

Hypertension and Sexual Health



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Submission: June 17, 2017; Published: July 19, 2017

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Keywords: Hypertension; Erectile Dysfunction; Cardiovascular disease; Dyslipidemia

Abbreviations: ED: Erectile Dysfunction; GS: Guanylate Cyclase; AC: Adenylate Cyclase; eNOS: Endothelial Nitric Oxide Synthase; nNOS: Neuronal Nitric Oxide Synthase; GTP: Guanosine Triphosphate; PKG: Protein Kinase G; PKA: Protein Kinase A; PDE: Phosphodiesterase; PDE5I: Phosphodiesterase Type 5 Inhibitors; PAH: Pulmonary Hypertension; AS-ODN: Antisense Oligodeoxynucleotides

Epidemiology

One out of three adult Indians have Hypertension, unfortunately less than 50 percent of the hypertensives get diagnosed, only 12 percent of hypertensive's in the urban population and 9 percent of hypertensives in rural population achieve Blood pressure control [1]. Let us now look into the worldwide statistics of hypertension and the morbidity and mortality associated with hypertension.

Hypertension is a major public health concern globally. According to estimates from the World Health Organization, approximately 40% of adults aged 25 years or more were diagnosed with hypertension in the year 2008. The number of people diagnosed with hypertension increased from 600 million in 1980 to 1 billion in 2008. The prevalence of hypertension in adults aged 25 years or more is the highest, at 46% in Africa, and the lowest at 35% in the Americas [2] (Figure 1).

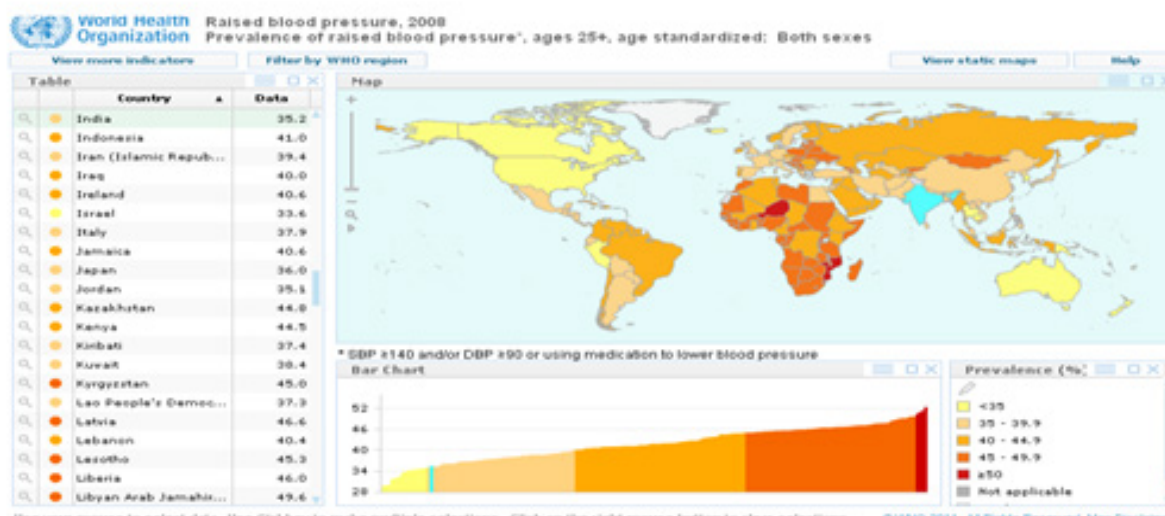


Figure 1: The prevalence has increased from 6.6% in 1988 to 35.2% in 2008.

Erectile Dysfunction is an Early Sign of Hypertension

Literature evidence shows a linear and continuous association between blood pressure level and cardiovascular morbidity and mortality, irrespective of age or sex. Similarly, reduction in blood pressure levels translates into a decreased incidence of cardiovascular and cerebrovascular complications. As shown in the slide, hypertension is an important contributor to the cardiovascular disease continuum. Dzau et al. first conceived the concept of cardiovascular disease continuum in 1991 [3].

Cardiovascular disease continuum is a sequence of events, precipitated by cardiovascular risk, which if left untreated, eventually leads to end-stage heart failure and death. HTN is an important risk factor which can precipitate this disease continuum. Other cardiovascular risk factors

include dyslipidemia, diabetes, obesity and smoking. There is growing evidence that early intervention in managing these cardiovascular risk factors is more crucial than treating the disease itself [4]. Thirty percent of Hypertensive men suffer from Erectile Dysfunction (ED), in fact there is a growing evidence which suggest that ED is an early sign of Hypertension. Erectile dysfunction in men and Hypertension occur due to Endothelial Dysfunction as endothelial dysfunction leads to contraction of the corpora smooth muscles of the penile architecture. Today the concept of endothelial health is that Penis is the Barometer of Endothelial health which forms the root of every cardiovascular pathophysiology. So an intact endothelium is a basic requirement for a normal vascular homeostasis, which allows contractions and relaxations of the corpora spongiosal smooth muscle, which determines the normal blood pressure maintenance.

Mechanism of Erection (Figure 2)

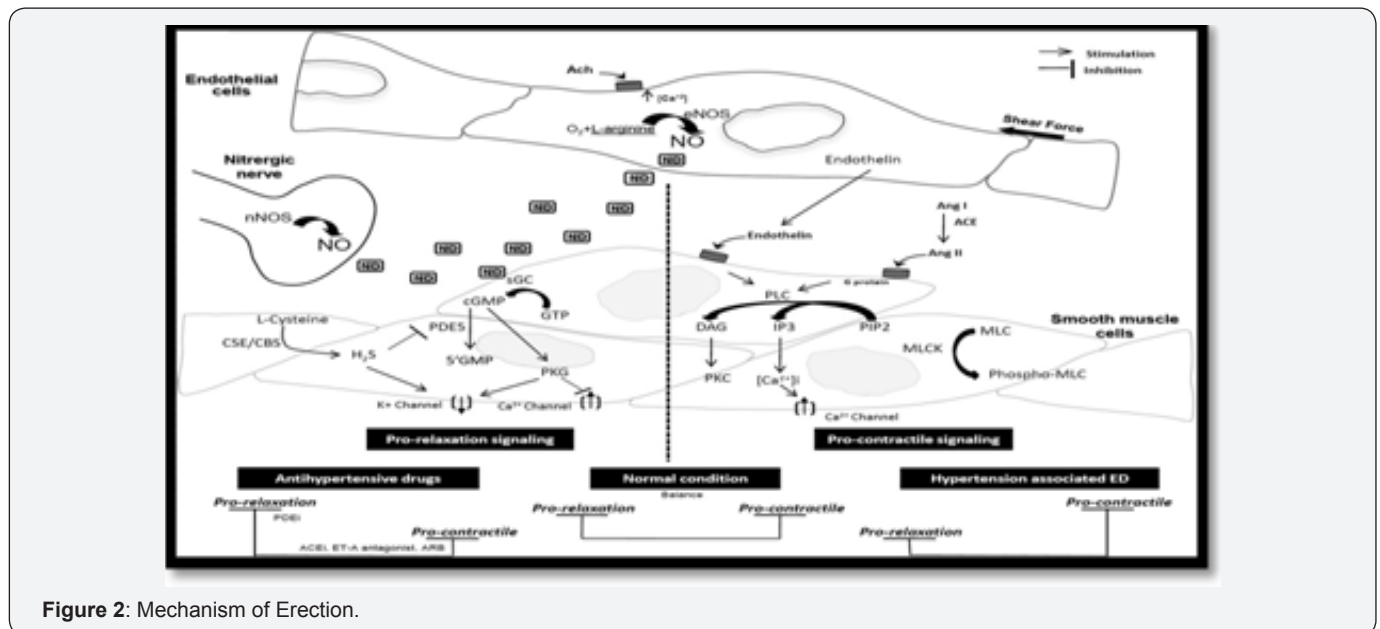


Figure 2: Mechanism of Erection.

ED is defined as the regular inability to reach or maintain a penile erection of sufficient quality to perform satisfactory sexual intercourse; it has been progressively associated with many comorbidities. There are two main intracellular mechanisms for relaxing the cavernosal VSM leading to normal erectile function: the guanylate cyclase (GS)/cGMP and adenylate cyclase (AC)/cAMP pathways. Both pathways results in NO release, which is the main factor initiating erection. NO is produced by endothelial (eNOS) or neuronal (nNOS) nitric oxide synthase via acetylcholine or neuronal stimulation. Upon its release, NO diffuses locally into adjacent VSMC of the corpus cavernosum and binds to GC, which catalyzes the conversion of guanosine triphosphate (GTP) to cGMP. Consequently, protein kinase G (PKG) is activated, leading to a decrease in cytosolic Ca²⁺ by various mechanisms. cGMP also blocks Rho-kinase activation.

The decay in cytosolic Ca²⁺ concentration induces relaxation of the VSMC in the penis, leading to dilation of arterial vessels, increased blood flow into the corpora cavernosa, allowing penile erection. Contributing to penile relaxation and reduction of intracellular Ca²⁺, other substances activate the enzyme AC, leading to cAMP production, which in turn activates protein kinase A (PKA) [5]. The erectile process is completely dependent on relaxation and intact endothelium function, which is also true for vascular homeostasis and normal BP maintenance. cGMP and cAMP levels are modulated by phosphodiesterase (PDE) enzymes, which cleave these signaling molecules to 5’GMP. Another mechanism involved in maintenance of the erectile process is the phosphatidylinositol 3-kinase (PI3-kinase) pathway that activates the serine/threonine protein kinase Akt (also known as PKB). PKB causes direct phosphorylation of eNOS, reducing the enzyme’s Ca²⁺ requirements and causing

increased production of NO. It has been suggested that rapid, brief activation of nNOS initiates the erectile process, where as PI3-kinase/Akt-dependent phosphorylation and activation of eNOS by augmented blood flow and endothelial shear stress lead to sustained NO production and maximal erection.

Mechanism of ED in Hypertension

Certain neurotransmitters like Angiotensinogen II which leads to contraction of the corpora spongiosa smooth muscle and sodium retention are also responsible for hypertension. Studies have shown a increase in Angiotensinogen II in the cavernous blood of patients having erectile dysfunction. Other neurotransmitter endothelin 1 which is also an endothelium derived peptide also through activation of its receptors ET A and ET B exert a vasoconstrictor effect on the corpora spongiosa and it also has a vasoconstrictor effect on internal pudendal artery which supplies blood to the penile vasculature. All these neurotransmitters bring about morphological changes in the penile vasculature by reduction of elastic fibers, increase in the collagen of the sinusoids and thinning of the tunica albugenia. Also seen is increase in connective tissue in the amyelinated nerves which results in diminished blood supply to the penis. During hypertension the endothelium produces less NO as its production is scavenged by increase in ROS generation. Many vascular diseases like atherosclerosis are known to begin because of interaction between ROS and NO and ultimately lead to diminish NO and damage to mitochondria which leads to apoptosis and cell death.

D- Anti-hypertensive Therapy

Anti-hypertensive Therapy though there are over 100 antihypertensive agents yet hypertension is a burning issue and a huge economic burden.

The class of antihypertensive drugs is,

- o Diuretics
- o Beta Blockers
- o Calcium Channel Blockers
- o Ace Inhibitors
- o Angiotensinogen 2 receptor Blockers
- o Centrally acting Agents

Most of the antihypertensive agents produce sexual dysfunctions like erectile dysfunction in males except Calcium Channel Blockers and Angiotensinogen receptor Blockers. Diuretics reduce sodium reserves, and reduce the blood volume and increase peripheral resistance. Beta Blockers directly cause erectile dysfunction, Calcium Channel blockers reduce the influx of Calcium and dilate the arteries. Ace inhibitors and angiotensinogen receptor blockers by increasing bradykinin levels and vasodilation.

Evaluation and Treatment of Ed in Hypertensive Patients

A detailed sexual history should be obtained in patients with new onset of hypertension before initiating drug therapy. The sexual complaints of the patients may necessarily not be due to medications or their side effects. The least number and lowest dose of blood pressure medication drugs should be used to manage hypertension. Patients who do not take medicines for hypertension because of the side effects should be followed up regularly.

Detailed sexual history in males includes asking about erections less than full, during coitus, early morning, during masturbation, in all sexual and asexual situations, adequate erections during foreplay lost before intromission, presence of underlying medical illness and ejaculatory disturbances.

Since AngII plays an important role in the etiology of ED during hypertension. Studies showed that treatment with ARBs improves endothelial function in the cavernosal tissue. Studies have shown that treatment of hypertensive patients with ARBs resulted in improved sexual activity and erectile function.

Treatment of ED with PDE5 Inhibitors

- o The phosphodiesterase type 5 inhibitors (PDE5I) are ideal and accepted treatment for ED. PDE5I act by inhibiting PDE5, the enzyme that catalyses the breakdown of the second messenger cGMP.
- o The PDE5I are used also for the treatment of pulmonary hypertension (PAH). However, patients treated with nitrates or nitrate-donors or vasodilators such as α -blockers should not take PDE5I, otherwise, combining these drugs will result in hypotension
- o Treatment with β -blockers is considered to cause ED.

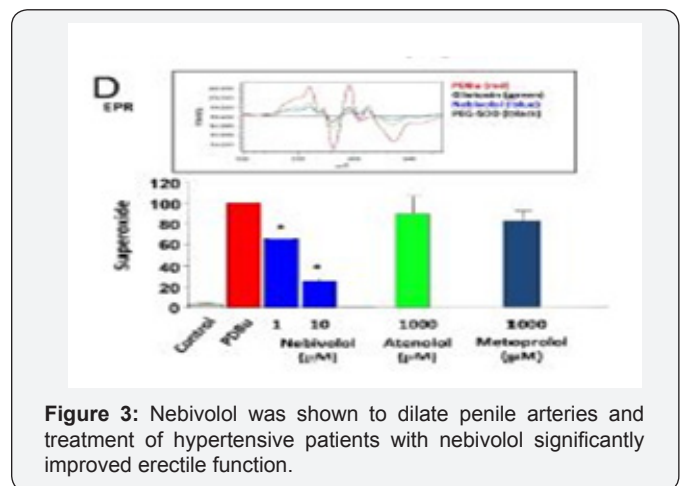


Figure 3: Nebivolol was shown to dilate penile arteries and treatment of hypertensive patients with nebivolol significantly improved erectile function.

- o However, the new generation β -blocker nebivolol may have positive effects on erectile function. Recent studies showed that nebivolol treatment improves endothelial function and reverses ED in animals through the activation

of the NO/cGMP pathway. Nebivolol was shown to dilate penile arteries and treatment of hypertensive patients with nebivolol significantly improved erectile function [6] (Figure 3).

o In a Randomised double blind parallel group multicentric clinical trial on Atpure (S Atenelol 25mg) versus Racemic Atenelol 50mg in stage 1 & 2 Hypertension revealed that in all the 300 patients studied at 6 centers in India, HR and BP reduction was not significantly different. A significant finding was that In Atenelol 50mg group, 2 patient s had Bradycardia, 7 had brochospasms & 24 patients have loss of libido. But in In S Atenelol 25mg none had Bradycardia or bronchospasms and no changes in Libido were seen [7] (Figure 4).

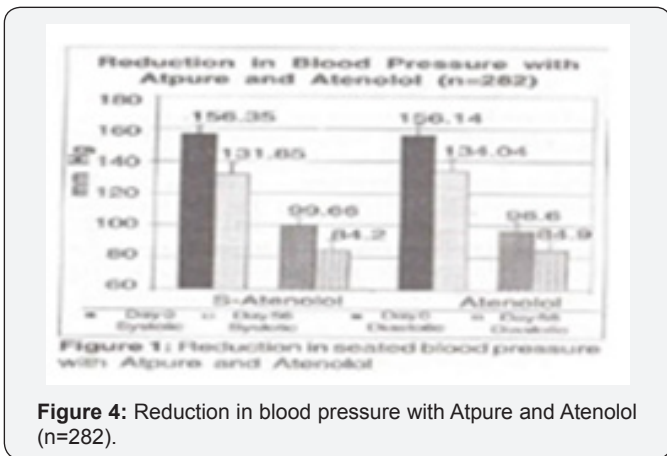


Figure 4: Reduction in blood pressure with Atpure and Atenolol (n=282).

o Treatment of patients with diuretics alone or with diuretics added to their therapy was shown to worsen sexual dysfunction. Amongst all diuretics Indepamide has shown to have less sexual side effects in men.

o In a meta analysis of randomized, double blind, placebo controlled trials on effect of oral L Agrinine supplementation on Blood pressure in humans revealed that oral L Arginine supplementations significantly lowers systolic as well as diastolic Blood pressure. L Arginine is known to improve endothelium dependant dilatation and reduces monocyte adhesion to endothelial cells in young men with coronary artery disease [8,9].

Future Therapies for Hypertension and Sexual Dysfunction [10]

Current drugs, although effective, have poor compliance, are expensive and short-lasting (hours or one day). Gene therapy offers a way to produce long-lasting antihypertensive effects (weeks, months or years). We are currently using two strategies: antisense oligodeoxynucleotides (AS-ODN) and antisense DNA delivered in viral vectors, to inhibit genes associated with vasoconstrictive properties. The results of these trials in rats have shown no sexual dysfunctions.

Conclusion

Erectile Dysfunction is a result of Endothelial Dysfunction. Erectile Dysfunction usually occurs before Hypertension sets in. Of all the antihypertensive drugs, ARB’s are the drugs which are sex neutral and amongst the beta blockers Nebevelol, amongst the diuretics Indepamide have less sexual dysfunctions in males. Atpure (S Atenelol 25mg) showed no decrease in sexual dysfunction.

Salt restricted Diet and Exercise irrefutably are the default treatment followed by proper evaluation prior to initiating antihypertensive therapy and In future Gene therapy in hypertension shall be a promising therapy.

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DOI: [10.19080/JOJUN.2017.03.555620](https://doi.org/10.19080/JOJUN.2017.03.555620)

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