Sexual Function in Untreated and Treated Hypertension

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Margus Viigimaa and Michael Doumas

29.1 Introduction

One of the most implicit dangers for public health that physicians have to detect early and treat is, without doubt, hypertension. Hypertension affects >25 % of the general population but its frequency is rapidly increasing with future projections being very discouraging. As the westernized way of living is rapidly expanding and as life expectancy increases, it has been estimated that by the year 2025 around 1.5 billion people worldwide will be hypertensive, thus making hypertension a major and alarming threat to public health [1]. This danger can be better perceived if we take into account the fact that long-standing high blood pressure severely affects all of the major organs of our body and that as such, its major health complications include: heart disease (left ventricular hypertrophy, heart failure, myocardial infarction), stroke, retinopathy, nephropathy, and structural and functional of blood vessel deformities [2].

For many decades, sexual dysfunction has been thought to have either a psychological or anatomical origin; however, accumulating data point toward a vascular disease in the vast majority of affected patients. Since hypertension affects all the vessels of the body, it could be assumed that the genital vessels would also be affected. In addition, the treatment of hypertension includes several different classes of antihypertensive drugs, so one could argue that sexual dysfunction could actually be a pharmacological side effect. This opened the way for more extensive

M. Viigimaa (✉)
Institute of Biomedical Engineering, Tallinn University of Technology, Tallinn, Estonia
e-mail: Margus.viigimaa@regionaalhaigla.ee

M. Doumas
Department of Internal Medicine, Aristotle University, 54643 Thessaloniki, Greece
e-mail: michalisdoumas@yahoo.co.uk

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scientific research to discover whether sexual dysfunction is more prevalent in hypertensive patients than in normotensive subjects, and if so, whether sexual dysfunction is the result of hypertension per se, a side effect of antihypertensive treatment, or a combination of both [3–6].

In order to establish a firm association between hypertension and sexual dysfunction, we have to consider whether (1) sexual dysfunction is more frequently encountered in hypertensive patients than in normotensive subjects, and (2) whether there is a pathophysiological link between high blood pressure and sexual dysfunction, suggesting a causal relationship and not an epiphenomenon.

To delineate the effect of hypertension per se or the effect of antihypertensive drugs, we should consider whether: (1) sexual dysfunction is more prevalent in untreated hypertensive patients than in normotensive subjects of similar characteristics; (2) sexual dysfunction is more prevalent in treated than in untreated hypertensive patients; and (3) initiation of antihypertensive therapy worsens sexual function and results in sexual dysfunction.

It would then be very interesting, from a clinical point of view, to examine whether the various antihypertensive drug classes exert different effects on sexual function, and if so, whether a change in administered antihypertensive drugs could in fact ameliorate or even restore sexual function. Therefore, we did so by critically evaluating the available data.

29.2 Sexual Dysfunction in Hypertension Compared to Normotension

Sexual dysfunction is defined by the World Health Organization as "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish [7]." Since sexual dysfunction affects both genders, a more specific definition has emerged to clarify what sexual dysfunction means for men and women, respectively. Regarding men, erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse [8]. On the other hand, sexual dysfunction for women is considered as the "persistent or recurrent decrease in sexual desire or in sexual arousal, or the difficulty or the inability to achieve an orgasm, or the feeling of pain during sexual intercourse [9]."

Considering the structural and functional alterations that hypertension can provoke to the penile vasculature (discussed in the next section of the chapter) [10], one would expect that the prevalence of sexual dysfunction in hypertensive individuals of both sexes would be much higher than in the normal normotensive population.

However, the first large study to investigate the prevalence of sexual dysfunction in hypertensive subjects, the Treatment of Mild Hypertension Study (TOMHS), seriously challenged this belief since it showed a low prevalence of sexual dysfunction in individuals with hypertension (14.4 % in men compared to 4.9 % in women) [11]. Nevertheless, this study had several significant limitations: (1) it was not designed to specifically assess sexual dysfunction and thus only one

question was used for evaluating sexual dysfunction; (2) it included only patients with mild hypertension whereas patients with severe hypertension and diabetes mellitus were excluded; (3) participating patients were aged between 45 and 69 years, and older patients were excluded; and (4) the study took place when both patients and physicians were not accustomed or even reluctant to discuss and reveal issues like sexual dysfunction.

Despite some initial doubts, several other well-conducted studies have, over the years, proved and supported the initial correlation between hypertension and a higher prevalence of sexual dysfunction. Furthermore, it has been shown that individuals with hypertension have up to a sevenfold higher incidence of erectile dysfunction than their normotensive counterparts, with a relative risk from 1.3 to 6.9 [12]. Overall, the existing data indicate that erectile dysfunction is on average twice as prevalent in hypertensive subjects compared with normotensive subjects.

Similar findings have been observed in hypertensive women, although the existing data are far from being conclusive. An increased frequency of sexual dysfunction in hypertensive women was also supported by a small case–control study of 104 US women with mild hypertension compared with 107 normotensive women [13]. In this study, hypertensive women reported a higher rate of pain during sexual intercourse, decreased vaginal lubrication, and a lower rate of successful orgasm than normotensive women. Another study of 417 women demonstrated that sexual dysfunction was evident in 42.1 % of hypertensive women compared with 19.4 % of their normotensive counterparts, with an odds ratio of 3.2 [14]. Nonetheless, further studies are needed to establish an association between hypertension and female sexual dysfunction, an association which is remarkably ignored and understudied.

Altogether, the available data clearly indicate that sexual dysfunction is more frequently encountered in hypertensive patients than in normotensive individuals. More importantly, the prevalence of sexual dysfunction in hypertensive patients is considerably high, highlighting the clinical significance of this feature of hypertension.

29.3 Pathophysiology of Sexual Dysfunction in Hypertension

Taking into account male erectile physiology, which is primarily a vascular phenomenon, and the beneficial role of nitric oxide and the detrimental role of angiotensin II in male erection, it can be concluded that an intact penile vasculature with an efficient level of vasodilation and blood flow are the prerequisites for a firm and successful erection to occur [15]. As such, it would be expected that any lesion of the vessels or a lack of ability to distend would lead to impaired blood flow to the penis and the inability to achieve or maintain an erection, thus leading to sexual dysfunction. Hypertension is a clinical entity that primarily targets the vessels, so it is not surprising but rather anticipated that a strong and close association between hypertension and sexual dysfunction has been observed.

More specifically, it has been proved that hypertension results in structural and functional abnormalities which lead to sexual dysfunction. The most prominent structural abnormality is atherosclerosis. An increase in blood pressure has been highly implicated in the atherosclerotic process. Penile arteries are also affected, which results in reduced blood supply to the cavernous bodies of the penis, thereby preventing the acquisition of a full erection [16]. Apart from atherosclerotic lesions, three other structural abnormalities have been implicated in the pathogenesis of sexual dysfunction in men due to hypertension: smooth muscle hypertrophy of the wall of the cavernous arteries, as well as hypertrophy of the smooth muscle layer of the cavernous space, and an increase in type III collagen fibers in the extracellular matrix [17].

Additionally, several studies have demonstrated the functional abnormalities that are due to hypertension, the most important being a blunting of the nitric oxide-induced relaxation mechanism of the penile vasculature, due to decreased nitric oxide bioavailability [18]. Another important contributing factor is the activation of the renin–angiotensin system in hypertension. Angiotensin II not only causes vascular hypertrophy but also provokes the contraction of the corporeal smooth muscle through its action on angiotensin type 1 receptors. The significance of angiotensin II in sexual function can be better understood if we take into account that production of angiotensin II is increased during the detumescence phase of an erection [19]. Furthermore, an intracavernosal injection of angiotensin II in experimental animals has been shown to terminate the erection whereas injection of an angiotensin receptor blocker (losartan) has the opposite result. Apart from angiotensin II, several other hormones and peptides have been implicated in the pathophysiology of sexual dysfunction in hypertensive patients. These include: sex hormones, bradykinin, endothelin-1, catecholamines, and Rho–Rho kinases.

Structural and functional abnormalities affecting the clitoris and the vagina have also been observed in hypertensive females and follow a similar pattern to the one observed in males [20]. The role of angiotensin II and that of decreased nitric oxide bioavailability should also be taken into account as the two main pathophysiological mechanisms underscoring female sexual dysfunction. The relative lack of data regarding sexual dysfunction in hypertensive women calls for further systematic research in this field.

Although the prevalence of sexual dysfunction in hypertensive patients is higher than in normotensive subjects, another important issue should be considered: whether the increased prevalence of sexual dysfunction in hypertensive individuals is due to hypertension per se or whether it is a side effect of antihypertensive drugs, or maybe a combination of both factors.

29.4 Sexual Dysfunction in Untreated Hypertension Compared to Normotension

Data regarding the prevalence of sexual dysfunction in hypertensive patients who have never received treatment are quite limited and regard mainly male patients. However, all available data point toward an increased prevalence of sexual

dysfunction in untreated hypertension compared to normotension [12]. In a study of men with untreated hypertension, though free of cardiovascular disease or other cardiovascular risk factors, and normotensive men of similar characteristics, it was found that hypertensive patients who had never received treatment had an almost 40 % higher prevalence of erectile dysfunction compared to normotensive individuals [21]. Likewise, in a similar study in women, it was found that female sexual dysfunction was significantly more prevalent in hypertensive than in normotensive women [14]. The available data are, however, far from conclusive and further studies are needed to clarify this issue.

29.5 Sexual Dysfunction in Treated Versus Untreated Hypertension

Available data come from observational studies that consistently suggest a higher prevalence of erectile dysfunction in treated than in untreated hypertension. In summary, treated hypertensive patients are twice as likely to suffer from erectile dysfunction as untreated patients [12]. Indeed, an observational study carried out in Greece revealed that the prevalence of erectile dysfunction in treated patients was double than the prevalence seen in patients who had never been treated (40.4 % versus 19.8 %) [21]. These findings would suggest that treating hypertension contributes to sexual dysfunction. It could be assumed that antihypertensive drugs may be implicated in this phenomenon [22]. However, it cannot be excluded from the existing data that treated patients had more severe hypertension, significantly higher target organ damage, or more comorbidities than untreated patients and that these factors may be the actual contributors to sexual dysfunction rather than the antihypertensive drug therapy.

29.6 Sexual Dysfunction with Antihypertensive Treatment: Potential Differences Between Drug Classes

Data regarding the effects of antihypertensive drugs on sexual function come from various studies: (1) animal studies; (2) observational studies; (3) small clinical studies; (4) large randomized trials; and (5) meta-analyses. The vast majority of available data concern male sexual function, with fewer data sets reporting female sexual function. Since several studies compared the effects of specific antihypertensive drug classes on sexual function, data regarding the effects of antihypertensive therapy and the differences between drugs is presented together in this section, first for erectile dysfunction and second for female sexual dysfunction.

Several lines of evidence from animal studies point toward diverse effects of antihypertensive drug classes on erectile function. It has been shown that the structural changes in penile vessels induced by hypertension can be reversed by some drugs, while remaining unaffected by others [23, 24]. In particular,

angiotensin receptor blockers and nebivolol exert beneficial effects on the structural and functional alterations induced by hypertension in spontaneously hypertensive rats, while such effects are not observed with calcium antagonists or atenolol, suggesting differences between antihypertensive drug categories, but also suggesting that such differences exist even between drugs of the same class.

Data from observational studies unveiled differences on sexual function in patients taking various antihypertensive drugs. Hypertensive patients taking beta-blockers and diuretics show significantly worse sexual function than patients who are administered newer drugs such as angiotensin receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists [21].

A few small clinical studies supported both the experimental and observational data [25–27]. They showed the detrimental role of beta-blockers on sexual function, since the number of sexual intercourses per month was significantly lower with beta-blockers than with placebo. This property is shared not only by the first-generation beta-blockers, such as atenolol, but also by the newer vasodilating agents, such as carvedilol. In contrast, angiotensin receptor blockers not only do not prove detrimental to sexual function compared to placebo, but they significantly improve the number of sexual intercourses per month in hypertensive patients compared to placebo, suggesting a beneficial role for this class of agents.

Data from large clinical trials evaluating the role of antihypertensive drugs on sexual function is significantly limited. Available data come from older studies Medical Research Council (MRC); Trial of Antihypertensive Interventions and Management (TAIM), Treatment of Mild Hypertension Study (TOMHS), Aliskiren Effect on Plaque Progression In Established Atherosclerosis Using High Resolution 3D MRI (ALPINE)] that were not specifically designed to explore the effects of antihypertensive agents on sexual function, not even as a secondary end point [12, 28–30]. In the MRC and TAIM trials, diuretics had a significantly worse effect than beta-blockers, which in turn had a significantly worse effect than placebo [28, 29]. TOMHS showed a much higher incidence of sexual dysfunction in the group of patients receiving chlorthalidone over a period of 2 years compared to placebo (17.1 % versus 8.1 %; $p = 0.025$); however, the statistical significance was lost during the following 2 years [12]. In contrast to previous findings, sex life satisfaction was similar with hydrochlorothiazide and candesartan in the ALPINE trial [30]. Only a substudy of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomised Assessment Study in Angiotensin converting Enzyme inhibitor intolerant subjects with Cardiovascular Disease (TRANSCEND) studies was specifically designed to assess erectile function by using a validated questionnaire [31]. In the ONTARGET study, sexual function remained practically unaltered with ramipril, telmisartan, and their combination, with no significant differences between treatment arms, while in the TRANSCEND study there were no differences in sexual function with telmisartan or placebo. It has to be considered, however, that the individuals participating in these trials were high-risk patients with significant cardiovascular comorbidities, and that renin–angiotensin system inhibitors were added on top of prior multidrug therapy; therefore, definite conclusions regarding

the effect of angiotensin receptor blockers on sexual function in untreated hypertensive patients cannot be drawn from these studies. Another study specifically designed to assess sexual dysfunction in hypertension, the Nitric Oxide, Erectile Dysfunction and Beta-Blocker Treatment (MR-NOED) trial, showed that nebivolol significantly ameliorates sexual function in hypertensive patients [32].

Data from meta-analyses are also restricted. Due to limited available data, no specific meta-analysis exists that examines the role of antihypertensive drugs on erectile function. Relevant information comes from meta-analyses assessing the adverse effects of older antihypertensive drugs. Sexual problems are frequently encountered when diuretics are used in combination with other drugs, and similar problems frequently affect patients taking beta-blockers [33, 34].

The negative effects of beta-blockers on sexual function have been recently debated [35]. The findings from two European studies suggest that erectile dysfunction following treatment with beta-blockers is mainly due to a placebo effect, and that beta blocker-induced erectile dysfunction is perceived and not real [36, 37]. It is noteworthy that the three randomized crossover studies carefully designed and conducted by Fogari and colleagues [25–27], whose aim is to specifically evaluate the effect of antihypertensive treatment on erectile function, provide strong evidence for a detrimental effect of beta-blockers. Although a placebo effect, at least in some patients, cannot be entirely excluded, available data indicate that a negative effect of beta-blockers on sexual function cannot be excluded [35].

Data regarding female sexual dysfunction associated with antihypertensive drugs are significantly scarcer than data regarding erectile dysfunction. Only a few studies address this aspect, which remains considerably understudied, possibly due to lack of familiarity by treating physicians and the absence of available drugs to effectively manage female sexual dysfunction. Existing data from experimental and observational studies and small clinical studies point toward similar effects of antihypertensive drugs in male and female sexual function [14, 20, 38]. However, the available data are far from conclusive and further research is needed in this area.

29.7 The Effect of Changing Antihypertensive Drugs on Sexual Function

According to the recommendations issued by the second Princeton Consensus, a change in class of antihypertensive medication rarely results in the restoration of sexual function [39]. However, the available data suggest significant benefits in sexual function when existing antihypertensive therapy is switched to either angiotensin receptor blockers or nebivolol [40–43]. It is noteworthy that the relevant data come from open-label, so definite conclusions cannot be reached until information from randomized controlled trials becomes available.

29.8 Conclusions

As the interaction between doctor and patient becomes closer and closer by the years, it will allow conditions such as sexual dysfunction to be discussed more frequently and openly. Formerly a taboo subject, sexual dysfunction unarguably plays a very important role on patients' and their partners' sexual lives thus exerting a major impact on quality of life. However, the strong association between hypertension and sexual dysfunction and the impact of antihypertensive drugs on sexual function have called in question whether sexual dysfunction in hypertensive individuals is the result of hypertension per se, a side effect of antihypertensive treatment, or a combination of both factors. Many lines of evidence indicate that hypertension per se is indeed associated with sexual dysfunction, while the drugs used in the treatment of hypertension can indeed have a deleterious effect on sexual function, although this is generally true of older generation drugs (beta-blockers, diuretics) than newer drugs, such as angiotensin receptor blockers and nebivolol, which might even improve sexual function. Therefore, a combination of both factors may frequently be encountered by doctors; it is the responsibility of the treating physician to uncover any underlying contributing factors to effectively manage hypertensive patients who also present with sexual dysfunction.

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