Hypertension and erectile dysfunction: breaking down the challenges

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Abstract

A diagnostic of hypertension increases the risk of erectile dysfunction (ED); likewise, ED can be an early sign of hypertension. In both cases, there is evidence that endothelial dysfunction is a common link between the two conditions. During hypertension, the sustained and widespread release of pro-contractile factors (e.g., angiotensin II, endothelin 1, aldosterone) impairs the balance between vasoconstrictors and vasodilators and, in turn, detrimentally impacts vascular and erectile structures. This pro-hypertensive state associates with an enhancement in the generation of reactive oxygen species, which is not compensated by internal antioxidant mechanisms. Recently, the innate immune system, mainly via Toll-like receptor 4, has also been shown to actively contribute to the pathophysiology of hypertension and ED not only by inducing oxidative stress but also by sustaining a low-grade inflammatory state. Furthermore, some drugs used to treat hypertension can cause ED and, consequently, reduce compliance with the prescribed pharmacotherapy. To break down these challenges, in this review, we focus on discussing the well-established as well as the emerging mechanisms linking hypertension and ED with an emphasis on the signaling network of the vasculature and corpora cavernosa, the vascular-like structure of the penis.

Keywords: hypertension, erectile dysfunction, vasoconstrictors, vasodilators, antihypertensive drugs, immune system.

"[…] health care professionals need to view ED as a potential cardiovascular risk factor and not just a urologic or psychogenic disorder." Robert A Kloner[1]

Introduction

Hypertension affects approximately 46% of the adult population in the United States[2]. More than 80% of hypertensive patients are recommended an antihypertensive medication, but unfortunately, out of those, less than 25% have the disease under control[3], which could explain why hypertension was the primary cause of death of more than 78,000 people in 2015[4]. Even though high blood pressure is a preventable and modifiable cause of death, hypertensive patients have a shorter life expectancy compared to their normotensive counterparts[5], primarily because of the increased risk of cardiovascular diseases and stroke[6]. Additionally, the aftermath of hypertension includes a strong association with the development of erectile dysfunction (ED)[7], a troublesome condition with a negative impact on the quality of life of sexually active partners[8].

ED, defined as the persistent inability to attain and/or maintain an erection for satisfactory sexual intercourse[9], has a 50% prevalence after the age of 40 in the general population[10], and it is exacerbated during hypertension[11]. High blood pressure affects the blood flow to the penis, a crucial step in the process of achieving and keeping an erection[12,13]. Therefore, it is not surprising that ED is a significant problem in hypertensive men. The interaction between high blood pressure and ED is not simple as ED can be diagnosed as an early marker or as a secondary complication of hypertension[14] (Figure 1). Such an intricate relationship mainly occurs because of alterations in the endothelium, which affects smooth muscle tone and contributes to the development and maintenance of both conditions.

The signaling mechanisms involved in the pathophysiology of hypertension and ED are well connected, as both conditions are linked to an enhancement in pro-contractile pathways, which, in turn, reduces vascular compliance. Furthermore, evidence shows that the immune system is actively contributing to the pathophysiology of hypertension and ED (for review, see [15] and [16], respectively). To add another layer of complexity in this interplay, the pharmacotherapy of hypertension can also affect erectile function[17]. To break down these challenges, in this review, we focus on discussing the well-established as well as the emerging mechanisms linking hypertension and ED with an emphasis

on the signaling network of the vasculature and corpora cavernosa, the vascular-like structure of the penis.

Vasoconstrictors: the pro-contractile challenges

The pathophysiology of hypertension strongly associates with an increase in the release of vasoconstrictors, especially angiotensin II (AngII), endothelin 1 (ET-1), and aldosterone. Herein, we highlight the specific contributions of these molecules, as their sustained release poses a significant challenge to the endothelial cells lining the inner wall of blood vessels and the blood-filled sinuses of the corpus cavernosum. The resulting endothelial dysfunction not only leads to but also sustains a pro-contractile state in the vasculature and vascular-like structures, a hallmark of hypertension, and ED.

A. Angiotensin II

The main vasoconstrictor peptide of the renin-angiotensin system (RAS), AngII, contributes to blood pressure regulation in (patho)physiological states through central and peripheral mechanisms. Additionally, AngII is locally produced and secreted by the corpus cavernosum[18], which might directly contribute to hypertension-associated ED[19]. In fact, men with ED have increased levels of AngII in the systemic and cavernous blood[20], suggestive of a mechanistic factor triggering penile detumescence. Exacerbation in local and systemic production of AngII, and consequently, hyperactivation of its type 1 receptor (AT1r) triggers the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme, a key source of reactive oxygen species (ROS) in the vasculature and corpus cavernosum. An increase in ROS production not only reduces the availability of nitric oxide (NO)[21], but it also stimulates the RhoA/Rho-kinase pathway [22], which affects penile erection independently of NO release[23]. Interestingly, the silencing of AngII can directly downregulate the RhoA/Rho kinase signaling in diabetic penile tissue improving erectile function[24]. Together these two factors, (a) reduced NO availability and (b) increased RhoA/Rho-kinase activity, augment smooth muscle contraction, favor penile flaccidity, and hinder the treatment of ED in hypertensive patients.

Indeed, it is well-established that sustained hyperstimulation of the AngII/AT1r axis in the vasculature and vascular-like structures also triggers endothelial dysfunction[25]. Furthermore, AngII has a positive effect in the sympathetic nervous system[26,27], which via α-adrenergic receptors intensifies the contractile tone of the arterioles and sinusoidal cavities of the corpus cavernosum. Undoubtedly, AngII-induced adaptations have pathological consequences for hypertension and ED. To date, this pathway, which involves multiple downstream signaling mechanisms, it is still the most widely discussed link between these two conditions.

B. Endothelin 1

Endothelial cells secret endothelium-derived contractile factors such as ET-1, which plays a core role in the pathophysiology of human hypertension[28]. This endogenous 21-amino acid peptide not only acts as an autocrine hormone via ET_B receptors, but it also has a robust paracrine effect in vicinal vascular smooth muscle cells (VSMCs) following stimulation of ET_A and ET_B receptors[28]. ET-1 levels are increased during salt-sensitive hypertension, and its blockade lowers blood pressure (for review, see [29]), which further associates with the prevention of end-organ damage in the kidney[30] and heart[31]. Precisely, in the vasculature, ET-1 activates the NADPH oxidase enzyme[32], and its byproduct, ROS, induces the release of ET-1 in a positive-feedback loop[33]. This mechanism, akin to bidirectional causality, favors a pro-hypertensive state. Evidence from animal models demonstrates that ET-1 might be a key target in salt-sensitive hypertension-associated ED[34,35], primarily because besides being responsive to ET-1 by expressing both of its receptors[36], human penile SMCs are also able to synthesize this vasoconstrictor peptide[37]. In isolated penile tissue, ET-1 causes smooth muscle contraction by affecting Ca^{2+} influx[38]. Interestingly, an *in vitro* study performed with human SMCs derived from corpus cavernosum showed that ET-1 has a more pronounced effect in Ca^{2+} mobilization in cells derived from patients with ED than those with healthy erectile function [39]. There is also evidence that ET-1 potentiates phenylephrine-induced contraction by hyper-activating RhoA/Rho-kinase in this tissue[40]. Considering that (a) an antagonist of ET_A improves erectile function in hypertensive animals[35] and that (b) men with ED have a significant increase in plasma levels of ET-1

compared with control subjects[41], it is reasonable to assume that the ET-1/ET_A axis might be a clinical target for hypertension-associated ED. Still, additional studies are needed to explore this pathway, especially because a recent study showed that an increase of ET-1 *per se* might not be enough to downregulate vascular relaxation[42].

C. Aldosterone

There is mounting evidence describing the role of aldosterone in blood pressure regulation by inhibition of natriuresis. This steroid-hormone has also been suggested to participate in the mechanisms of ED[43], as a population study uncovered that the plasma levels of aldosterone are an independent risk factor for this condition[44]. The link between aldosterone and ED was constructed because this hormone induces the production of ROS in SMCs[45] and the release of inflammatory cytokines in penile tissue via NF-κB[46], which is a transcriptional factor that crosstalk with ROS[47]. Moreover, aldosterone directly inhibits NO production *in vitro* by impairing endothelial nitric oxide synthase (eNOS)[48]. Since most of the effects of aldosterone are mediated through mineralocorticoid receptors, which are expressed in human penile corpus cavernosum[49], a previous study investigated the effects of aldosterone in penile contractility. Interestingly, the authors observed that aldosterone does not have a direct impact in contraction or relaxation, but that it augments the effect of noradrenaline[50]. Currently, it is becoming evident that aldosterone plays a role in hypertension-associated ED, but further studies are still needed to elucidate the precise mechanisms involved in this process as well as whether targeting aldosterone during hypertension could minimize ED.

Vasodilators: the pro-relaxation challenges

A major challenge encountered by the vasculature and vascular-like structure of the penis under hypertension, besides upregulation of vasoconstrictors, is the reduction in the availability of pro-relaxation factors, such as the gaseous transmitters NO and hydrogen sulfide (H_2S), which highlights these molecules as wells as their downstream pathways as potential common targets for hypertension

and ED. Also, during hypertension mechanisms that should be activated to counterbalance the pro-constriction state, including stimulation of the angiotensin (1-7)/Mas receptor axis and the redox-sensitive transcriptional factor nuclear factor erythroid 2-related factor 2 (Nrf2), are compromised as they elicit, in most cases, an inefficient response.

A. Nitric oxide

NO is a protective vasoactive gaseous transmitter with a pivotal role in vascular homeostasis. Therefore, it is not surprising that a reduction in NO availability is often encountered during hypertension, a condition closely associated with the dysfunctionality of small and large vessels. This is of major concern because eNOS-derived NO protects against atherosclerosis by inhibiting platelet aggregation and attachment, VSMCs proliferation, and leukocyte adhesion (for review, see [51]). Noteworthy, it has also been demonstrated, more than two decades ago, that deletion of eNOS or its pharmacological blockade leads to the development of arterial hypertension[52,53]. As discussed above, hypertension is accompanied by excessive production of ROS in vascular tissues, mainly via stimulation of the NADPH oxidase enzyme. The byproduct of this enzyme, superoxide, reacts with NO to form peroxynitrite, which leads to rapid scavenger of NO and likely triggers eNOS uncoupling, a key characteristic of endothelial dysfunction. eNOS uncoupling is observed in different animal models of hypertension[54–56], and not surprisingly, it contributes to the development of ED[57–60].

NO is the chief mediator of erectile function, and consequently, a reduction in its bioavailability causes ED. Both constitutive forms of the enzyme NOS, endothelial and neuronal, which generate NO following acetylcholine or neuronal stimulation, play a role in the mechanisms of erection. On the other hand, the inducible NOS isoform might contribute to the pathophysiology of ED[61]. During sexual arousal, NO diffuses into adjacent SMCs and activates the enzyme guanylate cyclase (GC), which is responsible for converting GTP into the second messenger, cGMP. The NO/cGMP pathway induces dilation mainly by triggering PKG, which reduces the concentration of cytosolic Ca^{2+}, and also by inhibiting Rho-kinase. During this process, the enzyme adenylate cyclase is also activated,

which in turn, leads to the production of cAMP followed by activation of PKA. Both cGMP and cAMP levels are controlled by the enzyme phosphodiesterase (PDE)[62]. The isoform PDE5, which hydrolyses cGMP has a direct effect not only upon erectile function but also on blood pressure, as a PDE-5 inhibitor prevents against the development of hypertension after infusion of L-NAME[63]. Altogether, as mentioned above, the current state of knowledge strongly indicates NO deficiency as a link between the pathogenesis and the pathophysiology of hypertension and ED.

B. Hydrogen sulfide

H_2S, an endogenous gaseous transmitter, is the product of the conversion of L-cysteine, especially by the enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE)[64]. The deletion of CSE in mice increases blood pressure and reduces endothelium-dependent relaxation in small resistance arteries[65]. Indeed, new evidence strongly supports a role for H_2S in the control of vascular tone[64] as it causes relaxation of smooth muscle by affecting multiple mechanisms, including K and L-type voltage-gated channels, adenylyl cyclase/cAMP, muscarinic receptors, and NO/cGMP axis[66] as well as by inhibiting PDE5[67]. Furthermore, human penile tissue expresses both CBS and CSE, and exogenous H_2S leads to a concentration-dependent relaxation response in this tissue[68]. Interestingly, corpus cavernosum isolated from spontaneously hypertensive rats (SHR) have reduced expression of CBS and CSE and impaired endogenous H_2S production[69], which could be a mechanism playing a role in hypertension-associated ED. Noteworthy, it has been previously demonstrated that in the absence of NO, a critical mechanism for smooth muscle relaxation, H_2S plays a compensatory role in cavernosal relaxation[70], and according to the literature, during hypertension, both pathways are compromised, posing an enhanced challenge to elicit penile engorgement for satisfactory sexual intercourse. It has also been discussed that H_2S counteracts oxidative stress by directly scavenging peroxynitrite[71] and by stimulating the transcriptional factor Nrf2[72]. Further investigation is warranted to understand the clinical implications of targeting this auxiliary relaxation pathway in hypertensive patients, which could open new avenues for the treatment of ED during hypertension.

C. Angiotensin (1,7)

Ang(1-7) is a counterregulatory peptide of the RAS with opposing actions to AngII[73]. It is synthesized by the conversion of AngI via endopeptidases or by the conversion of AngII via angiotensin-converting enzyme 2 (ACE2) (for review, see [74]). While studies conducted in the 1990s uncovered that infusion of Ang(1-7) in SHR lowers blood pressure[75] and that Ang(1-7) contributes to the antihypertensive effects observed following inhibition of ACE or antagonism of AT1r[76,77], it was not until the characterization of the ACE2/Ang(1-7)/Mas receptor axis that this protein was fully appreciated. The deletion of the Mas protooncogene prevents Ang(1-7)-mediated effects in the kidneys and the aorta[78]. Mas receptor knockout animals have endothelial dysfunction, high blood pressure, and imbalance in NO/ROS production[79]. Stimulation of Mas receptor by Ang(1-7) produces NO-dependent vasodilation[80], potentially in a mechanism that involves an increase in eNOS-induced NO production through Akt signaling pathways [81]. The protective effects of the Ang(1-7)/Mas receptor axis are also present in penile tissue as a previous study demonstrated that infusion of Ang(1-7) improves erectile function through NO, that deletion of the Mas receptor impairs erection and induces fibrosis, and that infusion of Ang(1-7) reverses salt sensitive-induced ED in rats[82]. The RAS is widely expressed, and during hypertension, there is an increase in its pro-hypertensive axis. Therefore, stimulating its protective axis might be an alternative to treat hypertension-associated ED.

D. Nrf2

Oxidative stress activates the transcriptional factor Nrf2, which, in turn, leads to the expression of antioxidant genes and protection against ROS-induced tissue damage[83]. This is mediated, at least in part, because Nrf2 increases NO availability by reducing ROS and asymmetric dimethylarginine generation and by enhancing eNOS expression and activity[84]. Such effects are of particular interest because the improvement in endothelial function following Nrf2 induction has been previously demonstrated to protect against blood pressure elevation in AngII-infused mice[85]. Moreover, a reduction in the expression of Nrf2 mediates vascular dysfunction in stroke-prone SHR[86]. While there is paucity of information regarding the effects of Nrf2 in erectile function during hypertension,

evidence from animal models of vascular dysfunction such as diabetes and aging supports the notion that targeting Nrf2 might be a therapeutic strategy to manage hypertension-associated ED. In diabetic animals, NOX-1 activation not only induces ROS generation, but it also impairs Nrf2, which together enhances Rho-kinase signaling leading to internal pudendal artery dysfunction, and in turn, might contribute to ED[87]. Corroborating these findings, the activation of Nrf2 with probucol improves erectile function by stimulating the HO-1/DDAH/PPAR-γ/eNOS pathway[88]. In aged rats, the Nrf2 activators, sulforaphane and oltipraz, improves endothelial and erectile function, respectively. Sulforaphane also improves relaxation in human penile resistant arteries as well as in human corpus cavernosum isolated from patients with ED[89]. To date, the use of Nrf2 activators show promising outcomes in pre-clinical studies and might, therefore, have a role in the treatment of human diseases that are induced by oxidative stress.

Vascular senescence: more than a chronological challenge for hypertensive patients

Chronological aging correlates with an increase in cell senescence and the appearance of age-related diseases[90]. An interesting aspect of some diseases, including hypertension, is the fact that they can exacerbate the cell senescence process. For example, recently, hyperactivation of the AngII/AT1r axis has been discussed as a key mechanism contributing to premature vascular aging (for review, see [91]). AngII is the most common and widespread pro-senescent factor in hypertensive conditions[92], which could be due to its potent pro-oxidant effects mediated via activation of the NADPH oxidase enzyme. The pathophysiological roles of AngII in the vasculature contribute to vascular remodeling, which is a hallmark of chronological aging, and it is enhanced during hypertension. Some features of this process include fibrosis, calcification of the vessel wall, and inflammation of perivascular adipose tissue (PVAT). Of note here, a recent study has perceptively discussed that PVAT not only affects vascular health by secreting anti-contractile factors but also by assisting in arterial stress relaxation[93]. Therefore, senescence is a topic of particular importance because it might be a key factor for the maintenance of high blood pressure[91], and consequently, ED. However, there is still limited

information about senescence itself as a mechanism inducing ED under hypertension. Because chronological aging is a significant risk factor for ED, hypertension-associated senescence of the vasculature might also play a role in erectile tissues. Still, further studies are justified to clarify potential tissue-specific mechanisms in the corpus cavernosum.

Antihypertensive drugs: a double-edged sword challenge

Hypertension, in most cases, can be controlled with antihypertensive agents, which are frequently associated with undesirable side effects, including ED[94]. The relationship between antihypertensive medications and ED has been extensively studied, largely because it might affect the adherence to the prescribed therapy regimen resulting in poor management of blood pressure.

In a recent review, Doumas, Boutari, and Viigimma[17] insightfully debated the interplay between antihypertensive drugs and ED. As they discussed, there is evidence that some antihypertensive medications, including diuretics, β-blockers, and centrally acting agents, can negatively impact erectile function independently of the fact that these drugs are lowering blood pressure. Between these drugs, diuretics and β-blockers are the ones most often associated with ED[95]. While the mechanism by which diuretics affect erectile function is not entirely clear, it seems that β-blockers, especially the non-selective ones, contribute to ED by blocking β-2 receptors[96], which consequently leads to a higher degree of constriction in penile arteries. Additionally, a study reported lower testosterone levels in hypertensive men treated with atenolol[97]. Noteworthy, the literature is not cohesive, and conflicting findings have been reported, including a study suggesting that when a patient knows about the link between β-blockers and ED, this can lead to anxiety, which might cause ED[98]. Interestingly, nebivolol, a third generation β-blocker with higher affinity for β-1 receptors, has a positive effect on the erectile response. In fact, it reverses erectile dysfunction in a murine model of diabetes[99], which could be explained by the fact that nebivolol stimulates eNOS activity and because it has antioxidant properties[100]. Intricate results are also observed when comparing the effects of AngII receptor blockers (ARBs) and ACE inhibitors as ARBs appear to have beneficial effects, whereas ACE

inhibitors have a neutral impact on this parameter. As previously discussed, an increase in the expression levels of AngII directly impacts erectile function. Therefore, while the results obtained with ARBs are somewhat expected, the neutral results acquired with ACE inhibitors are counterintuitive. Such results might occur in response to the partial blockade of AngII production[94]. Thus, further studies are needed to clarify the impact of ACE inhibitors in erectile function.

This topic, the use of antihypertensive drugs, is of particular interest because drugs used to treat ED target the enzyme PDE5, and therefore, rely on endogenous NO production. While PDE5 inhibitors have been shown to be a safe pharmacological approach in hypertensive patients taking antihypertensive drugs[101], as we discussed above, these patients have reduced availability of NO, and consequently, they might not fully benefit from the use of PDE5 inhibitors. In fact, PDE5 inhibitors are ineffective for approximately 30% of the cases, and the presence of comorbid conditions, such as hypertension, negatively affects the drug outcomes[102]. Undoubtedly, the management of hypertension and ED represents a double-edged sword challenge in the clinical setting where physicians have to balance between optimal blood pressure control and patient compliance while preserving the quality of life of sexually active patients.

Immune system activation: a missing challenge for hypertension and ED

The immune system contributes to the pathophysiology of hypertension[103]. Recently, its innate arm was also shown to impair penile function[104–108]. The innate immune receptor, Toll-like receptor 4 (TLR4), is an emerging link between hypertension and ED as its activation contributes to blood pressure regulation[15,109] and affects cavernosal function in murine models[104,105]. It appears that the crosstalk between TLR4, hypertension, and ED occurs mainly through AngII, which is an endogenous ligand of the TLR4-MD2 complex[110].

There is a vast literature supporting the role of TLR4 in the pathophysiology of hypertension-associated vascular dysfunction as stimulation of this receptor leads to oxidative stress, secretion of pro-inflammatory factors, hypercontractility of small and large vessels, and alterations in NO availability (for review, see [15,111]). In penile tissue, inhibition of TLR4 in AngII-infused hypertensive mice improves cavernosal function by reducing contractile response, oxidative stress, and inflammation as well as increasing NO availability[104]. In agreement with these findings, it has been reported that overexpression of a TLR4 downstream adaptor, MyD88, worsens ED in hypertensive rats by reducing the expression of the eNOS enzyme and increasing cyclooxygenase 2[108]. In DOCA-salt rats, a neurogenic model of hypertension, blockade of TLR4 lowers blood pressure and improves erectile function[112]. Additionally, we have previously suggested and demonstrated that stimulation of TLR4 with high glucose impairs Leydig cell functionality[113,114], which might have a role in the pathophysiology of reduced sexual desire via crosstalk with testosterone[115].

Regarding sterile inflammation, it has been consistently described in the literature that blockade of TLR4 attenuates the release of pro-inflammatory cytokines during hypertension. TLR4 plays a role in the secretion of interleukin-6 in the systemic circulation as well as in mesenteric arteries isolated from SHR rats[116,117]. Likewise, in Ang-II infused mice treated with a neutralizing peptide against TLR4, there is a significant reduction in the levels of tumor necrosis factor-α (TNF-α) in the blood and cavernosal homogenates[104]. There is an extensive literature describing the pivotal role of TNF-α in controlling penile function[118] as the infusion of TNF-α, and consequently, activation of its TNFR1 receptor, enhances contraction in penile tissue, worsening erectile function[119]. This process is also accompanied by a reduction in the expression profile of the enzymes eNOS and nNOS[119], which are rescued in animals lacking the TNF-α gene, increasing corpora cavernosa relaxation[120].

It is undeniable that further studies are needed to dissect the pathways involved in the interplay between immunity, hypertension, and ED, as well as potential overlapping mechanisms caused by dual activation of immune responses. For example, it has been previously demonstrated that stimulation of TLR1/2 enhances contractility in penile tissue via crosstalk with RhoA/Rho-kinase[107], but it is unknown whether this heterodimer receptor plays a role in disease-associated ED, including

hypertension. Another interesting report in the literature showed that the NLRP3 inflammasome plays a dual role in corpora cavernosa relaxation as its inhibition reduced NO-mediated relaxation, and its activation enhanced NO-dependent relaxation mechanisms in this tissue[106]. However, it is still unknown whether similar results would be obtained in hypertensive animals.

Thus far, considering the vast literature tying innate immune receptors to the pathophysiology of hypertension-induced complications in multiple organs and systems, it is reasonable to assume that these receptors are involved in the pathophysiology of vasculogenic ED under high blood pressure conditions. Emerging evidence shows that understanding the signaling network of these receptors will allow for the development of more tailored therapies, especially during resistant hypertension, which could avoid the development of undesirable off-target side effects.

Final considerations

As discussed in this review, a dysfunctional endothelium plays a prominent role in the pathogenesis and pathophysiology of hypertension and ED. A continuous increase in the release of vasoconstrictors (e.g., AngII, ET-1, and aldosterone) leads to endothelial dysfunction, which affects not only the vasculature but also the corpus cavernosum. In penile tissue, endothelial dysfunction is a hallmark for the development of ED, which can be an early sign of systemic vascular disease, including hypertension. On the other hand, persistent alterations in the vascular system precede hypertension, a significant risk factor for ED. In Figure 2, we highlight pathways shared by hypertension and ED via the vasculature and vascular-like structures of the penis. An interesting aspect of this figure is the clear emergence of ROS as a hub, which reaffirms that oxidative stress is a pathological mechanism with a negative impact for vascular and erectile structures.

It is noteworthy that while we gathered a consistent body of evidence pointing to endothelial dysfunction, substantiated by the increased release of vasoconstrictors and reduced availability of vasodilators, as a common challenge for hypertension and ED, there is, still, much to be understood regarding the overlapping pathways of these conditions. Over the last decade, it is becoming widely

accepted that the innate immune system contributes to the pathophysiology of vascular-related diseases. The literature consistently shows that targeting these receptors, mainly TLR4, improves vascular and erectile function. However, while it seems that the receptors of innate immunity impact the disease progression, we are only now uncovering their part in hypertension and ED. Such contributions to our understanding shift the way we are approaching these diseases, and ultimately, will open research avenues for the development of new therapeutics, that hopefully, will be more effective in the management of both conditions.

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Figure 1. Summary of the interplay between hypertension and ED. A sustained increase in the release of vasoconstrictors (e.g., AngII, ET-1, aldosterone) leads to endothelial dysfunction, which affects the corpus cavernosum and the vascular system. In penile tissue, endothelial dysfunction is a hallmark for the development of ED, which can be an early sign of systemic vascular disease, especially hypertension. On the other hand, persistent alterations in the vascular system precede hypertension, a major risk factor for ED.

Figure 2. Overview of the major pathways shared by hypertension and ED. During hypertension, there is an increase in the release of vasoconstrictor peptides (e.g., AngII, ET-1, aldosterone), which via specific receptors trigger NADPH oxidase-induced ROS. In fact, ROS is a hub mechanism that crosstalks with many pathways that are important for the maintenance of vascular and erectile function. An increase in the release of ROS activates the RhoA/Rho-kinase pathway, associates with premature vascular aging, stimulates the transcriptional factors Nrf2 and NF-κB, and impairs NO availability. Simultaneously, activation of TLR4 also induces the stimulation of NF-κB, which not only affects ROS but also induces the release of pro-inflammatory mediators. Additionally, while ROS stimulates Nrf2, the activation of Nrf2 *per se* leads to the expression of antioxidant genes, which aims at inhibiting the effects of ROS. Nfr2 is also stimulated by the gaseous transmitter H_2S, which has many compensatory functions, including the inhibition of the PDE5 enzyme. In hypertensive conditions, it also appears that the Ang1-7/Mas receptor axis, which counterbalances the effects of the AngII/AT1r axis, elicits an inefficient response.

Figure 1

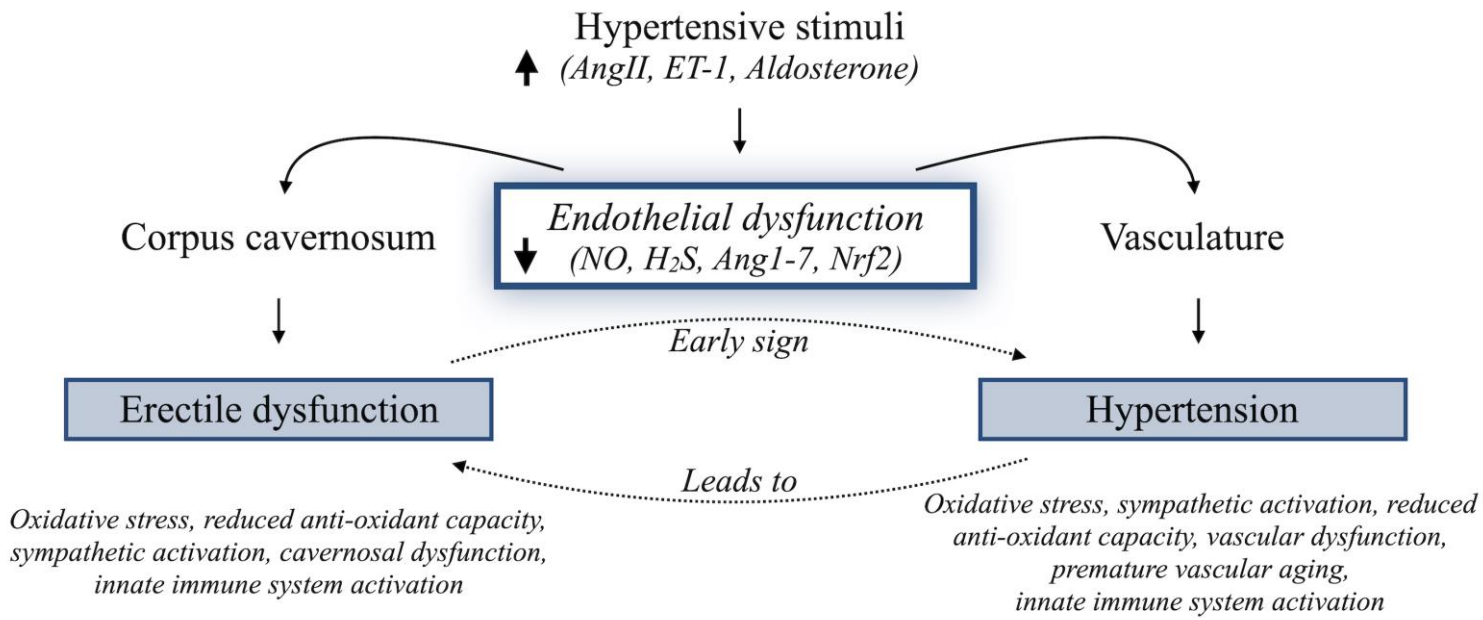

Figure 2