

Hypertension and sexual dysfunction: time to act

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Rationale for developing a working group on sexual dysfunction

Sexual dysfunction is a common clinical problem that severely affects the quality of life of both patients and their sexual partners. Sexual dysfunction is currently considered to be of vascular origin in the vast majority of the patients, due to atherosclerotic lesions of the penile arteries. It is thus not surprising that sexual dysfunction is more frequently seen in patients with cardiovascular disease and risk factors than in individuals without such conditions. Several lines of epidemiological data indicate that sexual dysfunction is frequently found in hypertensive patients and its prevalence is even higher when other cardiovascular risk factors co-exist. Guidelines for the management of hypertension either ignored or superficially addressed this issue up to now [1–3]. The 2009 reappraisal of European guidelines, however, has included for the first time a statement regarding the relationship between these two conditions and the effects of antihypertensive drugs on sexual function [4]. During the last five meetings of the European Society of Hypertension (ESH), round tables regarding the association between sexual dysfunction, hypertension, and cardiovascular disease have taken place; in addition, a newsletter on this topic has been released by ESH [5]. In autumn 2009, a Working Group on Sexual Dysfunction was founded within the ESH; the inaugural session of this Group was held during the 20th European Meeting on Hypertension, in Oslo at June 2010, with vivid participation of many interested physicians who expressed great interest. The primary aim of the group regards the awareness of all

clinicians dealing with hypertensive patients (hypertension specialists, cardiologists, internists, nephrologists, diabetologists, and general practitioners) about the magnitude of the problem, the recognition of sexual dysfunction and its management in hypertensive patients. An equally important objective is to familiarize other medical specialties managing sexual dysfunction (urologists, psychiatrists, gynaecologists) about the potential existence of cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus) and even asymptomatic cardiovascular disease. We anticipate that our first aim is going to be realized: by providing a forum to interested physicians in our society, in which they can express their clinical experience in this field; by a systematic effort to create a European Network regarding the epidemiology and the management of sexual dysfunction in hypertensive patients, initially based on Hypertension Excellence centres and then spread throughout; and by implementing an intense education programme in collaboration with National Hypertension Societies. Our second objective might be realized by a close collaboration with other societies dealing with sexual dysfunction, such as the Urologic, Gynaecologic, Sexual Dysfunction, Psychiatric, and so on, aiming to organize some joint activities that will promote sexual dysfunction as an ‘early diagnostic window’ for cardiovascular disease.

The magnitude of the problem

Sexual function represents an integral part of human’s general health and well being. Erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse [6]. The definition of female sexual dysfunction is more complex, describing it as 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 [7]. The prevalence of sexual dysfunction in the general population is not precisely known. Several epidemiological studies report a 7–53% prevalence in the general population with 15–20% being the most probable estimation [8–12]. What is really surprising for the unfamiliar physician is that female is more frequent than male sexual dysfunction (43 versus 31% in USA in 1999) [11]. However, available data regarding prevalence of male and female sexual

dysfunction in the general population and in specific subgroups with cardiovascular risk factors are far from conclusive, strongly pointing out the need for further investigation of the exact magnitude of the problem.

Pathophysiologic evidence linking hypertension with sexual dysfunction

Both hypertension and sexual dysfunction represent commonly encountered clinical entities which co-exist alone or in combination with other comorbidities. According to estimations, about 26.4% of the world's population was affected by arterial hypertension in 2000. The number of hypertensive adults is expected to rise by 60% by 2025, reaching 1.5 billion patients worldwide [13]. Given the continuous prolongation of life expectancy and the age-dependent relation of hypertension and sexual dysfunction, an outbreak in their prevalence is anticipated over the next decades. However, there is a more profound linkage between hypertension and sexual dysfunction. Accumulating evidence implicates essential hypertension *per se* in the pathophysiology of sexual dysfunction.

The vascular tissue is the main contributor to penile erection. Stimuli from the central and peripheral nervous system result in either vasoconstriction or vasodilatation of the penile vasculature, whereas an appropriate hormonal environment is essential for achieving an erection. Structural and/or functional abnormalities of the penile vessels may impair the ability to achieve an erection and represent the underlying cause of sexual dysfunction in the vast majority of male hypertensive patients. Evidence that increased blood pressure is responsible for stenotic lesions secondary to atherosclerosis, smooth muscle hypertrophy of the cavernous arteries, and implicit blood flow impairment in the penile vasculature, provides a direct causative link between hypertension and erectile dysfunction [14]. In addition, the longitudinal exposure to elevated levels of systemic blood pressure negatively affects the neurogenic and smooth muscle-induced relaxation in response to nitric oxide, the role of which is substantial for the acquisition and maintenance of penile erection [15]. It is even worth pointing out the contribution of angiotensin II to the contraction of the corporal smooth muscle, thus acting as an agent promoting termination of erection [16]. A number of different hormones with vasoactive properties have been also implicated in the pathophysiology of erection, including catecholamines, bradykinin, sex hormones, endothelin-1, carbon monoxide, and Rho-Rho kinases, but their exact role needs further investigation [17].

Female sexual physiology represents a neurovascular pathway as well, leading to genital engorgement, swelling, vaginal lubrication, and orgasm. Data regarding pathophysiology of sexual dysfunction in hypertensive women are significantly limited compared to those regarding men. However, there is remarkable evidence

supporting structural and functional alterations in analogy to those observed in men. Nitric oxide, catecholamines and angiotensin II appear to play a pivotal role in female genital tissue, similar to the one described in the male genital system. As such, hypertension exerts the same serious unfavourable effects on female sexual function. Further research in this field is urgently required to inarguably establish the causal association between hypertension and female sexual dysfunction.

The firm relevance of male and female sexual dysfunction to hypertension is reflected by its prevalence among hypertensive individuals. A higher prevalence in hypertensive patients is repeatedly reported, and it has been estimated that the possibility of developing erectile dysfunction is up to seven-fold higher in hypertensive patients compared to normotensive individuals, with relative risk ranging from 1.3 to 6.9 [8,10]. A vast amount of evidence indicates that sexual dysfunction is almost twice as frequent in hypertensive than normotensive individuals [18], and appears to be of higher severity in hypertensive patients [19]. Data regarding prevalence of sexual dysfunction in hypertensive women are scarce. A prevalence of 42.1% of sexual dysfunction has currently been reported in hypertensive female population, compared to 19.4% in normotensive women [20]. Overall, increasing systolic blood pressure, increasing age, duration of hypertension, inadequate blood pressure control, and β -blockers administration have been acknowledged as predicting factors of sexual dysfunction [19,20], but the identification of additional factors is of crucial importance. Obstructive sleep apnoea could be considered as an additional factor, since it is frequently accompanied by hypertension, whereas sexual dysfunction is highly prevalent in such patients [21,22].

Sexual dysfunction as an 'early diagnostic indicator' for cardiovascular disease

Cardiovascular disease is a predominant cause of mortality and its identification in the early asymptomatic stage is of crucial importance. Accumulating data suggest that erectile dysfunction can actually foretell the presence of asymptomatic cardiovascular disease. Indeed, erectile dysfunction is considered of vascular origin in the majority of cases, and both clinical entities share the same pathophysiology. Atherosclerotic process and endothelial dysfunction, with a predominant impairment of the nitric-oxide-dependent vasodilation, are mechanisms mutually encountered. Therefore, it has been rationally assumed that vascular lesions predisposing to cardiovascular disease will develop in the small diameter penile arteries (1–2 mm) prior to the larger ones, like the coronary (3–4 mm), the internal carotid (5–7 mm), and the femoral artery (6–8 mm), in accordance with the 'artery size hypothesis' [23].

Indeed, a high incidence of erectile dysfunction has been reported in patients with coronary artery disease, even in

asymptomatic patients, with endothelial dysfunction and subclinical inflammation holding a central pathophysiological role [24–26]. In such patients, erectile dysfunction has been correlated with the number of occluded vessels and was found to predate angina symptoms and the development of symptomatic coronary artery disease. It has been estimated that the mean interval between erectile dysfunction and onset of evident coronary artery disease is about 3 years [27]. Erectile dysfunction has been identified as an independent risk factor for cardiovascular disease, with a hazard ratio of 1.45 equal or greater compared to traditional risk factors (hyperlipidaemia, smoking, positive family history) [28]. Further prospective data in diabetic patients establish erectile dysfunction as an independent predictor of future cardiovascular events [29,30]. A similar predictive role for cardiovascular events has been shown in the ONTARGET and TRANSCEND trials in high-risk patients [31]. However, it has been recently shown in patients without cardiovascular disease that erectile dysfunction does not improve the prediction of cardiovascular disease beyond traditional risk factors [32]. The establishment of conclusive data requires further research in this field. Given the similarities of reproductive embryology and sexual physiology between the two sexes, it could be hypothesized that female sexual dysfunction may hold a similar predictive value for cardiovascular disease, but this remains to be proved. Anyway, it is of great significance that physicians are familiar with the possibility of underlying cardiovascular disease in patients with sexual dysfunction. Thus, an effective management can be provided that will detect cardiovascular disease at an early asymptomatic stage, and delay or even prevent the onset of cardiovascular events.

The effect of antihypertensive drugs on sexual function

Traditionally, hypertension has been known to exert its negative influence on erectile function via the administered antihypertensive medication. Impairment of sexual function attributable to the antihypertensive agents, real or perceived, is one of the most predominant causes for nonadherence and discontinuation of antihypertensive therapy. The significance of this fact in clinical practice, with all the longitudinal negative consequences regarding patients' health, overwhelms the attention paid in various studies. So far, erectile dysfunction has never been defined as a primary end-point in a large clinical trial. Available data show that older classes of antihypertensive agents are inferior to the newer regarding erectile function. In particular, the negative influence of β -blockers has been repeatedly confirmed [33–35], with the only possible exception of nebivolol. The latter, on the contrary, has been reported to exert beneficial effects, possibly due to nitric oxide modulation [36,37]. Diuretics are considered to impair erectile function as well, even when used as adjunct therapy [38]. Although data regarding calcium antagonists and angiotensin-converting

enzyme (ACE)-inhibitors are not yet definitive, a neutral effect on erectile function has been attributed [39,40]. On the contrary, angiotensin receptor blockers seem to positively affect erectile function [41–43], and have thus been recommended as first-line treatment in patients with pre-existing erectile dysfunction or as substitution therapy in cases with antihypertensive drug-induced erectile dysfunction [44]. Remarkably, the recently published substudy of the ONTARGET-TRANSCEND trials has not proven any benefits of angiotensin receptor blockers (ARBs) on erectile function [31]; it has to be noted, however, that ARBs were added on top of previous multidrug regime in high-risk patients. Regarding the newest medication acting in the renin–angiotensin axis, the renin inhibitor aliskiren, there is as yet a lack of solid information. There are remarkably few data regarding the widely prescribed antihypertensive combinations, thus rendering unsound the extraction of conclusions. Overall, only a well designed, randomized, double-blind, large, prospective trial may resolve questions about the specific effects of various drug classes on sexual function.

Phosphodiesterase-5 inhibitors in hypertensive patients

Phosphodiesterase (PDE)-5 isoenzyme catalyzes the breakdown of cyclic GMP (cGMP) and it is found in smooth muscle cells of the vasculature (arteries and veins) all over the body, including the genitalis. When PDE-5 inhibitors were first used in trials for asthma and angina pectoris treatment, penile erection was reported as the most common side effect. This observation led to the revolutionary release of the first PDE-5 inhibitor, sildenafil, as erectile dysfunction treatment in 1998. Since then, two newer PDE-5 inhibitors, vardenafil and tadalafil, have been approved for the same purpose, whereas others are in a development process. Compared to sildenafil, vardenafil is more potent, whereas tadalafil has a longer half-life (17 h) and lacks food interactions and visual side effects.

The vasorelaxing effects of PDE-5 inhibitors are responsible for small blood pressure reductions, which in combination with potential drug interactions rendered their administration in hypertensive patients an arguable issue in the past [45]. A vast amount of recent data supports that PDE-5 inhibitors are associated with few side effects, even when multidrug antihypertensive therapy is provided [46]. Blood pressure decrease attributed to these agents is usually small and clinically insignificant both in hypertensive and normotensive patients. However, co-administration with α -blockers may result in orthostatic hypotension. Current recommendations do not oppose to their concomitant administration, but low starting doses of PDE-5 inhibitors are preferred in patients on α -blocker treatment, and likewise, low starting doses of α -blockers are encouraged in patients taking PDE-5 inhibitors [47]. Given the partial α -blocking

activity of some β -blockers, caution should also be applied in patients under these drugs, although further clarification of their interactions is required. On the contrary, all three PDE-5 inhibitors are contraindicated in patients treated with short or long-acting nitrates. Organic nitrates increase cGMP production, whereas PDE-5 inhibitors decrease its catabolism, resulting in enhanced vasodilation and potentially hazardous episodes of symptomatic hypotension.

It should be highlighted that the use of PDE-5 inhibitors in hypertensive patients may provide important benefits as well. PDE-5 inhibitors exert their beneficial effects through improved adherence and monitoring of the patients. Hypertensive men with erectile dysfunction are more likely to initiate rather than discontinue, and add rather than reject, antihypertensive medication when receiving PDE-5 inhibitors [48]. Adherence to antihypertensive therapy is also significantly improved, with 36% of noncompliant patients becoming adherent after initiation of PDE-5 inhibitors in one study [49]. Indeed, a significant reduction in systolic blood pressure has been reported after initiation of these drugs. However, patients with untreated, poorly controlled, accelerated, or malignant hypertension should not initiate PDE-5 inhibitors before stabilization and evaluation of their condition by a cardiologist, just like any patient at 'high risk' for cardiovascular disease [50].

Overall, PDE-5 inhibitors can be safely used in hypertensive patients, with the above mentioned exceptions. Their contribution to the improvement of adherence is of unique value. However, initialization of PDE-5 inhibitors should follow alteration of antihypertensive drugs possibly responsible for erectile dysfunction. The development of PDE-5 inhibitor combining improvement of sexual function with antihypertensive properties represents one of the greatest challenges in this field. Preliminary data show promising results [51]; however, there is a long path to follow before any sound evidence is gathered. At the same time, promising phase III studies with drugs for female hypoactive sexual desire disorder generate great expectations that remain to be fulfilled.

Perspectives: interdisciplinary approach

In this study, we have briefly addressed the matter of sexual dysfunction, presenting the extent of the problem and underlining the need for a better understanding of the pathophysiologic mechanisms linking sexual dysfunction, hypertension, and cardiovascular disease. Up to now, approach of sexual dysfunction was rather superficial, with most physicians underestimating or overlooking the problem. However, accumulating evidence points towards the same origin for both sexual dysfunction and cardiovascular disease, and hypertension has been identified as a causative factor for both conditions. In this triangle, sexual dysfunction may play a pivotal role as an

independent predictive factor for cardiovascular disease, acting thus as a warning sign for early diagnostic or therapeutic interventions. On the contrary, management of sexual dysfunction induced by hypertension or antihypertensive medication represents a challenge in the everyday clinical practice. PDE-5 inhibitors have offered new perspectives in the therapeutic management of sexual dysfunction. Overall, sexual dysfunction is a broad area for future research, and further trustworthy information in each of the above-mentioned topics will be of undeniable value for physicians of all kinds. Under this light, the mission of the working group on sexual dysfunction emerges as extremely important. We therefore plan to:

- (1) Call ESH excellence centres in joining a network for the implementation of European protocols regarding the epidemiology, the pathophysiology, and the treatment of sexual dysfunction in hypertensive patients.
- (2) Attract grants for research in this field both at the level of basic research as well as at the level of clinical practice.
- (3) Co-ordinate promotional strategies, by regularly publishing announcements at the ESH website regarding the activities of the working group on sexual dysfunction, and calling ESH members to join these activities.
- (4) Collaborate with other Societies that are actively dealing with sexual dysfunction, working closely with them and perform joint actions.
- (5) Prepare a statement regarding sexual dysfunction in cardiovascular disease in collaboration with the European Society of Cardiology and societies of sexual medicine.

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