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·Original Article·

Beneficial effects of switching from β-blockers to nebivolol on the erectile function of hypertensive patients

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Abstract

Aim: To investigate the effect of substituting β-blockers with nebivolol on the erectile function of patients suffering from essential hypertension. **Methods:** Forty-four young and middle-aged men (31–65 years) with essential hypertension visited our outpatient clinic and took β-blocker treatment (atenolol, metoprolol or bisoprolol) for more than 6 months. All the patients completed a questionnaire regarding erectile function (International Index for Erectile Function). Patients were then switched to an equipotent dose of nebivolol for 3 months and, at the end of this time period, filled out the same questionnaire. **Results:** Twenty-nine out of the 44 (65.9%) patients who took β-blockers (atenolol, metoprolol or bisoprolol) had exhibited erectile dysfunction (ED). Their systolic and diastolic blood pressure did not change significantly with the treatment switch. In 20 out of these 29 (69%) patients, a significant improvement in the erectile function score was exhibited after 3 months of nebivolol administration, and in 11 of these 20 patients, erectile function was normalized. **Conclusion:** Nebivolol seems to have a beneficial effect on ED (possibly due to increased nitric oxide availability); however, further prospective, randomized, placebo-controlled studies are needed to confirm the beneficial effects of nebivolol. *(Asian J Androl 2006 Mar; 8: 177–182)*

Keywords: erectile dysfunction; essential hypertension; β-blockers; nebivolol

1 Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain or maintain penile erection sufficient for satisfactory sexual performance. ED is now widely recognized as an entity and its reported incidence has increased since the introduction of phosphodiesterase-5 inhibitors. It was estimated that approximately 30 million American men and more than 100 million men worldwide were afflicted with this condition that has a major effect on patients' and their sexual partners' quality of life [1].

Up to 25% of ED cases were related to medication side effects; antihypertensive drugs were the most implicated class [2]. Several lines of evidence suggested that β-blockers were associated with an increased risk of ED [3–6].

Nebivolol is a newly developed, highly selective β_1-blocker, which has been shown to cause vasodilatation, possibly by inducing nitric oxide (NO) production [7–9].

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NO was believed to play a crucial role in erectile function, because it mediates the relaxation of the trabecular muscle of the corpus cavernosum and thus facilitates penile erection [10–12].

The aim of the present study was to investigate the effect of substituting β-blockers with nebivolol on erectile function in patients with essential hypertension, presenting with or without ED.

2 Materials and methods

2.1 Study population

The present study was an open, prospective study of 44 young and middle-aged men (31–65 years) visited our outpatient clinic. All patients had arterial hypertension and were taking β-blockers (atenolol 50-100 mg/d: 40 patients; metoprolol 100 mg/d: two patients; bisoprolol 10 mg/d: two patients) for more than 6 months (range 6 months to 22 years). Secondary hypertension was excluded by clinical and, if appropriate, laboratory examinations. The study was conducted in accordance with the principles of the Helsinki declaration [13] and was approved by the Hospital Ethics Committee. All subjects gave informed consent and the procedures followed were in accordance with institutional guidelines. Patients with renal failure, diabetes mellitus and heart and liver diseases were excluded from the study due to the fact that there is an association between these conditions and ED.

2.2 History and physical examination

The patients' demographic data (age and body weight), cigarette consumption and alcohol intake were recorded. Blood pressure was measured using a mercury sphygmomanometer (Empire N, Rudolf Riester GMBH, Jungingen, Germany), following the standard methodology. Three blood pressure recordings were obtained consecutively, and blood pressure was determined as the mean of the second and the third recording.

A thorough physical examination was undertaken, and each patient was assessed for genital abnormalities, such as phimosis, hypospadias, signs of hypogonadism and prostate hyperplasia. Individuals with such conditions were excluded from the study and referred on to our urologic outpatient clinic.

2.3 Evaluation of erectile function

An ED evaluation was performed by means of a standardized questionnaire, using an inform-then-probe type of questions. First of all, the question: "Many people experience sexual problems. Has this ever appeared to you?" was asked to the individuals, in order to reassure them that their symptoms (if present) are not uncommon or embarrassing.

Then the patient was asked to complete a questionnaire regarding ED. The International Index for Erectile Function (IIEF) was chosen, since it is considered an accurate, widely-used test for defining the area of sexual dysfunction. Moreover, it provides information on several areas of sexual function, such as erectile function (questions 1–5, 15), intercourse satisfaction (questions 6–8), orgasmic function (questions 9, 10), sexual desire (questions 11, 12) and overall satisfaction (questions 13, 14). ED is classified (according to IIEF questionnaire scoring, using six questions) as severe (6–10 points), moderate (11–16 points), mild (17–25 points) and none (26–30 points).

2.4 Study design

Patients were told that erectile function may be affected by β-blocker therapy and that the aim of our study was to investigate the effect of a new β-blocker on erectile function, irrespective of whether ED was present or not. Moreover, the patients were also told that we did not know the effect of the new drug on erectile function. The doctor treating the patients was not aware of the status of the patients' erectile function, because other doctors evaluated the questionnaire. Thus, every effort was made to ensure the best possible blinding, although the study was open and not double-blinded.

The patients stopped taking the β-blockers they had been using and nebivolol therapy was initiated. No other changes were made regarding the management of the patients apart from the β-blocker switch. The dose of nebivolol (5–10 mg/d) was equivalent to (according to the Summaries of Product Characteristics [SPCs] of the two drugs, product monographs and studies conducted using these two drugs) previous β-blocker dosing (atenolol 50–100 mg/d). The mean dose of atenolol was 63 mg/d, while the mean nebivolol dose was 6.45 mg/d. Three months later, patients were asked to complete the same questionnaire.

2.5 Statistical analysis

Data were reported as mean ± SD. Statistical analyses were carried out using paired *t*-test to compare erectile function scores before and after switching from β-

blockers to nebivolol. Associations were considered to be statistically significant if the $P < 0.05$. Data were processed using the STATISTICA (Version 5.0, Statsoft Inc., Tulsa, OK, USA) statistical programme for Windows.

3 Results

3.1 Characteristics of study population

The patients' characteristics before and after nebivolol administration are described in Table 1. There were no statistically significant differences regarding systolic and diastolic blood pressure, heart rate, body weight, cigarette consumption and alcohol intake before and three months after the substitution of β-blockers with nebivolol.

3.2 ED before and after nebivolol

ED of any degree was found in 29 out of 44 patients (65.9%) taking β-blockers. Severe ED was found in 8 of 44 patients (18.2%), moderate ED was found in 13 of 44 patients (29.5%), and mild ED in 8 of 44 patients (18.2%) (Figure 1A).

Overall, the erectile function of 20 out of 29 (69.0%) patients with ED exhibited a statistically significant improvement after a 3-month period of nebivolol administration. Normal erectile function re-appeared in 11 of these patients. Of the eight patients with severe ED, one experienced no change, six experienced an improvement to moderate and one to mild dysfunction. Of the 13 patients with moderate ED, six experienced no change, one experienced an improvement to mild ED, five regained normal function, and one deteriorated to severe ED. Of the eight patients with mild ED, two remained the same class and six improved to normal erectile function. Erectile function remained unaltered in all patients with normal erectile function, with three patients exhibiting a slight deterioration, and six showing a slight improvement, while remaining within the normal limits. At the end of the study period, severe ED was found in only two patients, mode-rate ED in 12 patients, and mild ED in four patients (Figure 1B).

Figure 2 showed the erectile function scores before and after nebivolol administration, and Figure 3 showed the times of sexual intercourse per month before and after nebivolol. Both of the parameters improved signifi- cantly ($P < 0.001$) after the substitution of β-blockers with nebivolol.

Table 1. Characteristics of hypertensive patients before and after nebivolol administration. Data were expressed as mean ± SD (n = 44).

	Before nebivolol	After nebivolol
Age (years)	55.6 ± 7.1	55.9 ± 7.0
Systolic blood pressure (mmHg)	164.2 ± 14.3	165.1 ± 14.7
Diastolic blood pressure (mmHg)	91.3 ± 5.2	90.8 ± 5.1
Heart rate (beats/min)	61 ± 7	62 ± 8
Body weight (kg)	74.9 ± 7.8	75.2 ± 7.6
Current smokers (%)	36	36
Cigarettes per day		
None (%)	66	66
1 – 20 (%)	12	15
> 20 (%)	22	19
Alcohol(a glass of wine) per week		
None (%)	21	24
1 – 7 (%)	46	46
> 7 (%)	33	30

4 Discussion

Our findings indicated that the substitution of β-blockers with nebivolol resulted in a significant improvement in the erectile function of patients with essential hypertension; some patients even regained normal erectile function.

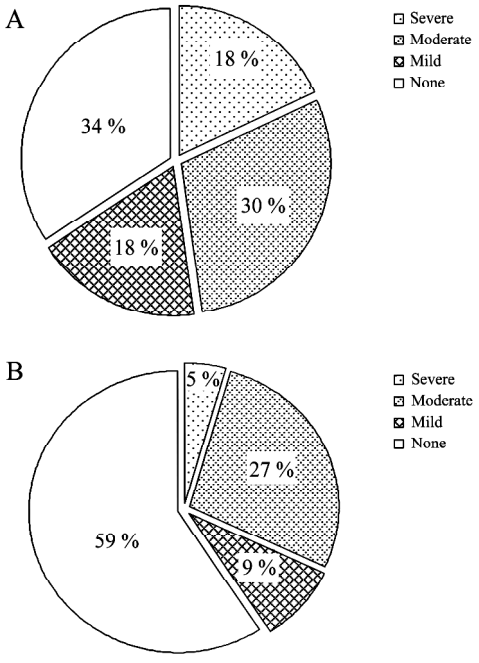

Figure 1. Prevalence of ED (severe, moderate, mild, none) in hypertensive patients before (A) and three months after (B) switching from β-blocker to nebivolol treatment.

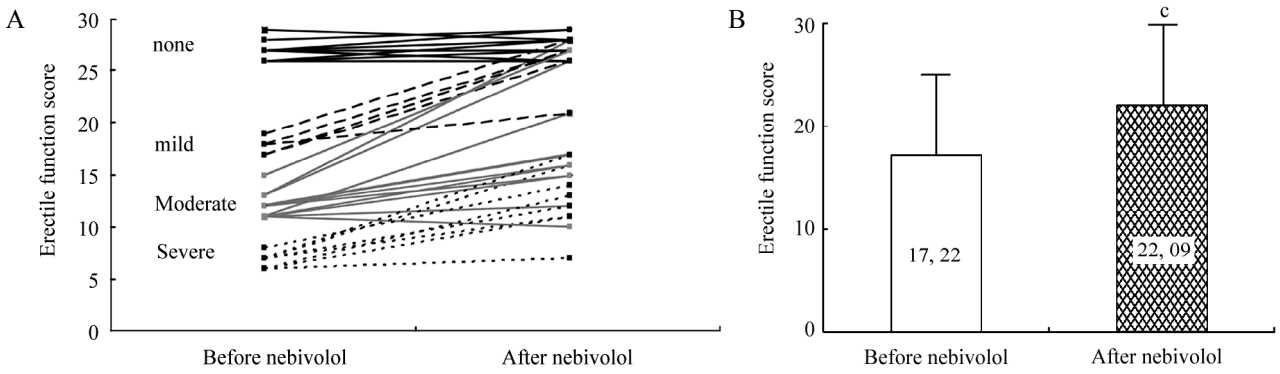

Figure 2. Erectile function score before and after nebivolol administration. (A): Change in each patient's erectile function score due to nebivolol use; The different types of lines represent the four different categories in the prevalence of erectile dysfunction: severe (6-10 points, dotted black line), moderate (11-16 points, continuous grey line), mild (17-25 points, interrupted black line), and none (26-30 points, continuous black line). (B): Patients' mean erectile function score (+SD) before and after nebivolol administration. $^cP < 0.01$, compared with patients before nebivolol administration, $n = 44$.

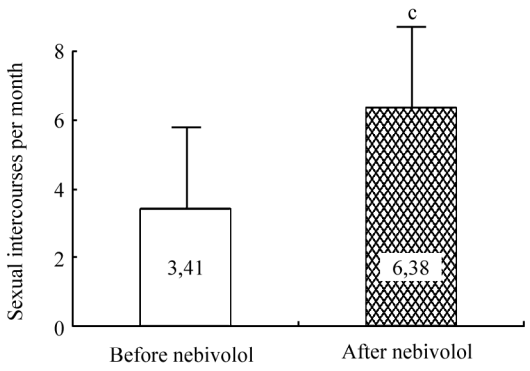

Figure 3. Times patients had sexual intercourse per month before and after nebivolol administration. $^cP < 0.01$, compared with patients before nebivolol administration, $n = 44$.

β-blockers seem to exert a negative effect on male erectile function [2]. Propranolol exerts this effect in doses exceeding 120 mg/d. β_1-selective blockers, such as atenolol, exhibit a milder negative effect (also dose-related) than propranolol [3]. Atenolol at doses of 50–100 mg/d significantly deteriorates the ability of patients to maintain erections [4]. Moreover, spouses of younger patients have noted a significant reduction in their partners' interests and abilities to fulfill their sexual function. In a previous double-blind, parallel study, atenolol seemed to be inferior to celiprolol in terms of its effect on sexual activity [4]. Moreover, atenolol seems to negatively affect erectile function more than other types of antihypertensives, such as lisinopril and valsartan [5, 6]. On the other hand, atenolol at low doses seems to have a less harmful profile. In the Antihypertensive Interventions and Management (TAIM) study, ED was more frequent in patients taking 50 mg of atenolol than that in patients taking a placebo (11% *vs.* 3%), but the difference was not statistically significant [14]. However, atenolol was frequently prescribed at a dose of 100 mg/d, and it appeared that this amount resulted in ED [15].

The exact mechanism of ED caused by β-blockers remained unclarified. The adverse effect of β-blockers on sexual activity may be due to an interference with the adrenergic system's function (which was involved in the integration phase of erection and ejaculation). However, recent evidence suggested that peripheral vasoconstriction induced by β-blockers may not explain the effects on erectile function. Carvedilol (a β-blocker with vasodilatory activity) markedly impaired sexual function compared with valsartan (an angiotensin II receptor blocker with vasodilatory activity) in a previous study [16].

Drug therapy seems to account for ED in approximately one of four cases, and ED is mostly readily reversible when the drug is stopped, or a suitable alternative is given [2]. In a recent study, patients on various antihypertensive medications were switched to losartan (an angiotensin II receptor antagonist) and exhibited a marked increase in sexual satisfaction [17]. In our study, the substitution of β-blockers with nebivolol resulted in a marked improvement in the erectile function of essential hypertensive patients presenting with ED.

Penile erection is a complex, neurovascular event, involving increased arterial inflow and restricted venous outflow, coordinated with corpus cavernosum smooth

muscle relaxation. NO has recently been recognized to play a key role in the physiology of penile erection [18]. Accumulating data suggest that NO derived from the autonomic innervation of the penis, functions locally as a neurotransmitter of nonadrenergic noncholinergic nerves. NO results in increased intracellular accumulation of cGMP leading to corporeal smooth muscle relaxation. Relaxation of the trabecular smooth muscle increases the compliance of the sinusoids, thus enhancing the rapid filling and the expansion of the sinusoidal system. Moreover, the subtunical venular plexuses are compressed between the trabecular and the tunica albuginea resulting in decreased venous outflow. The role of NO in the physiology of male sexual function establishes its importance as the principal modulator of penile erection [18]. Thus, drugs that can induce NO liberation may improve erectile function.

Nebivolol is a recently developed β_1-blocker, devoid of intrinsic sympathomimetic activity, with a high selectivity for β_1-adrenoceptors [7]. Nebivolol is a racemic mixture of *D*- and *L*-enantiomeres. The β_1-blocker property resides in the *D*-enantiomer. Nebivolol has also been shown to induce vasodilatation both in animal and human, and its vasorelaxant activity attributes to the *L*-enantiomer. Several lines of experimental evidence suggested that endothelium-derived NO played a crucial role in nebivolol-induced vasodilatation. Nebivolol produced endothelium-dependent relaxation that was abolished by endothelial denudation or NO inhibitors [8, 19]. Human data confirmed animal observations, because nebivolol increased the forearm blood flow in normotensive and hypertensive subjects, and this action was antagonized by NG-monomethyl-*L*-arginine (*L*-NMMA, an NO inhibitor) [20]. Moreover, nebivolol has been shown to increase the basal and stimulated release of endothelial NO in patients with essential hypertension [21]. Thus, nebivolol may exert favorable actions on erectile function through NO release in hypertensive patients.

In conclusion, previous data indicate that b-blockers significantly affect the erectile function of hypertensive patients. Nebivolol exerts favorable effects on the erectile function of hypertensive patients with ED while taking β-blockers, possibly because of the increased nitric oxide availability. The results of our study suggest that nebivolol has a beneficial effect on the erectile function of hypertensive patients with ED while on β-blocker therapy. However, further larger, prospective, randomized, placebo-controlled, double-blind studies are needed to confirm our results, and to verify the beneficial effect of nebivolol on erectile function.

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