

## HYPERTENSION AND SEXUAL DYSFUNCTION

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Sexual dysfunction represents a common condition in the general population placing a major burden on patients' and their sexual partners' quality of life. Sexual dysfunction has been traditionally attributed to psychogenic origins and managed by mental health professionals and urologists. However, advances in pathophysiology research point to a vascular origin of the problem in the majority of patients, possibly due to atherosclerotic lesions in the genital arteries that result in decreased blood flow. In addition, the discovery of phosphodiesterase-5 inhibitors has produced an easily available effective treatment, and nowadays patients seek help from cardiologists, internists and general practitioners in increasing numbers. Physicians skilled in hypertension management often feel unqualified to deal with sexual problems since adequate training regarding sexuality has not been offered in under- or in post-graduate training [1]. In our point of view, several important reasons exist to motivate hypertension specialists to become familiar with sexual dysfunction, including the following facts:

- sexual dysfunction can be detected in a significant percentage of hypertensive patients, affecting their quality of life. Since most patients are reluctant to address this issue, they either remain untreated or obtain drugs from unauthorized sources (Internet) without medical advice;
- sexual dysfunction may be an adverse event of antihypertensive medications. Since some drug categories may cause sexual dysfunction, a change in drug category may alleviate the symptoms;
- phosphodiesterase-5 inhibitors are vasodilators and reduce blood pressure. Although blood pressure reduction is usually modest, some susceptible patients (especially older and sodium-depleted) might exhibit symptomatic hypotension;
- sexual intercourse may be detrimental in high-risk patients, and patients with untreated, poorly-controlled, accelerated or malignant hypertension are considered as high-risk; thus, sexual activity has to be deferred until patients' stabilization and after appropriate medical counselling has been obtained;
- many patients with hypertension suffer from coronary artery disease or heart failure and are on nitrate treatment. Since PDE-5 inhibitors are contraindicated in patients receiving nitrates, and special precautions have to be taken, patients must be under close medical supervision;
- sexual dysfunction can be considered as an early sign of widespread atherosclerotic disease in other vascular beds as well. Thus, its detection offers an opportunity for early recognition of atherosclerotic lesions in other sites (coronary vessels, brain, kidney, peripheral arteries) through thorough investigation.

### Definition and prevalence

Erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse. It has been recently estimated that over 150 million men all over the world have some degree of erectile dysfunction, while the projection for the patient population in 2025 is 322 million men worldwide. The prevalence of erectile dysfunction in the general population varies markedly among different countries, ranging from 15% in Brazil to 74% in Finland, probably reflecting different sample populations and assessment methods, as well as cultural and religious differences in discussing and accepting such a social stigma [2–12].

The vast majority of available data indicates that erectile dysfunction is more frequent in patients with essential hypertension when compared to normotensive subjects, irrespective of the method used for erectile dysfunction evaluation. Severity and duration of hypertension, age and antihypertensive treatment seem to be major determinants of erectile dysfunction in hypertensive patients [13].

However, available data on hypertension is not of the highest quality, showing pronounced prevalence variation (26–79%) and sometimes relying on self-reporting of hypertension without validation of medical records; furthermore, the cohorts seem highly-selected in some studies without reporting co-morbidities, and the meth-

ods used for erectile function assessment are not appropriate [1, 14–16]. Thus, we believe that only a multinational study all over Europe, with accurate blood pressure measurement, careful recording of all concomitant conditions, and use of a validated method (the International Index for Erectile Function, IIEF) could precisely evaluate the prevalence of erectile dysfunction in hypertensive patients.

### Physiology and pathophysiology

Penile erection is the result of a complex interplay between psychological, neurological, hormonal and vascular factors. Since the sympathetic nervous system, the intact endothelium and notably nitric oxide have a central role in a successful erection, it is no surprise that essential hypertension is related to erectile dysfunction.

Hypertension induces structural changes in the penile vasculature thus decreasing arterial blood inflow, as well as functional abnormalities like increased sympathetic activity, endothelial dysfunction, reduced nitric oxide bioavailability and activation of the renin-angiotensin system. All of the above abnormalities may lead to impairment of penile vasodilatation, lack of relaxation and subsequent failure to achieve an orgasm.

### Relation to cardiovascular disease

Patients with erectile dysfunction have an increased risk of suffering from asymptomatic severe coronary heart disease [17]; moreover, erectile dysfunction correlates with the number of occluded coronary vessels as assessed by angiography [18]. In addition, it seems that erectile dysfunction and coronary heart disease share common risk factors, since erectile dysfunction is more prevalent in individuals with multiple cardiovascular risk factors [19].

Based on data demonstrating that the probability of undiagnosed coronary artery disease is very high in patients with erectile dysfunction (up to 40%) [20], we believe that erectile dysfunction might raise the possibility of underlying cardiovascular disease by being one of the first signs thereof. Therefore, erectile dysfunction can be considered as an "early diagnostic window" of coronary heart disease.

### Safety of sexual activity in hypertension

According to the Second Princeton Consensus Conference [21], patients with controlled hypertension are considered low-risk patients and may safely proceed with sexual intercourse, since sexual activity in such patients doubles the extremely low risk of a cardiac event. On the contrary, high-risk patients have a 10-fold increased risk of cardiac event during sexual intercourse as well as in the following two hours. Since patients with untreated, poorly controlled, accelerated, or malignant hypertension are considered high-risk patients, sexual activity should be deferred until their condition has been stabilized or a decision has been made by a cardiologist that sexual activity may be safely resumed [21].

### Quality of life

Erectile dysfunction compromises overall quality of life, exerting a major impact on patients' social and psychological well-being [22]. Moreover, it adversely affects patients' sexual partners' interest in sex and their quality of life [23], thus resulting in the loss of emotional and physical intimacy for both of them (sometimes even leading to divorce).

### Effects of antihypertensive drug therapy

Although essential hypertension is related to erectile dysfunction, an important issue has been raised as to whether this represents a result of hypertension *per se*, of antihypertensive treatment, or a combination of both [16, 24].

Erectile dysfunction is considered an adverse drug event in one out of five cases [25]. Antihypertensive agents represent one of the most implicated drug classes [25], and hypertensives who experience erectile dysfunction (real or perceived) become non-adherent to treatment and usually discontinue drugs.

Available data clearly demonstrate that older antihypertensive drugs exert negative effects on erectile function. In detail, centrally-acting antihypertensives, diuretics and beta-blockers have been related to erectile dysfunction, and many patients experience erectile dysfunction as a consequence of treatment with these drugs [26–28]. Although data regarding ACE-inhibitors and calcium antagonists are not quantitatively and qualitatively adequate, they point towards a neutral effect of these drugs on erectile function [24]. On the contrary, available data for alpha-blockers and especially for angiotensin receptor antagonists suggest that these drugs may have beneficial effects on erectile function [24, 29–32]. However, we believe that large, randomized trials, examining specifically erectile function, are needed to demonstrate clearly the effect of the different classes on erectile function.

Although the Second Princeton Consensus [21] states that a change in class of antihypertensive drugs rarely results in the restoration of sexual function, data from open studies challenge this statement indicating that a switch to angiotensin receptor blockers [29–31] or specific beta-blockers (nebivolol) [33] may reverse erectile dysfunction in hypertensive patients taking drugs from other classes. Thus, it seems that a switch to angiotensin receptor blockers might prove to be an effective approach for hypertensive men with erectile dysfunction while on other antihypertensive agents, before administering a phosphodiesterase-5 (PDE-5) inhibitor [24].

### PDE-5 inhibitors in hypertensive patients

Although all available PDE-5 inhibitors (sildenafil, tadalafil, vardenafil) may cause hypotension through increased nitric oxide bioavailability, and despite the statement of the American Heart Association (in 1999) indicating that sildenafil could be “potentially hazardous” in hypertensive patients taking complicated, multi-drug regimens [34], recent clinical data nonetheless clearly demonstrate that PDE-5 inhibitors may be safely co-administered with all classes of antihypertensive drugs, even in patients receiving multiple antihypertensive agents [35, 36].

The only class that need special precautionary measures are alpha-blockers; although, even these drugs are not absolutely contraindicated in hypertensive men taking PDE-5 inhibitors [37]. Since some beta-blockers possess simultaneous alpha-blocker properties, these drugs should also be used with caution.

### Female sexual dysfunction

Female sexual dysfunction can be defined as the persistent or recurrent decrease in sexual desire or arousal, the difficulty or even the

inability to achieve an orgasm and/or the feeling of pain during sexual intercourse (dyspareunia) [38]. Most women exhibit a combination of abnormalities in these four aspects of female sexuality (desire, arousal, orgasm, pain).

Female sexuality is markedly under-investigated compared to its male counterpart for several reasons: a) female perceptions about sex are much more complicated; b) the physiology and pathophysiology of female sexual function remain largely unclarified; c) no firm, objective measures of female sexual dysfunction exist; and d) so far, no effective therapy is available.

It came as a big surprise when the US National Health and Social Life Survey reported that female rather than male sexual dysfunction is more frequent [2]; several subsequent reports have confirmed this finding and attracted scientific interest in this topic [39–41]. However, available data regarding the relation between essential hypertension and female sexual dysfunction are far from conclusive [14, 41, 42]; nevertheless, most evidence points to a higher prevalence of sexual dysfunction in hypertensive women when compared to normotensive women. In a study of 417 hypertensive and normotensive women, increasing systolic blood pressure, increasing age and beta-blocker administration were significant predictors of female sexual dysfunction, while success in controlling blood pressure was related to a lower prevalence of sexual dysfunction in hypertensive women [41].

The relative lack of data in this field implies that specific studies with appropriate methods (Female Sexual Function Index, FSFI) have not been performed, rather than suggesting that hypertensive women do not experience sexual problems. We believe that despite the lag in female sexual dysfunction research, intense efforts to clarify the pathophysiology of female sexual dysfunction will lead to the development of effective treatment modalities; moreover, its relationship to essential hypertension needs further verification, along with the effect of antihypertensive treatment upon its appearance.

### Closing remarks

In conclusion, sexual dysfunction is more prevalent in hypertensive than in normotensive individuals. Erectile dysfunction may be the first sign of asymptomatic coronary heart disease and contribute to its diagnosis. Older antihypertensive drugs exhibit detrimental effects on sexual function, while the newer drugs have either neutral or beneficial effects. All classes can be safely co-administered with PDE-5 inhibitors, while special precautions should be taken for alpha-blockers. Finally, in our point of view, hypertension guidelines should neither ignore nor superficially address this rather important issue that greatly affects patients' and their sexual partners' quality of life.

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