Sexual Dysfunction in Patients With Hypertension: Implications for Therapy

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Sexual dysfunction associated with hypertension or antihypertensive therapies may impact the ability of patients to stay on therapy and lead to deterioration in patients' quality of life. Therefore, it is important for practitioners to become familiar with the wide variation in sexual side effects produced by antihypertensive agents and to discuss the potential occurrence of these side effects with their patients. In many cases, a change in the patient's drug regimen may help patients overcome specific sexual side effects experienced with certain treatments. Practitioners should consider selecting an antihypertensive therapy that is highly effective in lowering blood pressure but preserves patients' quality of life. The effect of medications on sexual function remains controversial. Some blinded trials report little difference between placebo and specific medications, whereas other studies indicate that antihypertensive medications increase sexual dysfunction, which has an impact on quality of life. Recent evidence suggests that losartan, an angiotensin II antagonist, is not typically associated with development of sexual dysfunction and may actually positively impact several indices of sexual function (erectile function, sexual satisfaction, and frequency of sexual activity) as well as perceived quality of life. Thus, angiotensin II antagonists may offer a therapeutic option to prevent or correct erectile dysfunction in patients with hypertension. The favorable effects of these agents on sexual function may be related, in part, to their ability to block angiotensin II, which has recently become recognized as an important mediator of detumescence and possibly erectile dysfunction. (J Clin Hypertens. 2002;4:424–432). ©2002 *Le Jacq Communications, Inc.*

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Despite the well known benefits of effective long-term antihypertensive drug therapy in reducing cardiovascular risk, almost three quarters of US adults with hypertension fail to achieve adequate blood pressure control.[1] This statistic is, in part, attributable to the rate of discontinuation of antihypertensive medications due to the occurrence of troublesome side effects. Appearance of treatment-related side effects may actually make patients feel worse than they did before beginning antihypertensive therapy, particularly since most patients with hypertension are asymptomatic.[2] As many as 70% of hypertensive patients who experience side effects are noncompliant with their antihypertensive medication, and patients experiencing a negative impact on their quality of life have a 40%–60% higher rate of therapy discontinuation than patients whose quality of life is unaffected.[3,4] On the other hand, blood pressure control may be associated with quality of life improvement (patients feeling better). The inability of patients to stay on therapy in the long term may be one of the factors contributing to the development of hypertension-related complications and higher overall health care expenditures.[5]

Sexual dysfunction induced by antihypertensive medications is one of the poorly recognized side effects impacting the patient's ability to stay on therapy. Moreover, this side effect of antihypertensive medications is strongly associated with an impaired quality of life.[6–8] Many commonly prescribed antihypertensive medications may give rise to sexual dysfunction, which often presents in men

as a decrease in libido, difficulty attaining or maintaining an erection, and ejaculation problems, and, in women, as a delay in orgasm.[9,10] Not all classes of antihypertensive agents share the same risk of inducing sexual problems; certain types of antihypertensive medications are generally associated with a lower risk of sexual dysfunction than others.[6] In fact, recent studies suggest that angiotensin II antagonists (AIIAs) may actually improve erectile function and sexual activity in male hypertensive patients.[11,12] The favorable effects of AIIAs on sexual function may be related to their ability to block angiotensin II (ANG II), which has been shown to terminate spontaneous erections when administered exogenously in an experimental model of penile function.[13]

In view of these observations, it is important for practitioners to be aware of the sexual side effects produced by antihypertensive agents so that the selected therapy may provide an optimum balance between antihypertensive efficacy and quality of life.[6,12] In the present review, we will 1) discuss the frequency of sexual dysfunction in hypertensive men and women; 2) summarize the spectrum of sexual problems associated with various classes of antihypertensive therapies; 3) assess the impact of sexual dysfunction on quality of life and the patients' ability to stay on therapy; 4) explore the emerging role of ANG II as an important factor in sexual dysfunction; and, finally, 5) describe the potential clinical benefits of AIIAs in treating patients with hypertension and sexual dysfunction.

SEXUAL DYSFUNCTION—ASSOCIATION WITH ANTIHYPERTENSIVE AGENTS AND THE DYSMETABOLIC SYNDROME OF HIGH BLOOD PRESSURE

Sexual dysfunction is a frequently encountered problem in patients with hypertension and may occur either as a side effect of some types of antihypertensive medications or as a component of the dysmetabolic syndrome of high blood pressure.[6,14] In hypertensive males, sexual dysfunction may present in a variety of ways, including a decreased incidence of sexual activity, difficulty attaining or maintaining an erection, and problems in ejaculating.[9] For the most part, sexual problems have been reported to occur more frequently in patients receiving antihypertensive medication than in those with either untreated hypertension or in normotension (Figure 1 and Table I).[9,11,15–18] However, as discussed below, this finding is not universal.[18] In the Treatment of Mild Hypertension Study (TOMHS),[19] a placebo-controlled trial, there was no difference in the incidence of sexual dysfunction among several antihypertensive agents when compared to placebo at 4 years. At 1 year, however, a greater incidence was noted with a diuretic than with other drugs.[19]

The concept of hypertension as a dysmetabolic syndrome has brought to the forefront the frequent association of high blood pressure with dyslipidemia, insulin resistance, coagulation disorders, and peripheral vascular disease.[20] The anatomic and hemodynamic characteristics of the penile circulation make the process of penile tumescence inextricably linked to blood pressure, perfusion pressure, and vascular compliance. In this context, Toblli et al.[21] reported that cavernous-tissue vascular fibrosis was present in rats with spontaneous hypertension and that the degree of vascular sclerosis in the rat penis was highly correlated with the level of arterial pressure. These intriguing observations suggest a vasculogenic mechanism of erectile dysfunction in hypertensive subjects, since peripheral arterial disease has begun to be recognized as an early consequence or direct contributor to high blood pressure.

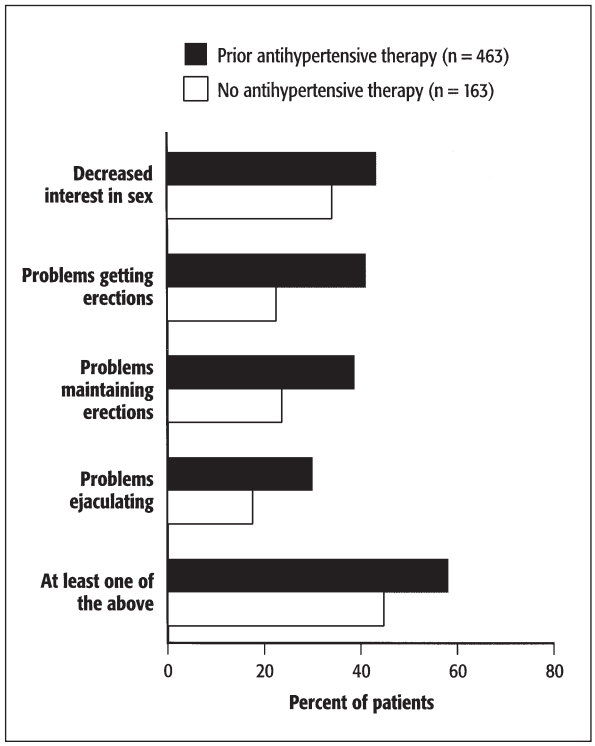

Figure 1. Male patients who had received prior antihypertensive therapy had a higher incidence of distress over sexual symptoms than those who had not received antihypertensive therapy. The sexual symptoms distress index, consisting of a series of four items commonly associated with male sexual distress, was assessed on a 5-point scale as part of a self-administered questionnaire. The study focused specifically on distress over symptoms of sexual dysfunction rather than an overall assessment of quality of life.
Data derived from Arch Intern Med. *1988;148(4):788–794.*[9]

Table I. Prevalence of Male Sexual Problems Among Normotensive Subjects and Treated and Untreated Hypertensive Patients

Study	Normotensive Subjects	Untreated Hypertensive Patients	Treated Hypertensive Patients
Riley et al., 1967[15]			
Impotence	–	26%	55%**
Ejaculation failure	–	14%	45%**
Bulpitt et al., 1976[16]			
Impotence	6.9%	17.1%	24.6%**
Ejaculation failure	0%	7.6%	25.6%**
Bauer et al., 1981[17]			
Impotence	10%	20%	19%
Ejaculation failure	6%	10%	9%
Croog et al., 1988[9]			
Sexual dysfunction†	–	44.2%	57.9%*
Llisterri et al., 2001[11]			
Sexual dysfunction	–	–	42.3%

*$p \leq 0.01$ vs. untreated hypertensive patients; **$p < 0.001$ vs. untreated hypertensive patients or normotensive subjects; †sexual dysfunction comprises problems with sexual desire, attaining/maintaining erections, or ejaculation problems

In keeping with the new animal studies, the recent findings of Llisteri and colleagues[11] demonstrate that erectile dysfunction in hypertensive patients aged 30–65 years was associated with medications that had not been usually considered to impair sexual function. Thus, hypertension-related erectile dysfunction may be a consequence of a reduction in penile perfusion pressure associated with the decrease in systemic arterial pressure induced by antihypertensive medications in the presence of an already decreased penile vascular compliance. Under this scenario, erectile dysfunction may represent a previously unrecognized early symptom of peripheral vascular disease.

PREVALENCE OF SEXUAL DYSFUNCTION IN HYPERTENSIVE PATIENTS

Several reports collectively spanning more than three decades indicate that 2.4%–58% of hypertensive males experience one or more symptoms of sexual dysfunction of varying degrees of severity during antihypertensive drug therapy.[9,11,15–17,19,22,23] It is also true, however, that hypertensive patients also experience sexual dysfunction prior to taking medication, when compared to normotensive subjects. This finding, while quite consistent with the physiologic changes noted in hypertensive individuals, is often neglected in the overall assessment of subjects and in the formulation of a therapeutic scheme. The large variations in the prevalence of sexual problems reported in the literature most likely reflect differences in study methodology (lack of control subjects), types of antihypertensive medications taken, the presence of confounding medications, age differences of study populations, and cultural and socioeconomic factors. In the clinical practice setting, the prevalence of sexual dysfunction is likely to be even higher than that reported in clinical trials because the personal nature of this problem often leads to an unwillingness of many patients and/or physicians to openly discuss this issue.

Although most research on sexual dysfunction has focused almost exclusively on men,[24] women with hypertension are also at risk of developing sexual dysfunction. According to a 1994 survey, sexually active women aged 60–80 years who were receiving antihypertensive medications (atenolol, enalapril, or isradipine) experienced sexual dysfunction, as manifested as a difficulty achieving orgasm, inadequacy of vaginal lubrication, and diminished libido.[10] However, in the absence of a control group of hypertensive women who were not receiving antihypertensive therapy, it is difficult to accurately assess the effect of antihypertensive medication on sexual functioning.

EFFECTS OF SEXUAL DYSFUNCTION ON QUALITY OF LIFE AND COMPLIANCE WITH THERAPY

Sexual dysfunction associated with antihypertensive agents may impact the ability of patients to stay on therapy and lead to an impaired quality of life.[6–8] Sexual dysfunction is an important reason that patients discontinue antihypertensive medications, as exemplified by the findings of the Medical Research Council (MRC) trial in 17,354 hypertensive patients studied over 5.5 years.[25] In this study, premature withdrawal due to impotence occurred at a significantly higher rate in patients receiving either a

Table II. Overview of Sexual Side Effects Reported During Therapy With Several Classes of Antihypertensive Agents

	Erectile Dysfunction	Decreased Libido	Impaired Ejaculation	Gynecomastia	Priapism
Diuretics					
Thiazides	✓	✓	✓		
Spironolactone	✓	✓		✓	
Beta blockers	?			✓	
Antiadrenergics					
Central-acting	✓	✓	✓		
Peripheral-acting	✓		✓	✓	✓
Vasodilators	✓				✓
CCBs			✓	✓	
ACE inhibitors					
AIIAs					

CCBs=calcium channel blockers; ACE=angiotensin-converting enzyme; AIIAs=angiotensin II antagonists
Based on data from *J Hypertens Suppl.* 1988;6(4):S649–651[31] and *Postgrad Med.* 1999;106(2):149–157.[36]

thiazide diuretic ($p<0.001$) or β blocker ($p<0.001$) than in placebo-treated patients (12.6% and 6.3% vs. 1.3% per 1000 patient-years, respectively). However, it must be pointed out that the MRC study was of single-blind design, and thus the findings should be interpreted with caution.

Sexual dysfunction associated with antihypertensive therapies may also impact the quality of life of hypertensive patients, especially as reported in instruments that address sexual functioning or distress.[4,26] As early as 1982, Jachuck and colleagues[27] reported an association of sexual dysfunction with impairment of quality of life in hypertensive patients treated primarily with diuretics, β blockers, or methyldopa (the last, of course, is no longer commonly used in antihypertensive therapy because of its high association with side effects). Approximately 78% of patients who had severe quality of life impairment (according to spouses' ratings) had a reduction in or no sexual interest. In contrast, only 38% of patients with mild impairment of quality of life had reduced sexual function. It must be noted, however, that not all studies have reported a relation between antihypertensive therapy and sexual dysfunction, and in one review of six randomized trials, short-term exposure to antihypertensive drugs was associated with a prevalence of self-reported impotence that was similar to that in placebo-treated patients.[23] Further, in the Trial of Antihypertensive Interventions and Management (TAIM),[28] a multicenter, randomized, placebo-controlled trial in patients with mild hypertension, low-dose antihypertensive drug therapy (with chlorthalidone or atenolol) actually improved, rather than impaired, quality of life.

TYPES OF ANTIHYPERTENSIVE THERAPY ASSOCIATED WITH SEXUAL DYSFUNCTION

Several widely prescribed antihypertensive agents, including diuretics, methyldopa, clonidine, guanethidine, and β blockers (especially those that are nonselective), are known to cause sexual problems or exacerbate existing problems (Tables II and III).[6,29,30] However, not all classes of antihypertensive agents share the same risk of inducing sexual problems, and certain classes of antihypertensive agents tend to be associated with a higher prevalence of sexual dysfunction than others.[6,12] As summarized in Table II, differences among the various classes of antihypertensive agents have been noted in men with respect to erectile dysfunction, decreased libido, impaired ejaculation, gynecomastia, and priapism. Conclusions regarding an association between antihypertensive therapy and sexual dysfunction are limited by the fact that several of the studies denoted in Table III were poorly controlled and results were based on questionnaires. This is one of the factors responsible for the lack of recognition of sexual dysfunction as a component of the hypertensive process rather than as a consequence of antihypertensive medications.

Compared with placebo or other classes of antihypertensive agents, a higher prevalence of male sexual dysfunction has been reported in some studies of diuretics, including spironolactone, which inhibits dihydrotestosterone binding, and thiazide diuretics (e.g., chlorthalidone), as well as β blockers

Table III. Summary of Studies Showing Differences in Effect of Various Antihypertensive Agents on Sexual Function in Hypertensive Men

STUDY	DESIGN	ANTIHYPERTENSIVE AGENT	PATIENTS WITH SEXUAL DYSFUNCTION (%)*	
Bulpitt and Dollery, 1973[45]	Questionnaire-based study in 373 HT patients	Diuretic	31.8%	
		Methyldopa + diuretic	35.7%	
		Bethanidine ± diuretic	66.7%	
		Guanethidine ± diuretic	54.5%	
		Reserpine + diuretic	33.3%	
		Methyldopa + bethanidine ± diuretic	47.4%	
Hogan et al., 1980[46]	Questionnaire-based study of SD in 861 HT males	HCTZ	9%[a]	
		Methyldopa + diuretic	13%[a]	
		Clonidine + diuretic	15%[a]	
		Propranolol + hydralazine + diuretic	23%[a]	
		Control (no HT, no medication)	4%	
Curb et al., 1985[47]	Study of SD in 5485 male HT patients	Chlorthalidone	5.1%	
		Spironolactone	1.8%	
		Reserpine	5.6%	
		Methyldopa	5.5%	
		Hydralazine	1.2%	
		Guanethidine	10.8%	
		Other	2.3%	
Scharf and Mayleben, 1989[48]	R, CO, on SF in 12 HT men	HCTZ	67%	
		Prazosin	42%	
Wassertheil-Smoller et al., 1991[28]	R, PC, MC 6-mo study of ED in 697 HT patients	Chlorthalidone	28%[b]	
		Atenolol	11%	
		Placebo	3%	
Chang et al., 1991[49]	R, PC 2-mo study of SD in 176 HT men	Thiazide diuretic	14%	
		Placebo	5%	
Grimm et al., 1997[19]	DB, R, PC, 4-yr study of ED in 557 HT men		24 mo	48 mo
		Acebutolol	9.2%	11.8%
		Amlodipine	8.3%	15.0%
		Chlorthalidone	17.1%[a]	18.3%
		Doxazosin	5.6%	11.1%
		Enalapril	9.7%	14.1%
		Placebo	8.1%	16.7%
Fogari et al., 1998[39]	DB, R, 16-wk study of SD in 90 HT men w/o history of SD	Lisinopril	3%	
		Atenolol	17.3%[c]	
			Men	Women
Prisant et al., 1999[23]	Analysis of self-reported SD in 1251 men and 661 women enrolled in 6 DB, R trials	Enalapril	2.9%	1.9%
		Amlodipine	3.9%	0.0%
		HCTZ	1.5%	0.0%
		Bisoprolol	1.8%	0.6%
		Bisoprolol + HCTZ	3.0%	0.0%
		Placebo	2.1%	0.0%
Fogari et al., 2001[12]	DB, R, CO, 16-wk study of SF in 148 HT men	Carvedilol	13.5%[d]	
		Valsartan	0.9%	
		Placebo	0.9%	
Burchardt et al., 2000[22]	Questionnaire-based study of ED 476 HT males	Thiazide diuretics	27.9%	
		Beta blockers	31.7%	
		ACEIs	26.9%	
		K^+-sparing diuretics	23.1%	
		CCBs	18.3%	
		Alpha blockers	13.5%	
		AIIAs	8.7%	
		Loop diuretics	5.8%	
		Direct vasodilators	2.9%	
Llisteri et al., 2001[11]	Questionnaire-based, prospective, 12-wk study of SD in 82 HT males with ED	ACEIs	40.2%	
		CCBs	19.5%	
		Beta blockers	15.9%	
		Diuretics	13.4%	
		Others	6.1%	
		Alpha blockers	2.4%	
		AIIAs	2.4%	

HT=hypertensive; SD=sexual dysfunction; R=randomized; CO=crossover; SF=sexual function; PC=placebo controlled; MC=multicenter; ED=erectile dysfunction; DB=double-blind; HCTZ=hydrochlorothiazide; ACEIs=angiotensin-converting enzyme inhibitors; CCBs=calcium channel blockers; AIIAs=angiotensin II antagonists; *includes one or more of the following: getting or maintaining erections, ejaculatory dysfunction, reduced libido, reduced sexual activity, orgasmic dysfunction; [a]$p<0.05$ vs. placebo or control; [b]$p=0.009$ vs. placebo; [c]$p<0.05$ vs. lisinopril; [d]$p<0.001$ vs. valsartan

(Table III).[9,12,19,22,31–33] Beta blockers (e.g., atenolol and propranolol) may potentially impact sexual functioning through a variety of mechanisms, including a reduction in central sympathetic outflow, impairment of vasodilation of the corpora cavernosa, effects on luteinizing hormone and testosterone secretion, and a tendency to produce sedation or depression, thereby causing a loss of libido.[12,31] However, as noted, deleterious effects of diuretics and β blockers on sexual function have not been consistently found, and several controlled studies, including TOMHS and a combined analysis of six randomized, blinded, prospective trials, have found little or no evidence for a greater risk of occurrence of adverse sexual sequelae between these agents and other antihypertensive medications.[23,34,35] Variations in the design of the studies, the inclusion of a placebo control arm, and the characteristic of the population under investigation are factors adding to the difficulties in recognizing the nature of the mechanisms that associate sexual dysfunction with hypertension and its medications.

Centrally acting antiadrenergic agents, such as methyldopa and clonidine, also give rise to male sexual dysfunction, possibly by decreasing sympathetic outflow as well as diminishing libido and ejaculation. Direct vasodilators, including hydralazine and minoxidil, may produce erectile dysfunction and priapism, but this appears to be uncommon.[36] There is little evidence to suggest that calcium channel blockers (CCBs) result in erectile dysfunction, although impotence associated with verapamil has been described,[37] and in our study, CCBs were second to angiotensin-converting enzyme (ACE) inhibitors in their association with erectile dysfunction.[11] Moreover, gynecomastia and problems with ejaculation have been reported with CCB therapy.[31,38]

EFFECTS OF AIIAs ON SEXUAL DYSFUNCTION IN HYPERTENSIVE PATIENTS

Therapy with AIIAs and ACE inhibitors is generally not associated with development of sexual dysfunction in patients with hypertension (Tables II and III),[6,12,31,39] although two questionnaire-based studies have reported a relatively high occurrence of sexual problems in patients receiving ACE inhibitors.[11,22] As noted by Rosen, "...hypertension therapy directed at the renin-angiotensin system was more likely to be associated with improvements in sexual distress

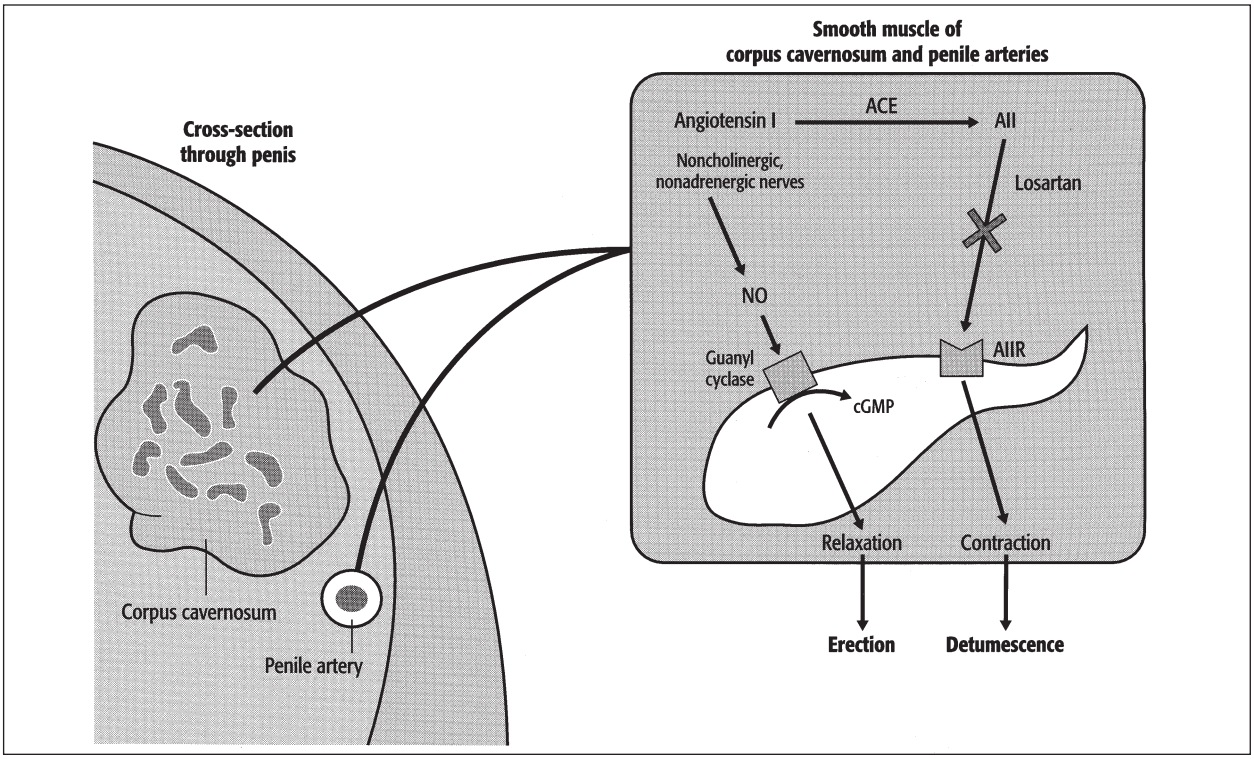

Figure 2. Schema depicting the possible role of angiotensin II (AII) as a regulator of penile erection through contractile effects on corporal and vascular smooth muscle. By blocking the effects of AII, the AII antagonist losartan produces a dose-dependent increase in cavernosal pressure and relaxation of smooth muscle, and hence, development of an erection. Losartan may therefore potentially offer a new therapeutic option to prevent and/or correct erectile dysfunction in patients with hypertension.[13,30,44]
ACE=angiotensin-converting enzyme; cGMP=cyclic guanosine monophosphate; AIIR=angiotensin II receptor; NO=nitric oxide
Drawing courtesy of VMF Designs, Winston-Salem, NC

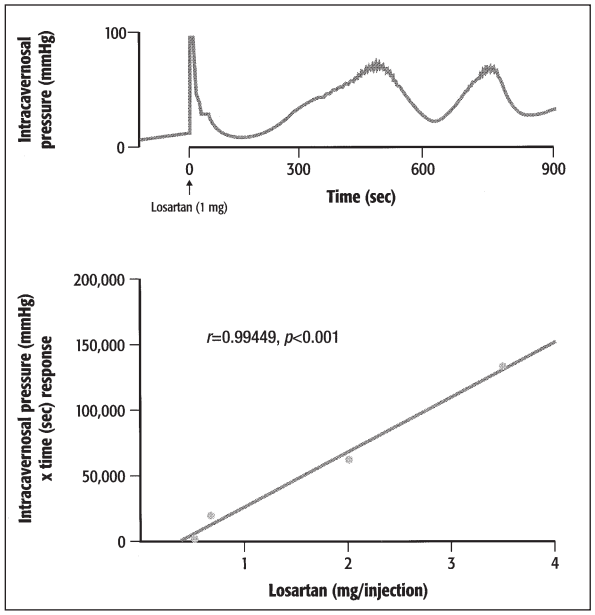

*Figure 3. Administration of 1 mg losartan (representing 1/30th of the dose producing a 10% decrease in blood pressure) in an experimental model of penile erection produced an immediate increase in intracavernosal pressure, followed by multiple waves of increased pressure. The increase in intracavernosal pressure was significantly correlated with losartan dose (*p<*0.001). Data derived from* J Urol. *1997;157(5):1920–1925.*[13]

scores than other forms of treatment, and less likely to lead to a deterioration in sexual function."[6] This statement is corroborated by two studies comparing β blockers with either an ACE inhibitor or an AIIA.[12,39] In both of these studies, the β blocker caused chronic worsening in sexual activity, whereas both the ACE inhibitor and AIIA had no long-term effect—in fact, the AIIA improved sexual activity. For example, in a double-blind, crossover study by Fogari and colleagues,[12] 160 hypertensive patients with newly diagnosed hypertension were randomized to receive valsartan 80 mg once daily or carvedilol 50 mg once daily for 16 weeks. Sexual activity was assessed with a self-administered questionnaire containing a series of questions addressing the patients' interest in sex, difficulties getting or maintaining erections, and the number of times patients had sexual intercourse over a 2-week period. Despite similar effects on blood pressure by the two agents, AIIA therapy increased sexual activity (8.3 episodes/month of sexual intercourse at baseline to 10.2 at week 16), whereas β blocker therapy significantly decreased sexual activity compared with baseline (8.2 to 3.7 episodes per month; $p<0.01$) and compared with AIIA ($p<0.01$).[12] Erectile dysfunction was a complaint of 15 patients receiving carvedilol (13.5%) and one patient receiving valsartan. These findings serve to illustrate the marked differences in the effects of β blockers and AIIAs on sexual function (despite similar efficacy in reducing blood pressure) and suggest that AIIAs may offer therapeutic advantages with respect to quality of life.

More recent evidence supporting a beneficial effect of AIIAs in positively influencing several indices of sexual function, including erectile function, sexual satisfaction, and frequency of sexual activity, as well as perceived quality of life, is provided by a recent open-label study by Llisterri and colleagues[11] in hypertensive patients aged 30–65 years. This study evaluated the effect of the AIIA losartan in hypertensive subjects either with (n=82) or without (n=82) a diagnosis of sexual dysfunction, all of whom were selected consecutively from primary care clinics. Sexual dysfunction was diagnosed by means of a well accepted, self-administered questionnaire revalidated in an independent study of 60 additional hypertensive subjects. Of the 323 hypertensive male and female subjects in the initial sample, 82 men with sexual dysfunction (prevalence of 42.3%; 95% confidence interval, 35.3–49.3; age range, 30–65 years) received a 12-week regimen of losartan 50 mg/day. AIIA treatment for 12 weeks produced marked and statistically significant increases in sexual satisfaction, from 7.3% of patients at baseline to 58.5% of patients after AIIA therapy ($p<0.001$). In addition, this medication increased the proportion of patients with a high frequency of sexual activity (40.5% vs. 62.3%), improved the quality of life in 73% of patients, and decreased the percentage of patients reporting erectile dysfunction (75.3% vs. 11.8%). Overall, only 11.8% of the treated subjects did not report an improvement in sexual function with losartan. In the control group of hypertensive patients without sexual dysfunction, the AIIA produced comparable reductions in arterial blood pressure but no significant changes in erectile dysfunction, sexual satisfaction, frequency of sexual activity, or perceived quality of life ($p>0.05$). Changes in sexual dysfunction variables were unrelated to age, duration of hypertension, level of education, marital status, or blood pressure levels, or type of antihypertensive agent subjects received prior to study entry.

The potentially beneficial effect of AIIAs on sexual function in hypertensive patients is consistent with their excellent tolerability and adverse event profile observed in both short-term and long-term trials in hypertensive patients.[40,41] AIIAs are well tolerated in hypertensive patients, as evidenced by the similarity in the percentage of patients with clinical adverse experiences in AIIA-treated and placebo-treated patients.[40] This may have important clinical ramifications with respect to patients staying on therapy, an assertion borne out by a recent study showing

that the percentage of patients continuing initial therapy with AIIAs was greater than that for ACE inhibitors, CCBs, β blockers, or diuretics.[42]

Collectively, these studies suggest that AIIAs, such as losartan, may offer a therapeutic option to prevent and/or correct erectile dysfunction in patients with hypertension. The favorable effects of AIIAs on sexual function may be related, in part, to their ability to block ANG II, which has recently been proposed as a potential mediator of erectile function.[42] In addition, AIIAs may also cross the blood-brain barrier and have a direct positive effect on the central nervous system, an assertion supported by the recent finding that losartan, but not hydrochlorothiazide, improves cognitive function in elderly hypertensive patients.[43]

EVOLVING ROLE OF ANG II AS A MEDIATOR OF ERECTILE DYSFUNCTION

While the physiology of erection is a complex, neurovascular event regulated by psychologic and hormonal factors,[30] corporal and vascular smooth muscle tone and contractility play a key role in modulating penile blood flow and, hence the erectile process. Erection occurs due to nitric oxide-mediated relaxation of corporal and arterial smooth muscle, allowing increased blood flow into the sinusoidal spaces (Figure 2).[30] Nitric oxide, released from the endothelium and from nonadrenergic, noncholinergic cavernous nerves during sexual stimulation, appears to be the principal mediator of erection, although vasoactive polypeptide and prostaglandins may also be involved.[30,36]

Recent evidence suggests that ANG II may play an important role in detumescence and possibly erectile dysfunction.[13,44] ANG II has been identified in human corpus cavernosum (primarily in endothelial cells lining blood vessels and smooth muscle bundles within the corpus cavernosum), where its tissue concentration is 200 times higher than plasma levels and 10 times higher than in aortic or mesenteric vessels.[13] Superfused cavernosal tissue from human subjects undergoing penile prosthesis implantation synthesizes (presumably via local endothelial ACE) and spontaneously secretes ANG II. Local ACE may therefore regulate smooth muscle tone in a paracrine fashion via production of ANG II, which in turn stimulates contraction of corporal and vascular smooth muscle via an ANG II receptor. This constricts blood flow through the penile arteries and reopens the venous plexus, thereby allowing penile flaccidity to return. This mechanism is consistent with a recent study indicating that the ACE *DD* genotype (a deletion polymorphism in the ACE gene associated with high circulating and tissue levels of ACE) may represent an important risk factor for vasculogenic erectile dysfunction.[44]

The potential involvement of ANG II in regulating erectile function is illustrated by the results of Kifor and colleagues,[13] who utilized a canine model of penile erection. Intracavernosal administration of ANG II terminated spontaneous erections in anesthetized dogs, an effect similar to that obtained with epinephrine. Administration of the AIIA in the same model resulted in a dose-dependent increase in cavernosal pressure and relaxation of smooth muscle, and thus the development of an erection (Figure 3). These intriguing studies suggest that ANG II may be an important mediator of erectile function and may offer a mechanistic explanation for the improvement in erectile function as well as satisfaction and frequency of sexual activity observed in clinical studies in male hypertensive patients with sexual dysfunction.[11]

SUMMARY

Occurrence of sexual dysfunction in patients with hypertension may not only negatively impact the ability of patients to stay on antihypertensive therapy, but can also lead to deterioration in quality of life. Therefore, it is important for practitioners to be aware of the wide variation in sexual side effects produced by antihypertensive agents and to be willing to discuss potential occurrence of these problems with patients.

Practitioners should consider choosing an antihypertensive therapy with the lowest possible potential for sexual side effects in order to attain an optimum balance between antihypertensive efficacy and quality of life. Recent studies indicate that AIIAs may offer a therapeutic option to prevent or correct erectile dysfunction in patients with hypertension. AIIAs have been shown to positively impact several indices of sexual function and perceived quality of life, effects possibly attributable to blockade of the effects of ANG II in mediating penile detumescence.

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