# Effects of Antihypertensive Therapy on Sexual Activity in Hypertensive Men

*Roberto Fogari, MD and Annalisa Zoppi, MD*

**Address**
Clinica Medica II, IRCCS Policlinico S. Matteo,
Piazzale Golgi, 2, 27100 Pavia, Italy.
E-mail: r.fogari@smatteo.pv.it

**Current Hypertension Reports** 2002, **4:**202–210
Current Science Inc. ISSN 1522-6417


Sexual dysfunction has a high prevalence among hypertensive men, and hypertension per se, regardless of drugs, has been suggested to affect sexual function. The available studies have not clarified which factors play a major role in the pathogenesis of sexual dysfunction in hypertensive men. Neurovascular factors, however, seem to be especially important, (in particular defective nitric oxide activity), although hormonal and psychogenic factors cannot be excluded. Further studies are needed to answer the important question of whether erectile dysfunction seen in hypertension may be one expression of vascular disease and target organ damage. The incidence of sexual dysfunction is exacerbated by antihypertensive drug treatment. There is evidence that some classes of drugs, such as diuretics, centrally acting sympatholitic drugs, and β-blockers have a greater impact on sexual function than other classes, such as calcium antagonists and angiotensin converting enzyme inhibitors. Present evidence on the effects of angiotensin II antagonists is limited, but some data suggest that sexual function in men receiving these drugs not only is not altered, but even improves. Since sexual function is an important aspect of quality of life for the individual, it is important in treating hypertension to ensure that the drugs used have the lowest possible potential for causing sexual problems. This ensures the best balance between therapeutic efficacy and quality of life, which is essential for compliance.

## Introduction

Sexual dysfunction, which frequently occurs in hypertensive patients, has gained increasing attention from both a pathophysiologic and clinical point of view. On one hand, although mechanisms are not yet clear, sexual dysfunction might be an expression of arterial vascular changes, probably atherosclerosis, and might reflect target organ damage. On the other hand, problems with sexual function may have an adverse impact on the quality of life of the individual, and therefore represent one of the major obstacles to compliance with antihypertensive treatment.

## Prevalence of Sexual Dysfunction in Hypertensive Men

Sexual dysfunction has a high prevalence among hypertensive men [1–7]. Symptoms of dysfunction include reduced libido, inability to obtain or maintain an erection (impotence), and premature or retarded ejaculation. These symptoms are frequently first reported by patients while receiving antihypertensive therapy, which has lead to a widespread belief that sexual dysfunction is caused by a specific hypotensive agent rather than by hypertension itself. Although the prevalence of sexual problems in hypertensive patients prior to treatment has been inadequately investigated, data from the literature indicate that the incidence of sexual dysfunction is considerably higher in untreated hypertensive men than among normotensive controls [2,3]. Bulpitt *et al*. [2] reported a rising order of prevalence of erectile difficulties in normotensive subjects (7%), untreated hypertensive men (17%), and treated hypertensive men (25%). Although the percentage of untreated hypertensives reporting sexual problems was not significantly different from the control group, it did suggest an independent contribution of hypertension to sexual dysfunction.

In the Australian National Blood Pressure Study [3] sexual complaints were more prevalent in the hypertensive men than in the normotensive controls, whereas no difference was found between untreated hypertensive men, hypertensive men receiving a placebo, and hypertensive men receiving active treatment. Croog *et al*. [4] observed that 44% of men not receiving antihypertensive drugs versus 58% of those taking antihypertensive medication reported distress over one or more sexual symptoms. In the Treatment of Mild Hypertension Study (TOHMS) [8], erection problems at baseline were strongly related to systolic blood pressure (SBP): men with SBP 140 mm Hg or more had more than twice the rate of erection problems as men with SBP less than 140 mm Hg. A similar finding, which is consistent with the understanding that elevated blood pressure contributes directly to impotence problems, was reported by Jensen *et al.* [6]. In a recent study involving 110 newly diagnosed, never treated hypertensive men and 110 healthy controls, all of whom were aged 40 to 49 years, married, without any previous sexual dysfunction symptoms, nondiabetic, nonobese, and nonsmoking, we found that in untreated hypertensive subjects sexual activity, assessed as mean number of sexual intercourse episodes

per month and considered as a good index of sexual desire, was 25% lower than in normotensive controls [9]. This further suggests that hypertension per se , regardless of drugs, may affect sexual function.

## Mechanisms of Sexual Dysfunction in Hypertensive Men

Sexual dysfunction seen in hypertensive men is probably the result of alterations in a number of the processes (neural, vascular, hormonal, psychologic) involved in normal sexual function.

### Neural factors

Complete male sexual response requires an intact central and peripheral autonomic nervous system [10]. The first component of this response is the penile erection. Both psychogenic stimuli (auditory, visual, olfactory, tactile, or imaginative) and reflexogenic stimuli (exteroceptive stimulation of the genital area) can act synergistically to produce an erection. The limbic system acts as an integrative center to coordinate sensory input at the cerebral level with visceral function. Dopaminergic neurons innervate the brain centers associated with libido and penile erection, and dopamine has been demonstrated to play a key role in sexual behavior [11]. Pathways near the pyramidal tracts connect the limbic system with thoracolumbar and sacral erection centers in the spinal cord. Efferent neural impulses from both centers can independently evoke an erection. Mediated by sympathetic nerves from the thoracolumbar center or by parasympathetic nerves from the sacral center, stimuli causes a relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue of the penis leading to a severalfold increase in blood flow. Adrenergic nerves regulate the tone of the trabecular smooth muscle in the corpora cavernosa through alpha- and beta-receptors. Biochemical mediators released locally from the endothelium or smooth muscle also participate in initiating and maintaining erection: nitric oxide (NO) released during nonadrenergic, noncholinergic neurotransmission from the endothelium appears to be the most important with respect to cavernosal smooth muscle relaxation [12,13•]. Following its synthesis and release from nerve terminals of the penis and from endothelium, NO activates guanylate cyclase in vascular and trabecular smooth muscle. The increased intracellular accumulation of cGMP is believed to cause smooth muscle relaxation via a chemical cascade [13•]. The second phase of the male sexual response is ejaculation, which is controlled by the sympathetic nervous system. The third phase, orgasm, is a cortical sensory phenomenon, in which the rhythmic contraction of the bulbocavernous and ischiocavernous muscles is perceived as pleasurable.

Hypertensive patients have impaired endothelium-mediated vascular tone largely dependent on decreased vascular activity of NO, which in turn may be related to reduced NO synthesis or increased breakdown [14]. Thus, one possible link between erectile dysfunction and hypertension may be defective NO synthesis or release also from nerve terminals. Since monoamine transmitters have been established to play a key role in mediating sexual behavior, involvement of monoamine pathways in the central nervous system might be a common basis for essential hypertension and sexual dysfunction in untreated hypertensive men.

### Vascular factors

Normal erectile response requires adequate blood supply to the penis as well as normal venous drainage [10]. Erection is developed and maintained as the arterial inflow to the corpora cavernosa is increased. At the same time, the veins constrict, trapping the blood in the tissues. The quality of erection depends on the intracavernous pressure that must reach at least 60 mm Hg to produce rigidity sufficient for vaginal intromission. If arterial blood supply is inadequate or excess venous drainage occurs, this pressure cannot be achieved. As already mentioned, NO released during nonadrenergic, noncholinergic neurotransmission and from the endothelium plays a major role in this process [12,13•]. Disturbances in the blood flow to the penis are thought to be the most frequent organic causes of male erectile dysfunction [15]. Impairments in the hemodynamics of erection have been demonstrated in patients with hypertension: in the study by Jensen *et al*. [6], which involved 101 male hypertensive patients, impotence was caused mainly by arterial penile dysfunction (89%) related to the severity of hypertension and target organ damage. Other studies, however, found a similar prevalence of impaired penile arterial blood supply among normotensive and hypertensive men with erectile dysfunction [15,16].

As already mentioned, alterations in the endothelial L-arginine-NO pathway and consequent decreased endothelium-dependent relaxation have been demonstrated in systemic hypertension [14]. This impairment of endothelial NO bioavailability could be one possible explanation why hypertension is frequently associated with erectile dysfunction [13•].

Whereas in humans microscopic studies have not been able to identify a pattern pathognomonic of the action of high blood pressure on erectile tissue, spontaneously hypertensive rats have been found to present morphologic changes in vessels as well as in the cavernous spaces of the erectile tissue (higher proliferative score in cavernous and vascular smooth muscle and higher fibrosis score in cavernous tissue) that have a high positive correlation with high blood pressure levels [17]. In addition, the increase in extracellular matrix expansion seems to affect not only the interstitium but also the neural structures of the penis. If demonstrated in humans, these alterations could provide one possible explanation for erectile dysfunction in hypertension: smooth muscle cell hyperplasia could produce greater impediment to achieve complete compliance of the cavernous spaces. Furthermore,

the increase in the surrounding connective tissue at the perineurium and endoneurium of the amyelinic nerves in cavernous tissue could also influence the relaxation mechanism for penis tumescence [17].

**Hormonal factors**

Hormonal abnormalities may provide another etiologic basis for sexual dysfunction in hypertensive men [16]. Hormones influencing male sexual activity are mainly testosterone, prolactin, and gonadotropins (luteinizing hormone). In addition to its profound influence on sexual differentiation, the major component of testosterone action on male sexuality is through effects on libido and sexual behavior. Low levels of androgens have been associated with hypertension [9,16,18]. Hughes *et al*. [18] reported that both total and free testosterone levels were lower in untreated individuals with essential hypertension compared with normotensive controls. Similar results were obtained by Jaffe *et al*. [16], who found that total testosterone and bioavailable testosterone levels were lower in hypertensive men with erectile dysfunction than in normotensive controls. Khaw and Barrett-Connor [19] observed an inverse relationship between blood pressure and endogenous testosterone in men.

Consistent with these observations is the study [9] we conducted in 110 middle-aged, sexually active, newly diagnosed, never treated, hypertensive men and 110 healthy normotensive controls, where we found that plasma testosterone levels were significantly lower in the hypertensive men than in normotensive controls, although they were not within the hypogonadal range. In this study, a significant inverse relationship between testosterone levels and SBP values was also observed in hypertensive men.

The finding that hypertension is associated with lower levels of plasma testosterone compared with normotensive controls suggests three hypotheses. First, serum testosterone influences blood pressure regulation. Little is known about this topic in humans. Reports have indicated that in spontaneously hypertensive rats, testosterone may contribute to the development of hypertension through sustained enhancement of tyrosine hydroxylase activity that leads to increased norepinephrine levels in blood vessels [20]. Second, elevated blood pressure can negatively affect steroidogenesis or clearance. And third, there are genes involved in the regulation of blood pressure that also affect steroidogenesis. Men with a family history of hypertension have been shown to have lower than normal serum testosterone levels [21], which suggests a possible genetic link between hypertension and serum testosterone levels. The genetic hypothesis is also supported by data obtained from natriuretic peptide receptor A gene-deficient and gene-duplicated mutant mouse models, which demonstrated that natriuretic peptide receptor A gene deficiency in male mice was characterized by both high blood pressure and low circulating testosterone levels [22].

The inverse correlation between testosterone levels and SBP suggests that testosterone reduction in hypertensive men could contribute to increased arterial stiffness. An interaction between androgens and the vessel wall has been hypothesized for the following reasons: 1) steroid receptors have been found in the cardiovascular system; 2) testosterone induces a direct relaxing effect on the vasculature in both normotensive and hypertensive rats [23]; 3) testosterone infused into coronary arteries in men with coronary artery disease causes vasodilation [24]; and 4) androgen withdrawal in men is associated with decreased central arterial compliance [25].

In animal models, androgens were found to stimulate nitric oxide release in cavernous body slices, whereas lack of androgens led to decreased NO production [26]. In hypertension, subtle alterations in NO production abetted by lowering of circulating testosterone might form the basis for deficient cavernous sinusoidal relaxation and erectile dysfunction.

Higher prolactin levels have been reported in hypertensive men. However, whether this relative hyperprolactinemia is associated with altered sexual function has not been established [16].

**Psychologic factors**

Psychologic factors play an important role in mediating sexual desire (libido) and the erectile response. In the hypertensive patient, the knowledge that having hypertension carries a high risk of cardiovascular complications and may require life-long therapy provides multiple psychologic reasons for impaired sexual function [1]. Indeed, in the study by Croog *et al*. [4], emotional symptoms such as depression, anxiety, and obsessive-compulsiveness showed a higher degree of correlation with sexual dysfunction symptoms than age in both untreated hypertensive men and those taking antihypertensive medications. By contrast, other authors failed to find a relationship between symptoms of anxiety, depression, obsession, and sexual symptoms in hypertensive men [2]. Thus, despite the suggestions from prevalence studies, there is no direct evidence that psychogenic mechanisms play a major role in the sexual dysfunction experienced by hypertensive men.

## Effects of Antihypertensive Drugs on Sexual Function

Sexual dysfunction is a significant side effect of many antihypertensive agents, and consequently is a major reason for noncompliance with therapy [1,27,28,29•]. At present, the incidence of sexual dysfunction due to various antihypertensive agents is not well documented, perhaps because of the personal nature of the problem and patients' reluctance to discuss it. Furthermore, some physicians are reluctant to ask direct questions about sexual function or may even ignore this problem while focusing on the lifesaving benefits of antihypertensive treatment. In

**Table 1. Effects of different classes of antihypertensive drugs on sexual function**

| Drug | Decreased libido | Erectile dysfunction | Impaired ejaculation | Priapism | Gynecomastia |
|---|---|---|---|---|---|
| Diuretics | | | | | |
| Thiazides | + | + | + | - | - |
| Spironolactone | - | + | - | - | + |
| β-Blockers | + | + | - | - | + |
| α-Blockers | - | + | + | + | - |
| Centrally acting antiadrenergics | | | | | |
| Methyldopa | + | + | + | - | + |
| Clonidine | - | + | + | - | + |
| Direct vasodilators | - | + | - | - | - |
| Calcium antagonists | - | ? | ? | - | + |
| Angiotensin converting enzyme inhibitors | - | - | - | - | - |
| Angiotensin II antagonists | - | - | - | - | - |

+, Present; -, absent; ?, unknown effect.

addition, studies of sexual dysfunction in hypertensive men have usually suffered from lack of specificity, since the data have often been collected as part of an overall evaluation of hypertension, its drug therapy, or both. Furthermore studies on this topic are difficult to compare because of different methodologies, lack of standardized measures, and evaluation of sexual activity unrelated to age, body weight, and marital status, which may all represent important confounding factors.

Antihypertensive drugs may affect the sexual function of the patient through their effects on the central and peripheral nervous systems, the vascular system, and hormonal changes. Such agents may impair the libidinal, erectile, and orgasmic phases of the sexual response, or may exert effects than indirectly affect sexuality. Table 1 summarizes the sexual side effects reported with the use of various antihypertensive drugs.

**Diuretics**

Adverse effects of thiazide and thiazide-like diuretics (*ie*, chlorthalidone) on male sexual function, including decreased libido, erectile dysfunction and difficult ejaculation, have been reported in several studies with an incidence that varies from 3% to 32% [1,8,30–33]. In the Medical research Council trial [30], 22% of men on diuretics (bendrofluazide), 13% on propranolol, and 10% on placebo complained of impotence, which was the most frequent principal reason for withdrawal from antihypertensive treatment. The Hypertension Detection and Follow-up Study reported that 5% of the men discontinued chlorthalidone therapy due to sexual dysfunction symptoms (primarily impotence) [31]. The trial by Chang *et al*. [32] showed that patients taking thiazide diuretics experienced significantly greater sexual dysfunction than control subjects, including decreased libido, difficulty in gaining and maintaining an erection, and difficulty with ejaculation. In the study by Wassertheil-Smoller *et al*. [33], problems with sexual interest, erection, and orgasm were greater among men receiving chlorthalidone compared with those given placebo or atenolol. Interestingly, in this trial, weight loss ameliorated the problem of chlorthalidone-induced sexual dysfunction. In the TOMHS study [8], patients randomized to chlorthalidone, even at low doses, reported a significantly higher incidence of erection problems than patients randomized to placebo (17.1% vs 8.1%). Combined use of a diuretic and other antihypertensive agents has been reported to be associated with a higher incidence of sexual dysfunction symptoms than use of a diuretic agent alone [4].

The mechanism by which thiazides affect erectile function or libido is unclear, but it has been suggested that these drugs exert a direct effect on vascular smooth muscles or involve a decreased response to catecholamines [29•]. In the study by Chang *et al*. [32], multivariate analysis suggested that sexual dysfunction was not mediated by low serum potassium levels or by low blood pressure values.

Impotence and decreased libido are the more frequent sexual side effects of spironolactone [1,27]. Although marked variation in the incidence of these effects has been reported, at usual clinical doses they occur in less than 5% of the cases [27]. Gynecomastia, another fairly frequent complication of spironolactone therapy, may be associated with mastodynia and is usually bilateral. The sexual side effects of spironolactone have been attributed to endocrine dysfunction: spironolactone is structurally similar to the sex hormones and inhibits the binding of dihydrotestosterone to androgen receptors, thus producing an increased clearance of testosterone [34].

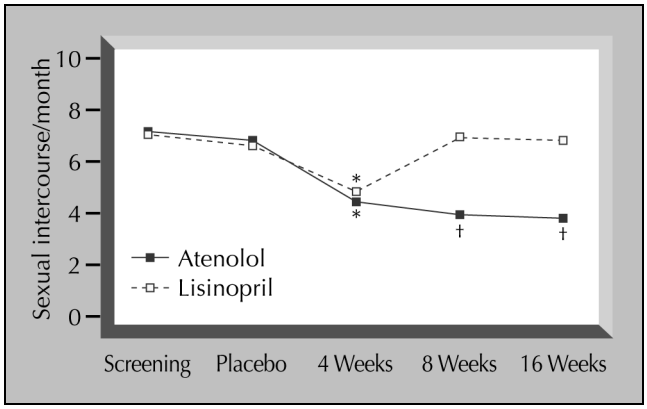


**Figure 1.** Sexual intercourse rate in middle-aged hypertensive men during treatment with atenolol or lisinopril. *$P < 0.05$. †$P < 0.01$ versus placebo. (*Data from* Fogari *et al*. [39].)

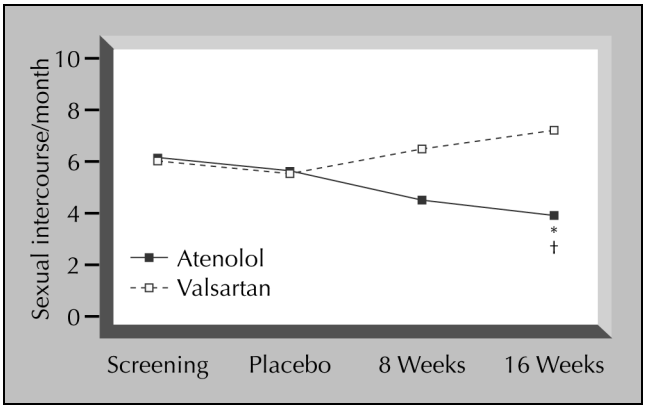


**Figure 2.** Sexual intercourse rate in middle-aged hypertensive men during treatment with atenolol or valsartan. *$P < 0.05$ versus placebo. †$P < 0.01$ versus valsartan. (*Data from* Fogari [40].)

### β-Blockers

β-Blockers have been frequently associated with sexual dysfunction, particularly impotence and decreased libido. The majority of reports dealing with sexual dysfunction due to β-blockade relate to propranolol [4,30,35,36]. Bauer *et al*. [35] observed that propranolol-induced impotence occurred in 11% of patients when the drug was used as monotherapy and in 23% when used in combination, whereas the Veterans Administration Cooperative Study group reported a 12.8% incidence of impotence whether the drug was used alone or in combination [36]. The use of propranolol in the Medical Research Council Trial was significantly associated with withdrawal from treatment due to impotence, although at a lower frequency than for thiazide therapy [30]. In the study by Croog *et al*. [4] specifically comparing the effects of propranolol, methyldopa, and captopril on sexual function over a 24-week treatment period, total symptom distress scores of treatment groups did not differ from each other in change from baseline, but problems in maintaining an erection were significantly worsened with propranolol therapy. However, in a more recent study undertaken to determine whether propranolol had adverse effects on cognitive function, depressive symptoms, and sexual function in hypertensive patients aged 22 to 59 years of age, no significant adverse effects on sexual function were found [37].

Whether the β1-selective β-blockers and those with vasodilating properties share the same side effects of propranolol on sexual function is less clear. In the TAIM study [33], the β1-selective β-blocker atenolol did not appear to have adverse effects on sexual function. Similarly, in the THOMS study [8], the β1-selective acebutolol did not have adverse effects on sexual function. By contrast, Suzuki *et al*. [38] reported that 26% of patients receiving atenolol had decreased potency and libido. A chronic worsening of sexual activity, assessed as number of sexual intercourse episodes per month, was also observed by us in two different studies assessing the effects of the β1-selective β-blocker atenolol compared with the angiotensin converting enzyme (ACE) inhibitor lisinopril [39] and the angiotensin II antagonist valsartan [40] on sexual function in middle-aged, untreated, hypertensive men. In both studies, atenolol-treated patients experienced a significant decrease in sexual intercourse rate, which was evident after 4 weeks of treatment and persisted throughout the treatment (Figs. 1 and 2).

Similar results were obtained in another study where we evaluated the effects of the more recent β-blocker carvedilol (provided with antagonistic properties at both α- and β-adrenergic receptors and with direct vasodilator activity) compared with valsartan on sexual activity (Fig. 3) [41•].

The mechanisms by which β-blockers induce sexual dysfunction remains to be clarified. One of the proposed mechanisms is inhibition of the sympathetic nervous system. β-Blockers reduce central sympathetic outflow and may impair vasodilation of the corpora cavernosa. Besides, β-blockers, especially the lipophilic ones, increase the tendency toward sedation or depression, which in turn may cause a loss of libido. A depression in serum testosterone levels in patients receiving β-blockers has been reported by some investigators [38,42], but not by others [16]. According to our data, which refer to atenolol, a reduction in testosterone values occurs in patients treated with this β-blocker, and seems to be more connected with reduced sexual interest than with erectile dysfunction [40].

### α-Blockers

Erectile dysfunction and decreased libido are relatively rare complications of α-blockers [1,27,29•]. Indeed, in the recent THOMS study [8], participants randomized to doxazosin experienced the lowest incidence of erection problems. Since α-adrenergic receptors mediate seminal emission, α-blockers may interfere with ejaculation. Priapism secondary to blockage of α receptors is rare with peripherally acting α-blockers [1,27,29•].

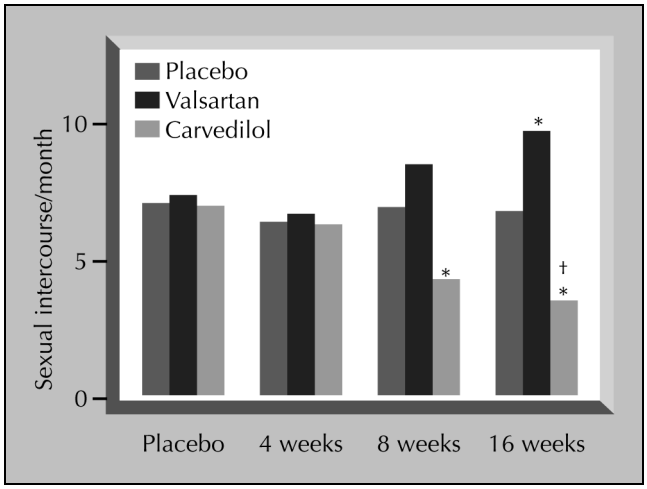


**Figure 3.** Sexual intercourse rate in middle-aged hypertensive men during treatment with carvedilol or valsartan. *$P < 0.05$ versus placebo. †$P < 0.01$ versus valsartan. (*Data from* Fogari *et al.* [41•].)

### Centrally acting antiadrenergic drugs

*Methyldopa*

Methyldopa acts as a false neurotransmitter that stimulates the adrenergic receptors in central vasomotor centers, thereby decreasing sympathetic nervous outflow from the brain. Since erectile processes are mediated by sympathetic nerve impulses, it is not surprising that treatment with this sympatholytic agent has been associated with erectile or ejaculatory dysfunction. Mental depression may also occur due to the central action of methyldopa and may contribute to decreased libido and erectile dysfunction secondary to the use of this drug. The incidence of sexual dysfunction symptoms with methyldopa varies in the different studies from 13% to 80% and is reported to be dose related [1,27,29•,43].

*Clonidine*

Clonidine has a mechanism similar to that of methyldopa and acts as a presynaptic α-adrenergic receptor antagonist. However, clonidine is widely advertised to have few or no sexual side effects [1,29•]. This claim is based on a low prevalence (10%) of sexual side effects reported by some authors [44]. These reports, however, are disputed by others reporting a higher prevalence of impotence [27].

### Direct vasodilators

Erectile dysfunction and priapism are rare side effects of direct-acting smooth muscle vasodilating drugs such as hydralazine and minoxidil [1,27,29•].

### Calcium channel blockers

Due to their mechanism of hypotensive action (vasodilation secondary to blockade of the voltage-dependent L-type calcium channels), calcium antagonists are not expected to cause sexual dysfunction symptoms [29•]. Indeed, in a total of 368 hypertensive men assigned to monotherapies of either the calcium antagonist isradipine, methyldopa, or placebo, sex disorders were reported significantly more in the methyldopa-treated group (13.7%) than in the isradipine group (6.7%) [43]. Amlodipine did not appear to affect erection function in the TOHMS study [8], nor did nifedipine slow release in another study [45]. However, the occurrence of impotence in a group of patients treated with verapamil has been reported by King *et al.* [46]. The mechanism for this effect is not clear. A possible explanation might be the inhibition of parasympathetic nerve function through interference with neurotransmitter function at a peripheral level. Nifedipine has been shown to block neurally released adenosine triphosphate in the rat vas deferens [47]. Although this is of uncertain significance in humans, it suggests the possibility of interference with peripheral neurotransmitters and/or receptors. Problems in ejaculation and gynecomastia, possibly related to hyperprolactinemia, were also reported by hypertensive patients treated with slow-release nifedipine [38].

### Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme inhibitors have not been generally associated with impairment of sexual activity [4,8,38,39]. Croog *et al.* [4] observed that hypertensive men treated with captopril fared better than those receiving propranolol or methyldopa in degree of change in distress over sexual symptoms. In the already cited study of comparison between the β-blocker atenolol and the ACE inhibitor lisinopril, which refers to a rather homogeneous, middle-aged, sexually active population of newly diagnosed, never treated hypertensive men, we observed that, unlike atenolol, which caused a chronic worsening of sexual function, lisinopril caused only a temporary decline in sexual activity. After 4 weeks of lisinopril treatment, the sexual intercourse rate was significantly reduced, but tended to recover with ongoing treatment (Fig. 1) [39]. Interestingly, the study design (two active treatment crossover periods of 4 weeks each preceded by a 4-week placebo period) allowed us to evaluate the time course of the effects of atenolol and lisinopril on sexual activity (Fig. 1). During the first placebo period, the level of sexual activity tended to decline, perhaps as a consequence of psychologic factors related to the diagnosis of hypertension and the need for drug treatment. The further decrease in sexual activity observed after 4 weeks of treatment with both atenolol and—although to a lesser extent—lisinopril suggests an acute effect of antihypertensive treatment, not drug-specific, perhaps related again to psychologic factors or to blood pressure lowering itself. Ongoing with the treatment we observed a recovery of sexual function in the lisinopril-treated but not in the atenolol-treated patients, which suggests a chronic effect of antihypertensive therapy, drug-specific, probably related to pharmacologic mechanisms. During the second placebo period, sexual intercourse rate, although higher than during active treatment, remained lower compared with baseline, especially in the atenolol-treated patients, who previously experienced major impair-

ment of sexual activity. Cross-over treatment confirmed the occurrence of an acute, nondrug-specific effect of antihypertensive treatment characterized by a decrease in sexual intercourse rate with both drugs, although more marked with atenolol, followed by a chronic worsening of sexual activity only in the atenolol-treated patients.

In this study the number of patients reporting decreased libido was significantly lower in the lisinopril (2%) than in the atenolol-treated group (11%). Also, impotence was reported less frequently with the ACE inhibitor (1%) than with the β-blocker (5%).

The fact that ACE inhibitors work through channels other than the sympathetic nervous system in lowering blood pressure might explain in part their reduced impact on sexual function [4]. Besides, ACE inhibitors have been reported to reverse endothelial dysfunction by preventing the effects of angiotensin II, prolonging the half-life of nitric oxide, and decreasing the degradation of bradykinin [48]. This latter substance is a potent stimulator of nitric oxide and prostacyclin release and therefore would not be expected to cause erectile dysfunction.

**Angiotensin II $AT_1$ receptor antagonists**

Present evidence of the effects of angiotensin II $AT_1$ receptor antagonists on sexual function is limited, but some data suggest that in men receiving these agents sexual function not only is not altered but even improves [40,41•,49]. In a study comparing the effects of antihypertensive treatment with the angiotensin II antagonist valsartan or the β-blocker carvedilol on sexual function in 120 middle-aged, never treated, hypertensive men, we observed that, unlike carvedilol, valsartan produced only a temporary, nonsignificant decline in sexual activity (assessed as number of sexual intercourse episodes per month) after 4 weeks of treatment, whereas it even improved this function ongoing with the treatment. After 16 weeks of therapy, hypertensive men receiving valsartan experienced a 19% increase in sexual intercourse rate, which, by contrast, was reduced by 50% in the carvedilol-treated patients (Fig. 3) [41•]. In addition, erectile dysfunction was a complaint of one patient with valsartan (0.9%), 15 patients with carvedilol (13.5%), and one patient in the placebo group (2.5%), the difference between the two active treatments being statistically significant. Similar results were obtained by Llisterri *et al*. [49] with another angiotensin II antagonist, losartan, that improved erectile function and both satisfaction and frequency of sexual activity in hypertensive patients with sexual dysfunction symptoms. In another study undertaken to compare the effects of the β-blocker atenolol and the angiotensin II antagonist valsartan on sexual activity and plasma testosterone levels in untreated hypertensive men, we observed that unlike atenolol, valsartan not only did not worsen sexual activity, assessed as number of sexual intercourse episodes per month, but tended to improve it [40]. Although in this study the observed increase in sexual activity did not reach statistical significance, probably due to the scant number of the sample, patients receiving valsartan experienced a 21% increase in sexual intercourse rate that, by contrast, was reduced by 25% in the atenolol-treated patients, with a significant difference between the two treatments. In addition, plasma testosterone levels were unaffected by valsartan treatment, which suggests that the trend towards sexual activity improvement induced by this drug was not related to changes in this sex hormone. Hypothetical explanations for this effect include the following: 1) Possible local effects. In an experimental animal model, intracavernosal injection of angiotensin II caused contraction of cavernosal smooth muscle and terminated spontaneous erection, whereas administration of an angiotensin II receptor antagonist resulted in smooth muscle relaxation and, therefore, erection. This suggests that angiotensin II is an important modulator of erectile function [50]. 2) Possible effects of the activated renin-angiotensin system on some as yet unknown nervous center modulating sexual activity. 3) Possible agonist interaction of some angiotensin II metabolite (possibly angiotensin IV) with the central dopaminergic system, which has been demonstrated from animal data to play a major role in sexual behavior [11]. 4) General improvement of the quality of life indices (general well-being, physical symptoms, cognitive function, work performance, and so forth) due to the angiotensin II antagonists.

## Conclusions

Sexual dysfunction is common in hypertensive men, and hypertension per se has been suggested to affect sexual function. Several factors may have a role in the sexual dysfunction of hypertensive men, but the studies available do not allow us to state which factors play the major role. Especially important in this regard seem to be neurovascular factors (in particular defective NO activity), although hormonal and psychogenic factors cannot be excluded. Further studies are needed to clarify whether erectile dysfunction seen in hypertension may be an expression of vascular disease and target organ damage. Antihypertensive drugs exacerbate the incidence of sexual dysfunction in hypertensive men. Diuretics, centrally-acting sympatholytic drugs, and β-blockers, especially the nonselective ones, have been found to have a greater impact on sexual function, whereas calcium antagonists and ACE inhibitors are claimed to have less effects on sexual function, and preliminary data suggest that angiotensin II antagonists even seem to improve it. Since sexual dysfunction may adversely affect the quality of life of the hypertensive patients in treatment, physicians should take an accurate baseline sexual history and monitor sexual symptoms as therapy progresses. Selecting the most suitable medication for the individual patient can result in blood pressure control with a minimum of sexual symptoms, helping to assure that the patient will continue to comply with the treatment.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


1. Bansal S: **Sexual dysfunction in hypertensive men. A critical review of the literature.** *Hypertension* 1988, **12:**1–10.
2. Bulpitt CJ, Dollery CT, Carne S: **Changes in symptoms of hypertensive patients after referral to hospital clinic.** *Br Heart J* 1976, **38:**121–128.
3. Bauer GE, Hunyor SN, Baker J, Marshall P: **Clinical side effects of antihypertensive treatment: a placebo-controlled, double-blind study.** *Postgrad Med Comm (Special report)* 1981, 49–54.
4. Croog SH, Levine S, Sudilovsky A, *et al.*: **Sexual symptoms in hypertensive patients. A clinical trial of antihypertensive medications.** *Arch Intern Med* 1988, **148:**788–794.
5. Feldman HA, McKinlay JB, Goldstein I, Longcope C: **Erectile dysfunction, cardiovascular disease and cardiovascular risk factors: prospective results in a large random sample of Massachusetts men.** *J Urol* 1998, **159:**91.
6. Jensen J, Lendorf A, Stimpel H, *et al.*: **The prevalence and etiology of impotence in 101 male hypertensive outpatients.** *Am J Hypertens* 1999, **12:**271–275.
7. Johannes CB, Araujo AB, Feldman HA, *et al.*: **Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study.** *J Urol* 2000, **163:**460–463.
8. Grimm R, Grandits GA, Prineas RJ, *et al.* for the TOMHS Research Group. **Long-term effects on sexual function of five antihypertensive Drugs and Nutritional Hygienic Treatment in hypertensive Men and Women. Treatment of Mild Hypertension Study (TOMHS).** *Hypertension* 1997, **29:**8–14.
9. Fogari R, Zoppi A, Preti P, *et al.*: **Sexual activity and plasma testosterone levels in hypertensive males.** *Am J Hypertens* 2002, **15:**In press.
10. Anderson KE, Wagner G: **Physiology of penile erection.** *Physiol Rev* 1997, **75:**191–236.
11. Melis MR, Argiolas A: **Dopamine and sexual behaviour.** *Neurosci Biobehav Rev* 1995, **19:**19–38.
12. Burnett AL, Lowenstein CJ, Bredt DS, *et al.*: **Nitric oxide: a physiologic mediator of penile erection.** *Science* 1992, **257:**401–403.
13. • Sullivan ME, Thompson CS, Dashwood MR, *et al.*: **Nitric oxide and penile erection:is erectile dysfunction another manifestation of vascular disease?** *Cardiovasc Res* 1999, **43:**658–665.

The authors consider the evidence that impaired NO activity plays an important role in the pathogenesis of erectile dysfunction, and suggest that this impaired NO activity may be similar to that which occurs in other forms of vascular disease or in the presence of cardiovascular risk factors (*ie*, hypertension, diabetes, smoking, dyslipidemia).

14. Panza JA: **Nitic oxide in hypertension.** In *Hypertension: A Companion to Brenner and Rector's The Kidney.* Edited by Oparil S, Weber MA: Philadelphia: WB Saunders; 2000:158–165.
15. Virag R, Bouilly P, Frydman D: **Is impotence an arterial disorder?A study of arterial risk factors in 440 impotent men.** *Lancet* 1985, **1:**181–184.
16. Jaffe A, Chen Y, Kisch ES, *et al.*: **Erectile dysfunction in hypertensive subjects. Assessment of potential determinants.** *Hypertension* 1996, **28:**859–862.
17. Toblli JE, Stella I, Inserra F, *et al.*: **Morphological changes in cavernous tissue in spontaneously hypertensive rats.** *Am J Hypertens* 2000, **13:**686–692.
18. Hughes GS, Mathur RS, Margolius HS: **Sex steroid hormones are altered in essential hypertension.** *J Hypertens* 1989, **7:**181–187.
19. Khaw KT, Barrett-Connor E: **Blood pressure and endogenous testosterone in men: an inverse relationship.** *J Hypertens* 1988, **6:**329–332.
20. Kumai T, Tanaka M, Watanabe M, *et al.*: **Possible involvement of androgen in increased norepinephrine synthesis in blood vessels of spontaneously hypertensive rats.** *Jpn J Pharmacol* 1994, **66:**439–444.
21. Endre T, Mattiason I, Berglund G, Hulthen UL: **Low testosterone and insulin resistance in hypertension prone men.** *J Hum Hypertens* 1996, **10:**755–776.
22. Pandei KN, Oliver PM, Maeda N, Smithies O: **Hypertension associated with decreased testosterone levels in natriuretic peptide receptor-A knockout and gene-duplicated mutant mouse models.** *Endocrinology* 1999, **140:**5112–5119.
23. Honda H, Unemoto T, Kogo H: **Different mechanisms for testosterone-induced relaxation of aorta between normotensive and spontaneously hypertensive rats.** *Hypertension* 1999, **34:**1232–1236.
24. Webb CM, McNeill JG, Collins P: **Testosterone increases coronary blood flow in men with coronary artery disease [abstract].** *J Am Coll Cardiol* 1998, **31(Suppl A):**2A.
25. Dockery F, Rajkumar C, Agarwal S, *et al.*: **Androgen deprivation in males is associated with decreased arterial compliance and reduced central systolic blood pressure.** *J Hum Hypertens* 2000, **14:**395–397.
26. Heaton JPW, Varrin SJ: **Effects of castration and exogenous testosterone supplementation in an animal model of penile erection.** *J Urol* 1994, **151:**797–800.
27. Papadopoulos C: **Cardiovascular drugs and sexuality. A cardiologist's review.** *Arch Intern Med* 1980, **140:**1341–1345.
28. Rosen RC, Kostis JB, Jekelis A, Taska LS: **Sexual sequelae of antihypertensive drugs:treatment effects on self-report and physiological measures in middle-aged male hypertensives.** *Arch Sex Behav* 1994, **23:**135–152.
29. • Kochar M, Mazur LI, Patel A: **Sexual dysfunction. Uncovering a connection with hypertension and antihypertensive therapy.** *Postgrad Med* 1999, **106:**149–157.

This article reviews the mechanics of male sexual function and dysfunction, particularly in conjunction with hypertension and antihypertensive therapy, and discusses available treatment options.

30. Report of Medical Research Council Working Party on Mild to Moderate Hypertension: **Adverse reaction to bendrofluazide and propranolol for the treatment of mild hypertension.** *Lancet* 1981, **2:**539–543.
31. Curb JD, Borhani NO, Blaszkowski TP, *et al.*: **Long-term surveillance for adverse effects of antihypertensive drugs.** *JAMA* 1985, **253:**3263–3268.
32. Chang SW, Fine R, Siegel D, *et al.*: **The impact of diuretic therapy on reported sexual function.** *Arch Intern Med* 1991, **151:**2402–2408.
33. Wassertheil-Smoller S, Blaufox MD, Oberman A, *et al.*: **Effect of antihypertensives on sexual function and quality of life: the TAIM study.** *Arch Intern Med* 1991, **114:**613–620.
34. Loriaux DL, Menard R, Taylor A, *et al.*: **Spironolactone and endocrine dysfunction.** *Ann Intern Med* 1976, **85:**630–636.
35. Bauer GE, Baker J, Hunyor SN, Marshall P: **Side-effects of antihypertensive treatment: a placebo-controlled study.** *Clin Sci Mol Med* 1978, **55(Suppl):**341–344.
36. Veterans Administration Cooperative Study Group on Antihypertensive Agents: **Propranolol in the treatment of essential hypertension.** *JAMA* 1977, **88:**716–717.
37. Perez-Stable E, Halliday R, Gardiner PS, *et al.*: **The effects of propranolol on cognitive function and quality of life: a randomized trial among patients with diastolic hypertension.** *Am J Med* 2000, **108:**359–336.
38. Suzuki H, Tominaga T, Kumagai H, *et al.*: **Effects of first-line antihypertensive agents on sexual function and sex hormones.** *J Hypertens* 1988, **6:**S649–S651.
39. Fogari R, Zoppi A, Corradi L, *et al.*: **Sexual function in hypertensive males treated with lisinopril or atenolol: a cross-over study.** *Am J Hypertens* 1998, **11:**1244–1347.
40. Fogari R: **Effect of antihypertensive treatment with valsartan or atenolol on sexual activity and plasma testosterone in hypertensive men.** *Eur J Clin Pharmacol* 2002, In press.

41.• Fogari R, Zoppi A, Poletti L, *et al.*: **Sexual activity in hypertensive men treated with valsartan or carvedilol: a cross-over study.** *Am J Hypertens* 2001, **14:**27–31.

This study first evaluated the effects of an angiotensin II antagonist, valsartan, compared with the β-blocker, carvedilol, on sexual activity in a rather homogeneous population of middle-aged, newly diagnosed, never treated hypertensive men.

42. Andersen P, Seljeflot I, Herzog A, *et al.*: **Effects of doxazosin and atenolol on atherothrombogenic risk profile in hypertensive middle-aged men.** *J Cardiovasc Pharmacol* 1998, **31:**677–683.
43. Yodfat Y, Bar-On D, Amir M, Cristal N: **Quality of life in normotensives compared to hypertensive men treated with isradipine or methyldopa as monotherapy or in combination with captopril: the LOMIR-MTC-IL study.** *J Hum Hypertens* 1996, **10:**117–122.
44. Saunders E, Kong BW: **Sexual activity in male hypertensive patients while taking clonidine.** *Urban Health* 1980, 22–26.
45. Morrisette DL, Skinner MH, Hoffman BB, *et al.*: **Effects of antihypertensive drugs atenolol and nifedipine on sexual function in older men: a placebo-controlled, cross-over study.** *Arch Sex Behav* 1993, **22:**99–109.
46. King B, Pitchon R, Stern E, *et al.*: **Impotence during therapy with verapamil.** *Arch Intern Med* 1983, **143:**1248–1249.
47. Stone TW: **Differential blockage of ATP, noradrenaline and electrically evoked contractions of the rat deferens by nifedipine.** *Eur J Pharmacol* 1981, **74:**373–377.
48. Mancini GB, Henry GC, Macaya C, *et al.*: **Angiotensin converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary heart disease: the TREND (trial on Reversing Endothelial Dysfunction) Study.** *Circulation* 1996, **94:**1490.
49. Llisterri JL, Lozano Vidal JV, Aznar Vicente J, *et al.*: **Sexual dysfunction in hypertensive patients treated with losartan.** *Am J Med Sci* 2001, **321:**336–341.
50. Kifor I, Williams GH, Vickers MA, *et al.*: **Tissue angiotensin II as a modulator of erectile function. I-Angiotensin peptide content, secretion and effects in the corpus cavernosum.** *J Urol* 1997, **157:**1920–1925.