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The Role Erectile Dysfunction Plays in Cardiovascular Diseases

Sandra Crestani[1,2], Kenia Pedrosa Nunes[2], Maria Consuelo Andrade
Marques[1], José Eduardo Da Silva Santos[3] and R. Clinton Webb[2]
[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 proinflamatory, 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, Vicenzini 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 Bucchardt 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 recepotors 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 inactives 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 cavenosum. 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 arginage 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 avaibility 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 angioten-receptor blocker (ARB) therapy (94).

Regarding the α-adrenoceptor agents to treat hypertension, has been showed that direct cavernosal injection of α1-antagonists cause erection in both, experimental and humans, although this effect is not observed with α2-selective drugs. Notably, it has been observed that patients treated with α1-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 efectively 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	44
Miocardial infarction	571	57	57	50
Miocardial infarction or angina	801	68	649	84
Stroke	181	16	157	8
Congestive Heart failure	33	7	25	1
Transient ischemic attack	113	7	96	10
Arrhythmia	193	21	149	23
First cardiovascular event	1186	113	955	118
Death due to any cause	457	75	382	0

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, incracavernosal 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 oclusion 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.
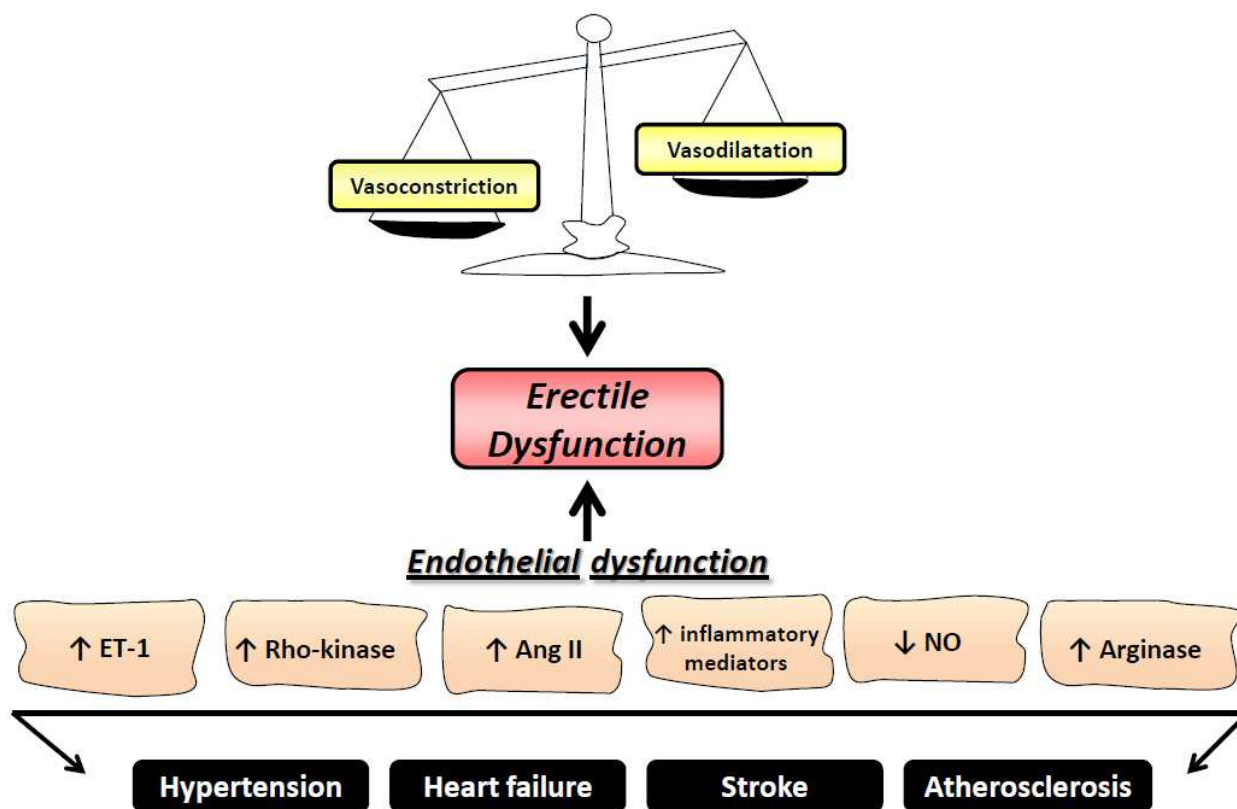

Fig. 1. **Endothelial dysfunction is a common situation in both CVD and ED**. Generally ED is caused by unbalance between vasoconstrictors (Ang II, ET-1, Rho-kinase, arginase) and vasodilators (NO) endogenous agents. Endothelial dysfunction leads to ED development and later to onset of CVD.

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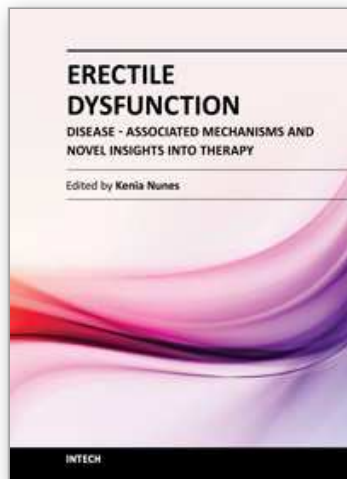
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Edited by Dr. Kenia Nunes

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.

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