Sexual Activity in Hypertensive Men Treated With Valsartan or Carvedilol: A Crossover Study

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The aim of this study was to compare the effect of anti-hypertensive treatment with valsartan or carvedilol on sexual activity in hypertensive men who were never treated for hypertension. A total of 160 newly diagnosed hypertensive men (diastolic blood pressure [DBP] ≥ 95 mm Hg and < 110 mm Hg), aged 40 to 49 years, all married and without any previous sexual dysfunction, were enrolled. After a 4-week placebo period, the patients were divided into two groups: a) 120 patients were randomized to receive carvedilol 50 mg once daily or valsartan 80 mg once daily for 16 weeks according to a double-blind, cross-over design; after another 4-week placebo period, patients were crossed over to the alternative regimen for a further 16 weeks; b) 40 patients were treated with placebo according to a single-blind design for 16 weeks. At the screening visit and every 4 weeks thereafter, blood pressure (BP) was evaluated and patients were interviewed by a questionnaire about their sexual activity. Blood pressure was significantly lowered by both treatments, with a 48% of normalization with valsartan and 45% with carvedilol. During the first month of therapy, sexual activity (assessed as number of sexual intercourse episodes per month) declined with both drugs as compared with baseline, although the decrease was statistically significant in the carvedilol (from 8.2 to 4.4 sexual intercourse episodes, P < .01) but not in the valsartan-treated patients (from 8.3 to 6.6 sexual intercourse episodes, not significant). Ongoing with the treatment the sexual activity further worsened with carvedilol (3.7 sexual intercourse episodes per month) while fully recovered and also improved with valsartan (10.2 sexual intercourse episodes per month). The results were confirmed by the cross-over. Erectile dysfunction was a complaint of 15 patients with carvedilol (13.5%), one patient with valsartan (0.9%), and one patient in the placebo group. These findings suggest that carvedilol induces a chronic worsening of sexual activity, whereas valsartan not only does not significantly worsen sexual activity but may even improve it. Am J Hypertens 2001;14:27–31 © 2001 American Journal of Hypertension, Ltd.

Key Words: Sexual activity, hypertension, valsartan, carvedilol.
Angiotensin II (Ang II) receptor antagonists are a new class of antihypertensive agents that have proved to be good with respect to their effect on quality of life. However, their effects on sexual function have not been specifically evaluated. Similarly, to our knowledge, no study has focused on the effects on sexual function of the more recent β-adrenergic blocking agents. With this background, we undertook the present study to evaluate the effects of the Ang II receptor antagonist valsartan and of the β-blocker carvedilol on sexual function in newly diagnosed, never treated essential hypertensive subjects who were homogeneous for gender, age, marital status, and lack of previous sexual dysfunction symptoms. We specifically focused on one aspect of male sexual function, i.e., sexual activity (assessed as sexual intercourse frequency), which is considered to be a good index of sexual interest. We chose to compare valsartan and carvedilol, as they were the more recently available agents of their class when we began the study.

Methods

A total of 160 newly diagnosed hypertensive subjects were enrolled according to the following inclusion criteria: men aged 40 to 49 years, all married, with never-treated essential hypertension (diastolic blood pressure [DBP] ≥ 95 and < 110 mm Hg) and without sexual dysfunction symptoms. Patients with diabetes mellitus, obesity, smoking habits, major cardiovascular and noncardiovascular diseases, or conditions requiring any other concomitant medication were excluded from the study. The study protocol was approved by the local Ethical Committee, and all patients gave their informed consent. After a 4-week run-in period on placebo the patients were divided into two groups: a) 120 patients were randomized to receive carvedilol, 50 mg once daily, or valsartan, 80 mg once daily, for 16 weeks according to a double-blind, cross-over design; after another 4-week placebo period, patients were crossed-over to the alternative regimen for a further 16 weeks; or b) 40 patients were treated with placebo according to a single-blind design for 16 weeks. They were randomized to placebo following a protocol according to which, for every four patients eligible for the study, three were actively treated and one was administered placebo. Patients were checked at the screening visit (baseline) and every 4 weeks thereafter. At each visit, sitting blood pressure (BP) was measured using a standard mercury sphygmomanometer, Korotkoff I and V phases, and patients were given a questionnaire with instructions for self-completion. The questions dealing with sexual dysfunction (Have you noted a decrease of interest in sex? Did you have problems in gaining an erection? Did you have problems in maintaining an erection? How many times did you have sexual intercourse in the last 2 weeks?) were part of a series of questions on various aspects of quality of life. This type of questionnaire has been shown to be more sensitive than clinical interviews in eliciting problems with sexual function.

After assurance of confidentiality, questionnaires coded by identification numbers were completed by the respondent in a private area and responses were returned in a sealed envelope. The primary measure of treatment effects on sexual function was sexual activity, assessed as mean number of sexual intercourse episodes per month. The number of patients complaining of sexual dysfunction symptoms also was assessed. Results are expressed as mean values ± SD. The statistical analysis of the data was performed by analysis of variance, and considered only those patients who completed the trial and who did not complain of erectile dysfunction during the trial (96 patients in the active treated group and 35 in the placebo group). A value of $P < .05$ was considered significant. Patients who reported erectile dysfunction symptoms were excluded from the analysis of the data, as they would have altered the findings of the study. In fact, impairment of erectile function has such a psychologic impact to induce men to avoid sexual intercourse due to fear of failure, so that considering patients with erectile dysfunction would have introduced a misleading factor and the results would have not truthfully expressed the specific impact of drugs on sexual activity, considered as the index of sexual interest. To verify the basic assumptions of crossover design, besides the evaluation of period effect, the presence of carry-over or sequence effect was also investigated. However, no variable period effect or, more specifically, no sequence effect was found.

Results

A total of 160 men aged 46.6 years entered the study; 148 completed it. Six patients were lost to follow-up, two interrupted the trial for hypotension (one with valsartan and one with carvedilol) and four patients in the placebo group for hypertension (DBP ≥ 110 mm Hg). Table 1 shows the baseline clinic and demographic characteristics of the patients in the study groups.

Valsartan and carvedilol similarly lowered BP levels, with no difference between treatments. The systolic blood pressure (SBP) and DBP mean decreases were already

### Table 1. Baseline characteristics of hypertensive men in the two treatment groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Active (n = 120)</th>
<th>Placebo (n = 40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.6 ± 3</td>
<td>46.5 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 2</td>
<td>25.1 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>160.1 ± 10</td>
<td>159.3 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>100.6 ± 6</td>
<td>101.1 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>89 ± 10</td>
<td>90 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>214 ± 23</td>
<td>216 ± 24</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
significant after 4 weeks of treatment with both valsartan \((-18.1/11.2\ \text{mm Hg}, \ P < .001 \ \text{vs placebo})\) and carvedilol \((-18.6/11.8\ \text{mm Hg}, \ P < .001 \ \text{vs placebo})\) and persisted after 16 weeks \((-19.8/11.6\ \text{mm Hg} \text{ and } -18.2/11.4\ \text{mm Hg}, \text{ respectively; both } P < .001 \ \text{vs placebo})\). Normalization of BP (DBP < 90 mm Hg) was achieved by 48% of the patients treated with valsartan and by 46% of those treated with carvedilol. As shown in Fig. 1, during the first placebo period the number of sexual intercourse episodes per month tended to reduce as compared with baseline, although not significantly. After 4 weeks of active treatment, sexual activity decreased with both drugs; however, the reduction was statistically significant only in the carvedilol-treated patients \((8.3 \pm 4.2 \text{ episodes/month, } -46\%, \ P < .01 \ \text{vs baseline})\) and not in those treated with valsartan \((8.2 \pm 4.6 \text{ episodes/month, } -21\%, \text{ NS})\). Ongoing with the treatment, sexual activity further worsened with carvedilol \((3.7 \pm 1.4 \text{ episodes/month, } P < .01 \ \text{vs baseline})\), whereas it fully recovered and even improved, although not significantly, with valsartan \((10.2 \pm 4.6 \text{ episodes of sexual intercourse/month, NS vs baseline})\), the difference between the two drugs being highly significant \((P < .01)\). During the second placebo period, the sexual intercourse rate slightly decreased, reaching baseline levels in the valsartan-treated patients \((8.4 \pm 4.9\) \text{ episodes/month, valsartan (7.2 } \pm 4.1\)), although it remained lower as compared with baseline. Crossover treatment confirmed the decrease of sexual activity after 4 weeks of treatment with carvedilol \((8.4 \pm 4.8 \text{ to } 4.5 \pm 2.6 \text{ episodes of sexual intercourse/month})\) and no change with valsartan \((7.2 \pm 4.1 \text{ to } 7.2 \pm 4.8 \text{ episodes of sexual intercourse/month})\). Again, sexual activity worsened after 16 weeks of treatment with carvedilol \((3.8 \pm 1.7 \text{ episodes of sexual intercourse/month})\), whereas it fully recovered and even improved, although not significantly, with valsartan \((10.1 \pm 4.9 \text{ episodes of sexual intercourse/month})\), with the difference between the two treatments being highly significant \((P < .01)\).

Preliminary tests allowed us to exclude the presence of a carry-over or sequence effect: in the patients who began the treatment with carvedilol the sexual intercourse rate was 7.5 \pm 4.3 episodes of sexual intercourse/month at the end of the first placebo period (pretreatment) and 7.2 \pm 4.1 at the end of the second placebo period (posttreatment), with no significant difference between them. In the patients who began the treatment with valsartan the sexual intercourse rate was 7.7 \pm 4.4 at the end of the first placebo period and 8.4 \pm 4.9 at the end of the second placebo period, with no significant difference between them. Therefore, we combined the first and second treatment periods for each drug and compared the results with those of the patients treated with placebo for 16 weeks (Fig. 2). After 4 weeks of treatment, sexual activity tended to reduce in all patients, but particularly in those treated with carvedilol. Ongoing with the treatment, placebo did not further affect the sexual intercourse rate, whereas carvedilol progressively worsened it \((1.1 \pm 0.9 \text{ episodes of sexual intercourse/month at 8 weeks, } 0.9 \pm 0.7 \text{ at 12 weeks, and } 0.8 \pm 0.6 \text{ at 16 weeks, } P < .05 \ \text{vs placebo})\) and \(P < .01 \ \text{vs valsartan at each time interval})\), whereas valsartan improved it \((2.4 \pm 1.9 \text{ episodes of sexual intercourse/month at 8 weeks, } 2.6 \pm 1.8 \text{ at 12 weeks, and } 2.6 \pm 1.7 \text{ at 16 weeks, } P < .05 \ \text{vs placebo at 12 and 16 weeks})\). Considering the percent changes in the sexual intercourse rate, at 4 weeks the mean number of sexual intercourse episodes was reduced by 43% with carvedilol and by 20% with valsartan, with a statistically significant difference between the two drugs \((P < .05)\). The difference was even greater after 16 weeks of treatment, when the sexual intercourse rate was reduced by 50% with carvedilol but was increased by 19% with valsartan.

Erectile dysfunction was spontaneously reported by 15 patients \((13.5\%)\) during carvedilol (four complete impotence, six major difficulty in gaining an erection, five difficulty in maintaining an erection), by one patient during valsartan \((0.9\%; \text{ difficulty in maintaining an erection})\).
and by one patient in the placebo group (2.5%; difficulty in gaining an erection). The difference between the two active treatments was statistically significant ($P < .001$).

**Discussion**

Although the mechanisms are unclear, hypertension itself is associated with sexual dysfunction, and the incidence of sexual problems is considerably higher among untreated hypertensive men than among normotensive ones.\(^1,6,11,28,29\)

The risk for sexual dysfunction in hypertensive patients is exacerbated by drug treatment: the proportion of men reporting sexual difficulties has been reported to be higher among those taking antihypertensive drugs than among untreated ones.\(^4,30\) Hence, in treating patients with hypertension, it is important to ensure that the drugs used have the lowest possible potential for causing problems with sexual function, to obtain the best balance between therapeutic efficacy and quality of life, which is essential for compliance.\(^31\)

In the present study, which compared the effects on sexual life of two recent antihypertensive agents, carvedilol and valsartan, in a middle-aged, sexually active population of newly diagnosed, never-treated hypertensive men, we observed the following: First during treatment with placebo, 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. In fact, it is well established that the patient’s knowledge of the diagnosis has a negative impact on reported symptoms and quality of life measures.\(^32\)

Second treatment with the $\beta$-blocker carvedilol produced a chronic worsening of sexual activity, which confirms previous observations\(^1,6,11,14–19,23\) about the negative impact of $\beta$-blockers on sexual function. Considering the time course of the effects of carvedilol on sexual activity, the decrease was already evident after the first 4 weeks of treatment, probably because of the combination of psychologic factors, pharmacologic mechanisms, and BP lowering itself, but persisted with the treatment. The negative impact of therapy with carvedilol on sexual function was confirmed by the higher percentage of patients who complained of sexual dysfunction symptoms as compared with that of patients treated with valsartan or placebo. Interference with adrenergic nervous system function (which is involved in the integration of erection and ejaculation), the regulation of luteinizing hormone secretion, and the stimulation of release of testosterone,\(^33\) may underlie the adverse effect of $\beta$-blockers on sexual activity.

Third, unlike carvedilol, valsartan produced only a temporary, nonsignificant decline in sexual function after 4 weeks of treatment, whereas it even improved this function ongoing with the treatment. After 16 weeks of therapy, patients receiving valsartan experienced a 19% increase in sexual intercourse rate, which, by contrast, was reduced by 50% in the carvedilol-treated patients.

Fourth, no differences were found between the two treatment groups with regard to BP control, which allows us to exclude the possibility that the observed difference in the effects on sexual activity was due to the different BP-lowering effects of carvedilol and valsartan.

We hypothesize three possible mechanisms to explain the sexual activity improvement induced by valsartan: 1) it could be one expression of the general improvement of the quality of life indices (general well-being, physical symptoms, cognitive function, work performance, etc) due to the ang II receptor antagonists; 2) it could be a consequence of some yet-unknown effect of the activated renin-angiotensin system on some nervous center modulating sexual activity or on some hormonal system (this hypothesis agrees with the observation that hypertension therapy directed at the renin-angiotensin system is more likely to be associated with improvements in sexual distress scores than other forms of treatment and is less likely to lead to a deterioration in sexual function\(^6,11,12,23\) or 3) it could be relative to some local effect; in an experimental animal model, intracavernosal injection of Ang II caused contraction of cavernosal smooth muscle and terminated spontaneous erection, whereas administration of an Ang II receptor antagonist resulted in smooth muscle relaxation and, thus, erection, which suggests that Ang II is an important modulator of erectile function.\(^34\)

In conclusion, our findings show that the $\beta$-blocker carvedilol and the Ang II receptor antagonist valsartan have different effects on sexual function in hypertensive men and that, despite similar antihypertensive efficacy, valsartan may have some advantages in terms of the quality of sexual life.

**References**