway contributes to erectile dysfunction associated with mineralocorticoid hypertension. *J Sex Med*. 2008 Dec;5(12):2793-807.
- [64] El Melegry NT, Ali ME, Awad EM. Plasma levels of endothelin-1, angiotensin II, nitric oxide and prostaglandin E in the venous and cavernosal blood of patients with erectile dysfunction. *BJU Int*. 2005 Nov;96(7):1079-86.
- [65] de Nucci G, Gryglewski RJ, Warner TD, Vane JR. Receptor-mediated release of endothelium-derived relaxing factor and prostacyclin from bovine aortic endothelial cells is coupled. *Proc Natl Acad Sci U S A*. 1988 Apr;85(7):2334-8.
- [66] de Nucci G, Warner T, Vane JR. Effect of captopril on the bradykinin-induced release of prostacyclin from guinea-pig lungs and bovine aortic endothelial cells. *Br J Pharmacol*. 1988 Nov;95(3):783-8.
- [67] Becker AJ, Uckert S, Stief CG, Truss MC, Machtens S, Scheller F, et al. Possible role of bradykinin and angiotensin II in the regulation of penile erection and detumescence. *Urology*. 2001 Jan;57(1):193-8.
- [68] Lima VV, Rigsby CS, Hardy DM, Webb RC, Tostes RC. O-GlcNAcylation: a novel post-translational mechanism to alter vascular cellular signaling in health and disease: focus on hypertension. *J Am Soc Hypertens*. 2009 Nov-Dec;3(6):374-87.
- [69] Xing D, Feng W, Not LG, Miller AP, Zhang Y, Chen YF, et al. Increased protein O-GlcNAc modification inhibits inflammatory and neointimal responses to acute endoluminal arterial injury. *Am J Physiol Heart Circ Physiol*. 2008 Jul;295(1):H335-42.

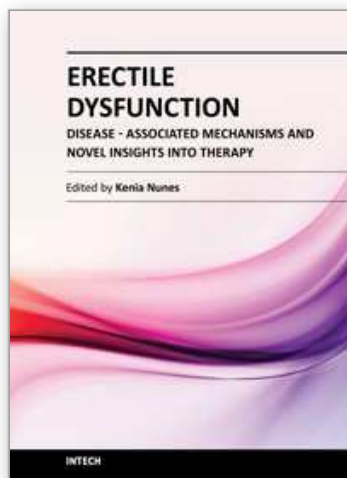
- [70] Lima VV, Giachini FR, Choi H, Carneiro FS, Carneiro ZN, Fortes ZB, et al. Impaired vasodilator activity in deoxycorticosterone acetate-salt hypertension is associated with increased protein O-GlcNAcylation. *Hypertension*. 2009 Feb;53(2):166-74.
- [71] Musicki B, Kramer MF, Becker RE, Burnett AL. Inactivation of phosphorylated endothelial nitric oxide synthase (Ser-1177) by O-GlcNAc in diabetes-associated erectile dysfunction. *Proc Natl Acad Sci U S A*. 2005 Aug 16;102(33):11870-5.
- [72] Kifor I, Williams GH, Vickers MA, Sullivan MP, Jodbert P, Dluhy RG. Tissue angiotensin II as a modulator of erectile function. I. Angiotensin peptide content, secretion and effects in the corpus cavernosum. *J Urol*. 1997 May;157(5):1920-5.
- [73] Iwamoto Y, Song K, Takai S, Yamada M, Jin D, Sakaguchi M, et al. Multiple pathways of angiotensin I conversion and their functional role in the canine penile corpus cavernosum. *J Pharmacol Exp Ther*. 2001 Jul;298(1):43-8.
- [74] Lin CS, Ho HC, Gholami S, Chen KC, Jad A, Lue TF. Gene expression profiling of an arteriogenic impotence model. *Biochem Biophys Res Commun*. 2001 Jul 13;285(2):565-9.
- [75] Mori M, Gotoh T. Regulation of nitric oxide production by arginine metabolic enzymes. *Biochem Biophys Res Commun*. 2000 Sep 7;275(3):715-9.
- [76] Cox JD, Kim NN, Traish AM, Christianson DW. Arginase-boronic acid complex highlights a physiological role in erectile function. *Nat Struct Biol*. 1999 Nov;6(11):1043-7.
- [77] Rodriguez S, Richert L, Berthelot A. Increased arginase activity in aorta of mineralocorticoid-salt hypertensive rats. *Clin Exp Hypertens*. 2000 Jan;22(1):75-85.
- [78] Demougeot C, Prigent-Tessier A, Bagnost T, Andre C, Guillaume Y, Bouhaddi M, et al. Time course of vascular arginase expression and activity in spontaneously hypertensive rats. *Life Sci*. 2007 Feb 27;80(12):1128-34.
- [79] Demougeot C, Prigent-Tessier A, Marie C, Berthelot A. Arginase inhibition reduces endothelial dysfunction and blood pressure rising in spontaneously hypertensive rats. *J Hypertens*. 2005 May;23(5):971-8.
- [80] Ryoo S, Gupta G, Benjo A, Lim HK, Camara A, Sikka G, et al. Endothelial arginase II: a novel target for the treatment of atherosclerosis. *Circ Res*. 2008 Apr 25;102(8):923-32.
- [81] Michell DL, Andrews KL, Chin-Dusting JP. Endothelial dysfunction in hypertension: the role of arginase. *Front Biosci (Schol Ed)*. 2011;3:946-60.
- [82] Durante W, Johnson FK, Johnson RA. Arginase: a critical regulator of nitric oxide synthesis and vascular function. *Clin Exp Pharmacol Physiol*. 2007 Sep;34(9):906-11.
- [83] Bivalacqua TJ, Burnett AL, Hellstrom WJ, Champion HC. Overexpression of arginase in the aged mouse penis impairs erectile function and decreases eNOS activity: influence of in vivo gene therapy of anti-arginase. *Am J Physiol Heart Circ Physiol*. 2007 Mar;292(3):H1340-51.
- [84] Numao N, Masuda H, Sakai Y, Okada Y, Kihara K, Azuma H. Roles of attenuated neuronal nitric-oxide synthase protein expression and accelerated arginase activity in impairing neurogenic relaxation of corpus cavernosum in aged rabbits. *BJU Int*. 2007 Jun;99(6):1495-9.
- [85] Peyton KJ, Ensenat D, Azam MA, Keswani AN, Kannan S, Liu XM, et al. Arginase promotes neointima formation in rat injured carotid arteries. *Arterioscler Thromb Vasc Biol*. 2009 Apr;29(4):488-94.

- [86] Wassertheil-Smoller S, Blaufox MD, Oberman A, Davis BR, Swencionis C, Knerr MO, et al. Effect of antihypertensives on sexual function and quality of life: the TAIM Study. *Ann Intern Med.* 1991 Apr 15;114(8):613-20.
- [87] Menard J. The 45-year story of the development of an anti-aldosterone more specific than spironolactone. *Mol Cell Endocrinol.* 2004 Mar 31;217(1-2):45-52.
- [88] Fogari R, Zoppi A, Poletti L, Marasi G, Mugellini A, Corradi L. Sexual activity in hypertensive men treated with valsartan or carvedilol: a crossover study. *Am J Hypertens.* 2001 Jan;14(1):27-31.
- [89] Angulo J, Wright HM, Cuevas P, Gonzalez-Corrochano R, Fernandez A, Cuevas B, et al. Nebivolol dilates human penile arteries and reverses erectile dysfunction in diabetic rats through enhancement of nitric oxide signaling. *J Sex Med.* 2010 Aug;7(8):2681-97.
- [90] Mandras SA, Uber PA, Mehra MR. Sexual activity and chronic heart failure. *Mayo Clin Proc.* 2007 Oct;82(10):1203-10.
- [91] DiBianco R. A large-scale trial of captopril for mild to moderate heart failure in the primary care setting. *Clin Cardiol.* 1991 Aug;14(8):676-82.
- [92] Dusing R. Effect of the angiotensin II antagonist valsartan on sexual function in hypertensive men. *Blood Press Suppl.* 2003 Dec;2:29-34.
- [93] Canguven O, Lagoda G, Sezen SF, Burnett AL. Losartan preserves erectile function after bilateral cavernous nerve injury via antifibrotic mechanisms in male rats. *J Urol.* 2009 Jun;181(6):2816-22.
- [94] Bohm M, Baumhakel M, Teo K, Sleight P, Probstfield J, Gao P, et al. Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. *Circulation.* 2010 Mar 30;121(12):1439-46.
- [95] Papatsoris AG, Korantzopoulos PG. Hypertension, antihypertensive therapy, and erectile dysfunction. *Angiology.* 2006 Jan-Feb;57(1):47-52.
- [96] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation.* 2005 Sep 20;112(12):e154-235.
- [97] Bocchi EA, Vilas-Boas F, Perrone S, Caamano AG, Clausell N, Moreira Mda C, et al. I Latin American Guidelines for the Assessment and Management of Decompensated Heart Failure. *Arq Bras Cardiol.* 2005 Sep;85 Suppl 3:49-94; 1-48.
- [98] Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation.* 2010 Feb 23;121(7):e46-e215.
- [99] Baraghoush A, Phan A, Willix RD, Jr., Schwarz ER. Erectile dysfunction as a complication of heart failure. *Curr Heart Fail Rep.* 2010 Dec;7(4):194-201.

- [100] Chew KK, Bremner A, Stuckey B, Earle C, Jamrozik K. Sex life after 65: how does erectile dysfunction affect ageing and elderly men? *Aging Male*. 2009 Jun-Sep;12(2-3):41-6.
- [101] Schwarz ER, Rastogi S, Kapur V, Sulemanjee N, Rodriguez JJ. Erectile dysfunction in heart failure patients. *J Am Coll Cardiol*. 2006 Sep 19;48(6):1111-9.
- [102] Boger RH, Bode-Boger SM, Frolich JC. The L-arginine-nitric oxide pathway: role in atherosclerosis and therapeutic implications. *Atherosclerosis*. 1996 Nov 15;127(1):1-11.
- [103] Yavuzgil O, Altay B, Zoghi M, Gurgun C, Kayikcioglu M, Kultursay H. Endothelial function in patients with vasculogenic erectile dysfunction. *Int J Cardiol*. 2005 Aug 3;103(1):19-26.
- [104] Smith CJ, Sun D, Hoegler C, Roth BS, Zhang X, Zhao G, et al. Reduced gene expression of vascular endothelial NO synthase and cyclooxygenase-1 in heart failure. *Circ Res*. 1996 Jan;78(1):58-64.
- [105] Nunes KP, Rigsby CS, Webb RC. RhoA/Rho-kinase and vascular diseases: what is the link? *Cell Mol Life Sci*. 2010 Nov;67(22):3823-36.
- [106] Becker AJ, Uckert S, Stief CG, Truss MC, Hartmann U, Jonas U. Systemic and cavernous plasma levels of endothelin (1-21) during different penile conditions in healthy males and patients with erectile dysfunction. *World J Urol*. 2001 Aug;19(4):267-71.
- [107] Pedersen CA, Boccia ML. Vasopressin interactions with oxytocin in the control of female sexual behavior. *Neuroscience*. 2006;139(3):843-51.
- [108] Rastogi S, Rodriguez JJ, Kapur V, Schwarz ER. Why do patients with heart failure suffer from erectile dysfunction? A critical review and suggestions on how to approach this problem. *Int J Impot Res*. 2005 Dec;17 Suppl 1:S25-36.
- [109] Schwarz ER, Rodriguez J. Sex and the heart. *Int J Impot Res*. 2005 Dec;17 Suppl 1:S4-6.
- [110] Neri A, Zukerman Z, Aygen M, Lidor Y, Kaufman H. The effect of long-term administration of digoxin on plasma androgens and sexual dysfunction. *J Sex Marital Ther*. 1987 Spring;13(1):58-63.
- [111] Gupta S, Salimpour P, Saenz de Tejada I, Daley J, Gholami S, Daller M, et al. A possible mechanism for alteration of human erectile function by digoxin: inhibition of corpus cavernosum sodium/potassium adenosine triphosphatase activity. *J Urol*. 1998 May;159(5):1529-36.
- [112] Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. *JAMA*. 2005 Dec 21;294(23):2996-3002.
- [113] Billups KL. Sexual dysfunction and cardiovascular disease: integrative concepts and strategies. *Am J Cardiol*. 2005 Dec 26;96(12B):57M-61M.
- [114] Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med*. 1990 Jul 5;323(1):27-36.
- [115] Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ. Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. *N Engl J Med*. 1992 Jan 9;326(2):90-4.
- [116] Ignarro LJ, Bush PA, Buga GM, Wood KS, Fukuto JM, Rajfer J. Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. *Biochem Biophys Res Commun*. 1990 Jul 31;170(2):843-50.

- [117] Escrig A, Marin R, Abreu P, Gonzalez-Mora JL, Mas M. Changes in mating behavior, erectile function, and nitric oxide levels in penile corpora cavernosa in streptozotocin-diabetic rats. *Biol Reprod.* 2002 Jan;66(1):185-9.
- [118] Arnold WP, Mittal CK, Katsuki S, Murad F. Nitric oxide activates guanylate cyclase and increases guanosine 3':5'-cyclic monophosphate levels in various tissue preparations. *Proc Natl Acad Sci U S A.* 1977 Aug;74(8):3203-7.
- [119] Hedlund P, Aszodi A, Pfeifer A, Alm P, Hofmann F, Ahmad M, et al. Erectile dysfunction in cyclic GMP-dependent kinase I-deficient mice. *Proc Natl Acad Sci U S A.* 2000 Feb 29;97(5):2349-54.
- [120] Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med.* 1998 May 14;338(20):1397-404.
- [121] Padma-Nathan H, Hellstrom WJ, Kaiser FE, Labasky RF, Lue TF, Nolten WE, et al. Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. *N Engl J Med.* 1997 Jan 2;336(1):1-7.
- [122] Porst H. The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. *J Urol.* 1996 Mar;155(3):802-15.
- [123] Kirby M, Jackson G, Betteridge J, Friedli K. Is erectile dysfunction a marker for cardiovascular disease? *Int J Clin Pract.* 2001 Nov;55(9):614-8.
- [124] Moncada S, Higgs A. The L-arginine-nitric oxide pathway. *N Engl J Med.* 1993 Dec 30;329(27):2002-12.
- [125] Kelm M, Rath J. Endothelial dysfunction in human coronary circulation: relevance of the L-arginine-NO pathway. *Basic Res Cardiol.* 2001 Apr;96(2):107-27.
- [126] Kim N, Azadzi KM, Goldstein I, Saenz de Tejada I. A nitric oxide-like factor mediates nonadrenergic-noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. *J Clin Invest.* 1991 Jul;88(1):112-8.
- [127] Stroes E, Kastelein J, Cosentino F, Erkelens W, Wever R, Koomans H, et al. Tetrahydrobiopterin restores endothelial function in hypercholesterolemia. *J Clin Invest.* 1997 Jan 1;99(1):41-6.
- [128] Heitzer T, Brockhoff C, Mayer B, Warnholtz A, Mollnau H, Henne S, et al. Tetrahydrobiopterin improves endothelium-dependent vasodilation in chronic smokers : evidence for a dysfunctional nitric oxide synthase. *Circ Res.* 2000 Feb 4;86(2):E36-41.
- [129] Tiefenbacher CP, Bleeke T, Vahl C, Amann K, Vogt A, Kubler W. Endothelial dysfunction of coronary resistance arteries is improved by tetrahydrobiopterin in atherosclerosis. *Circulation.* 2000 Oct 31;102(18):2172-9.
- [130] Bush PA, Gonzalez NE, Ignarro LJ. Biosynthesis of nitric oxide and citrulline from L-arginine by constitutive nitric oxide synthase present in rabbit corpus cavernosum. *Biochem Biophys Res Commun.* 1992 Jul 15;186(1):308-14.
- [131] Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL, Bank AJ. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol.* 2004 Jan 21;43(2):179-84.
- [132] Bocchio M, Desideri G, Scarpelli P, Necozone S, Properzi G, Spartera C, et al. Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *J Urol.* 2004 Apr;171(4):1601-4.

- [133] Jin L, Ying Z, Hilgers RH, Yin J, Zhao X, Imig JD, et al. Increased RhoA/Rho-kinase signaling mediates spontaneous tone in aorta from angiotensin II-induced hypertensive rats. *J Pharmacol Exp Ther*. 2006 Jul;318(1):288-95.
- [134] Zhou Q, Liao JK. Rho kinase: an important mediator of atherosclerosis and vascular disease. *Curr Pharm Des*. 2009;15(27):3108-15.
- [135] Hamid SA, Bower HS, Baxter GF. Rho kinase activation plays a major role as a mediator of irreversible injury in reperfused myocardium. *Am J Physiol Heart Circ Physiol*. 2007 Jun;292(6):H2598-606.
- [136] Rikitake Y, Kim HH, Huang Z, Seto M, Yano K, Asano T, et al. Inhibition of Rho kinase (ROCK) leads to increased cerebral blood flow and stroke protection. *Stroke*. 2005 Oct;36(10):2251-7.
- [137] Sato M, Tani E, Fujikawa H, Kaibuchi K. Involvement of Rho-kinase-mediated phosphorylation of myosin light chain in enhancement of cerebral vasospasm. *Circ Res*. 2000 Aug 4;87(3):195-200.
- [138] Higashi M, Shimokawa H, Hattori T, Hiroki J, Mukai Y, Morikawa K, et al. Long-term inhibition of Rho-kinase suppresses angiotensin II-induced cardiovascular hypertrophy in rats in vivo: effect on endothelial NAD(P)H oxidase system. *Circ Res*. 2003 Oct 17;93(8):767-75.
- [139] Bao W, Hu E, Tao L, Boyce R, Mirabile R, Thudium DT, et al. Inhibition of Rho-kinase protects the heart against ischemia/reperfusion injury. *Cardiovasc Res*. 2004 Feb 15;61(3):548-58.
- [140] Miyata K, Shimokawa H, Kandabashi T, Higo T, Morishige K, Eto Y, et al. Rho-kinase is involved in macrophage-mediated formation of coronary vascular lesions in pigs in vivo. *Arterioscler Thromb Vasc Biol*. 2000 Nov;20(11):2351-8.
- [141] Puetz S, Lubomirov LT, Pfitzer G. Regulation of smooth muscle contraction by small GTPases. *Physiology (Bethesda)*. 2009 Dec;24:342-56.
- [142] Mills TM, Lewis RW, Wingard CJ, Linder AE, Jin L, Webb RC. Vasoconstriction, RhoA/Rho-kinase and the erectile response. *Int J Impot Res*. 2003 Oct;15 Suppl 5:S20-4.
- [143] Jin L, Burnett AL. RhoA/Rho-kinase in erectile tissue: mechanisms of disease and therapeutic insights. *Clin Sci (Lond)*. 2006 Feb;110(2):153-65.
- [144] Kishi T, Hirooka Y, Masumoto A, Ito K, Kimura Y, Inokuchi K, et al. Rho-kinase inhibitor improves increased vascular resistance and impaired vasodilation of the forearm in patients with heart failure. *Circulation*. 2005 May 31;111(21):2741-7.
- [145] Shimokawa H, Hiramori K, Iinuma H, Hosoda S, Kishida H, Osada H, et al. Anti-anginal effect of fasudil, a Rho-kinase inhibitor, in patients with stable effort angina: a multicenter study. *J Cardiovasc Pharmacol*. 2002 Nov;40(5):751-61.
- [146] Miao L, Calvert JW, Tang J, Parent AD, Zhang JH. Age-related RhoA expression in blood vessels of rats. *Mech Ageing Dev*. 2001 Oct;122(15):1757-70.



Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy

Edited by Dr. Kenia Nunes

ISBN 978-953-51-0199-4

Hard cover, 214 pages

Publisher InTech

Published online 29, February, 2012

Published in print edition February, 2012

Erectile dysfunction is a widespread problem, affecting many men across all age groups and it is more than a serious quality of life problem for sexually active men. This book contains chapters written by widely acknowledged experts, each of which provides a unique synthesis of information on emergent aspects of ED. All chapters take into account not only the new perspectives on ED but also recent extensions of basic knowledge that presage directions for further research. The approach in this book has been to not only describe recent popular aspects of ED, such as basic mechanism updates, etiologic factors and pharmacotherapy, but also disease-associated ED and some future perspectives in this field.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sandra Crestani, Kenia Pedrosa Nunes, Maria Consuelo Andrade Marques, José Eduardo Da Silva Santos and R. Clinton Webb (2012). The Role Erectile Dysfunction Plays in Cardiovascular Diseases, *Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy*, Dr. Kenia Nunes (Ed.), ISBN: 978-953-51-0199-4, InTech, Available from: <http://www.intechopen.com/books/erectile-dysfunction-disease-associated-mechanisms-and-novel-insights-into-therapy/the-role-erectile-dysfunction-plays-in-cardiovascular-diseases>

INTech
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen