European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Nebivolol protects erectile functions compared to Metoprolol in hypertensive men with atherogenic, venogenic, psychogenic erectile dysfunction: A prospective, randomized, cross-over, clinical trial

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ARTICLE INFO

Keywords:
Hypertension
Nebivolol
Metoprolol
Nitric oxide
Erectile functions

ABSTRACT

Introduction: Both hypertension and β-blocker drugs used for treating hypertension (HT) can cause erectile dysfunction (ED). Nebivolol, unlike other β-blockers, may not cause impotence since it increases the release of Nitric Oxide (NO), which is the main mediator of erection. This study investigated the effect of Nebivolol and Metoprolol on erectile functions in hypertensive men.

Materials and methods: Married men whose blood pressure were >140/90 mmHg were included in the study. All patients were assessed for ED, and the cause of ED was then investigated. Nebivolol or Metoprolol was started for one month in all patients. After one-month drugless period, the β-blockers were switched. Blood pressures, pulses and sexual function tests were evaluated, and plasma NO levels were measured at the end of the treatments and during the drugless period.

Results: There was no difference in antihypertensive efficacy between the two drugs ($p = 0.828$;0.194 for systolic and diastolic BP). Metoprolol caused a significant decrease in IIEF-5 score, whereas Nebivolol did not cause a decrease in IIEF-5 score on patients with psychogenic, arteriogenic, and venous failure related ED (respectively, $p<0.001$,0.004,0.005 for Metoprolol; $p = 0.201$,0.598,0.088 for Nebivolol). In the non-ED group, both drugs decreased the IIEF-5 score, but the decrease for Metoprolol ($p = 0.001$) was more than that for Nebivolol ($p = 0.012$). Plasma NO levels did not change with Metoprolol ($p = 0.268$) but increased with Nebivolol ($p<0.001$). There was a positive correlation between plasma NO values and IIEF-5 score used for the assessment of sexual functions ($r = 0.284$, $p = 0.026$).

Conclusion: Nebivolol may be advantageous in terms of preserving sexual functions because of increasing NO in eligible hypertensive male patients.

1. Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain a sufficient erection to engage in sexual intercourse [1]. Erectile functions are related to the quality of life of individuals. Clinical research studies show that the erectile dysfunction caused by any reason negatively affects the quality of life of both men and their sexual partners [2,3]. ED etiologies include vascular, neurogenic, hormonal, metabolic, psychogenic, and medication side-effects [4].

Hypertension (HT) and some anti-hypertensive drugs can also negatively affect erectile functions. The prevalence of ED among hypertensive patients is approximately double of that in normotensive population [5,6]. Hypertension is associated with many systemic complications, especially vascular complications. The negative effect of hypertension on erectile function is associated with endothelial dysfunction, atherosclerosis, concomitant diabetes, metabolic syndrome, obesity, and vascular pathologies. As the duration of HT increases, the incidence of impotence may also increase. Antihypertensive

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https://doi.org/10.1016/j.ejim.2022.06.013
Received 20 January 2022; Received in revised form 10 April 2022; Accepted 17 June 2022
Available online 23 June 2022

drugs such as thiazide diuretics, beta-blockers, and spirolonactone can exacerbate ED [7]. Especially, evidence supports the detrimental role of β-blockers on erectile function [8]. It has been reported that the prevalence of ED can be up to 71% with the use of beta blockers for at least 6 months. β-blockers can cause ED because of different causes such as inhibition of sympathetic activity, weakness, fatigue, sedation, and sleep disturbance. However, some studies has been reported that Nebivolol, which induces nitric oxide release, can improve erectile functions [9]. Nebivolol is a new generation β-blocker drug that highly selective β1-adrenergic receptor antagonist and induces nitric oxide (NO)-mediated vasodilation by β3 agonism [10].

NO is released from the endothelium as non-adrenergic, non-cholinergic neurotransmitter and is the basic neurotransmitter stimulating penile erection. NO increases the production of cyclic guanosine monophosphate (cGMP), and this provides erection as a result of relaxation at penile cavernous sinus and penile vascular smooth muscles. In other words, NO is the main neurotransmitter of erection and does not depend on the source [11–13]. Nebivolol causes release of NO and activation of endothelial nitric oxide synthase (eNOS) at penis corpus cavernous and penile smooth muscle cells [14].

Considering all of these, Nebivolol, unlike other β-blockers, may have positive effect on erectile functions or at least like other β-blockers may not cause impotence since it increases NO release which is the main mediator of erection.

We designed a prospective, cross-over, randomized clinical trial that investigated the effect of Nebivolol and Metoprolol on erectile functions in hypertensive men.

2. Material and methods

2.1. Patient selection

This was a prospective, randomized, cross-over, clinical study, which was conducted at outpatient Internal Medicine clinic of a university hospital.

The study protocol was approved by the Local Ethical Committee, and written informed consent was obtained from all patients before enrolling in the study.

Married men whose blood pressure were >140/90 mmHg on two separate measurements were included in the study. In addition to this, patients who were diagnosed with new HT, patients previously using Metoprolol or Nebivolol with HT diagnosis and patients using antihypertensive agents apart from β-blocker as a result of their HT diagnosis but having over 140/90 mm Hg blood pressure were also included in this study after the application of an appropriate β-blocker combination.

Since the effect to be monitored was β-blocker treatment effect, all patients used both drugs.

Initially, patients previously having pelvic trauma, pelvic and prostate surgery, neurological disease, anxiety, major depression, hypothalamo-pituitary axis hormone abnormality, thyroid disease, congestive heart failure, peripheral arterial disease, severe liver failure, using possible ED-causing drugs, and still using drugs for ED were not included in this study.

2.2. Sex life assessment and classification of ED

At first, general systemic examination, the structure of genital organs, whether genital organs have anatomic deformity, and secondary sexual characteristics were assessed. Detailed anamnesis and sexual functions assessment questioning were administered to the patients who met the inclusion criteria.

The International Index of Erectile Function (IIEF-5) [15] and the Sexual Encounter Profile (SEP) [16] tests were used to search whether ED existed in patients. Patients who negatively answered any of the SEP questions and/or got an IIEF-5 score under 21 were regarded as with ED.

Then, it was investigated whether ED was organic or psychogenic. With this aim, a papaverine test, having an high ratio in identifying organic and vasculogenic impotence from psychogenic impotence, was conducted in patients with ED [17]. Papaverine hydrochloride (1 scale, 2 ml, 0,06 gr) was injected into the penis root (intracavernosal) with an insulin injector. Tumescence and rigidity response were determined. The test was accepted as positive if an erection occured 5 min after the papaverine injection and couldnot be bent with palpation. Organic and vasculogenic impotence were excluded following a positive result for a papaverine test.

Vascular pathology (arterial/venous failure) distinction was carried out in patients with a negative papaverine test by applying Penile Colored Doppler Ultrasonography (USG). The vein structure was examined in detail after an intracavernous papaverine injection. The aim of distinction of ED etiology was to monitor the effects of drugs on psychogenic and vascular complications caused by ED separately. Assessment of patients is shown in Fig. 1.

2.3. Study design

The study was planned as a clinical, prospective study with a cross-over design.

All patients included in the study were assessed for ED, and the cause of ED was searched using the abovementioned diagnosis methods. Peroral β-blocker was then started for one month in all patients. A randomization table was used to determine the drug that would be first delivered to patients. However, the currently used drug was accepted as beginning drug for the patients who previously used Nebivolol and Metoprolol. The drugs and their doses were determined as follows.

- Nebivolol hydrochloride (Vasoxen tablet) 5 mg one tablet peroral per day,
- Metoprolol succynathe (Beloc zok tablet) 50 mg one tablet peroral per day.

The beta-blocker was discontinued after 1 month, and after a one-month drugless period, the other beta-blocker was started. In patients using combined drugs for HT, only β-blocker drugs were discontinued in the drugless period since the effect to be monitored was the effect of β-blockers. Blood pressures of patients were measured every 15 days in periods both with drug and without drug. In the follow-ups, patients having blood pressure over 160/100 mmHg were excluded from the study, and appropriate antihypertensive drugs combination were started.

In period with or without drug every 4 weeks, blood pressures were measured, SEP and IIEF-5 questions were asked to patients to examine their sexual status, and blood samples were taken for their NO levels. In SEP questionnaire, especially at the beginning and after treatments, the answer to the 3rd question (Yes/No) was assessed. This question was related to the penetration of the erect penis into the vagina and its continuity (Does your erection last long enough for you to have successful intercourse?). The answer to this question has been evaluated in other studies as well [18]. The study design is shown in Fig. 2.

2.4. Exclusion criteria from study

The following criteria were determined as exclusion criteria: presence of decompensated heart failure and 2nd or 3rd degree atrioventricular block, P-R intervalence > 0.24, pulse rate ⟨ 45 per minute, systolic blood pressure < 100 mmHg, presence of severe chronic obstructive lung disease and peripheral arterial disease, and blood pressure ⟩ 160/100 mmHg in drug and drugless period.

2.5. Calculation of nitric oxide levels

Plasma samples were kept in −80 °C deep freezer by placing them in 1 ml plastic cuvettes with the pipette method. Nitric oxide metabolites

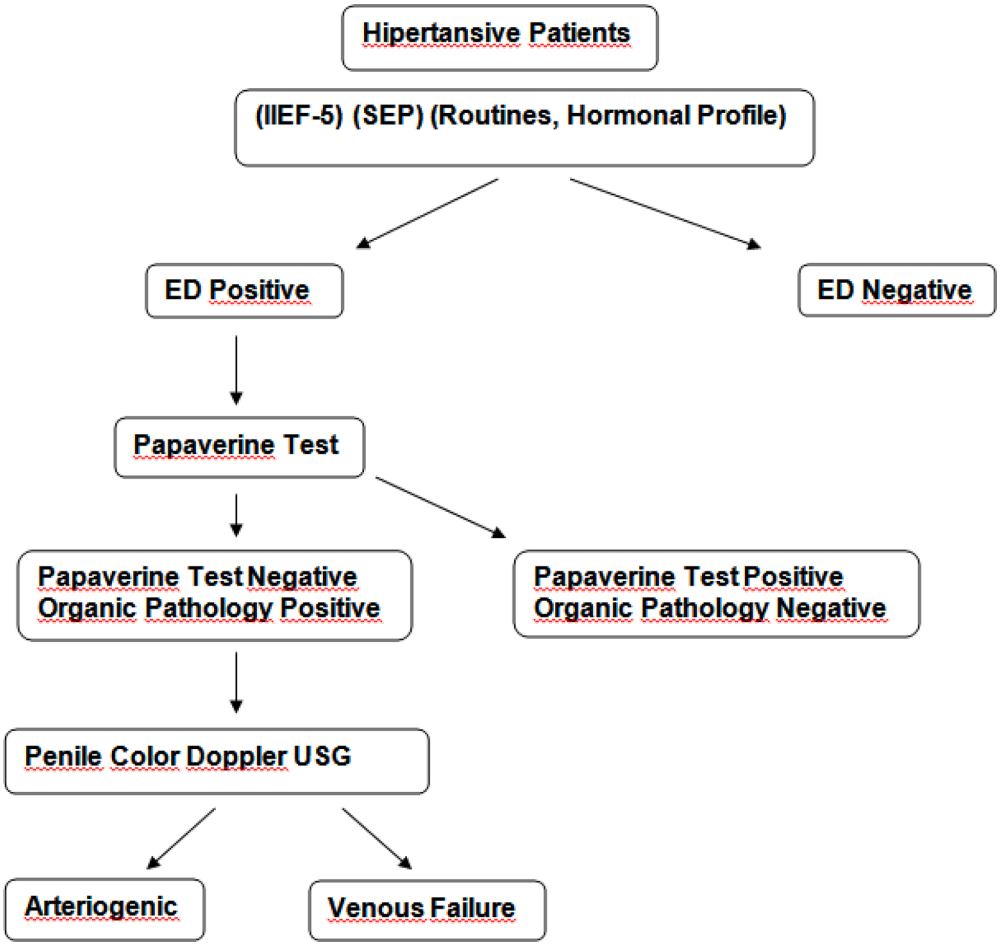

Fig. 1. Assessment of erectile functions in hypertensive patients.

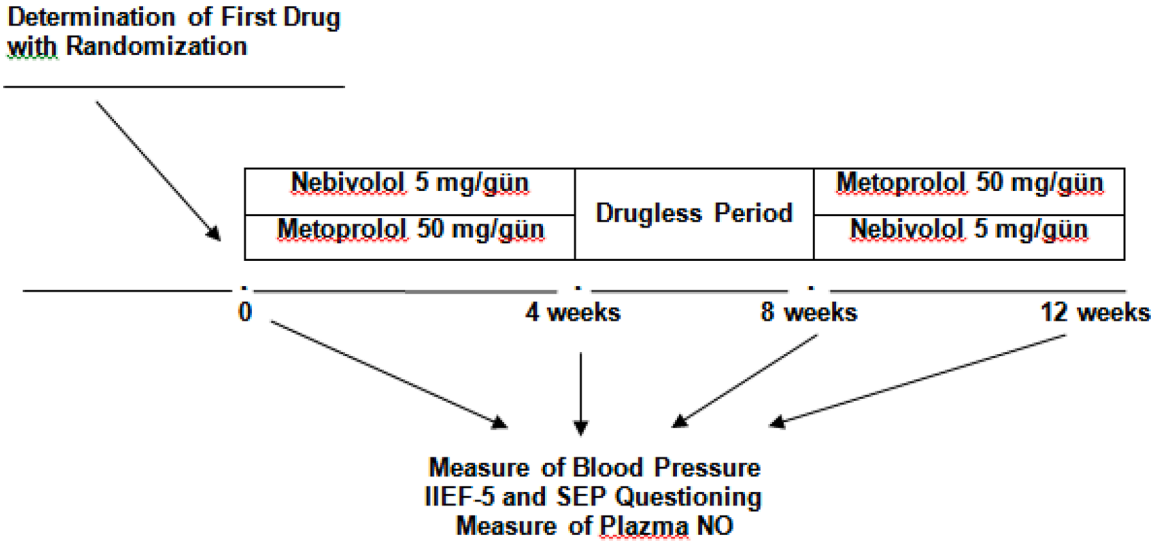

Fig. 2. Study design.

were determined by the photometric method using the Nitrate/Nitrite Colorimetric Assay Kit (Catalog No. 780,001 Cayman Chemical Company, USA). The results were obtained using the ELX 808 IU Ultra Microplate Reader (BIO-TEK INSTRUMENTS, INC., USA). Half logarithmic standard graph was generated by calculating the average absorbance value (X axis as concentration, Y axis as absorbance) for each reference standard. The concentration corresponding to the absorbance value read for each sample was determined by the simple interpolation method.

2.6. Statistical analysis

The obtained data were uploaded to the current Statistical Package for Social Sciences (SPSS) program. Results are expressed as average value ± standard deviation.

Blood pressure, heart rate, and IIEF-5 score changes were evaluated with the paired samples T test in all patients without subgrouping, and with the Wilcoxon signed rank test in the subgroups. The answer to the 3rd question in SEP questionnaire was assessed by the chi-square test. Student's *t*-test was used to compare change ratios for blood pressure and pulse rate for both drugs. Correlations among age, plasma NO and sexual functions were evaluated with Pearson's correlation test.

P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Patients characteristics

A total of 73 hypertensive married male patients were included in the study. Following the start of the study, 12 patients were excluded from the study because their blood pressure regulation could not be maintained in the drugless period and other combined treatments were given to them. Of the remaining 61 patients, 22 had newly diagnosed HT and 39 had previously diagnosed HT. Of 39 patients with previous HT, 12 were using β-blockers and 27 were using other antihypertensive drugs.

The average age of patients was 54.27 ± 7.57 years, and the mean duration of HT diagnosis was 4.68 ± 3.32 years. The mean baseline systolic blood pressure in patients was 150.03 ± 12.70 mmHg, and the diastolic blood pressure was 96.42 ± 6.85 mmHg. The laboratory findings were as follows: mean creatinine was 0.97 ± 0.16 mg/dL, ALT was 30.37 ± 11.80 u/L; total testosterone was 5.36 ± 1.58 ng/mL; thyroid stimulating hormone was 1.39 ± 0.69 IU/L; and prolactine was 7.10 ± 2.68 ng/mL.

In the sexual function evaluation, of the 61 patients who completed the study, 13 had no ED (21.3%), 27 had psychogenic ED (44.2%), 10 had arteriogenic ED (16.3%), and 11 had venous insufficiency-related ED (18%).

3.2. Changes in blood pressure and pulse rate

Systolic and diastolic blood pressures and pulse rates were significantly decreased with both Nebivolol 5 mg/day and Metoprolol 50 mg/day after four weeks of treatment (paired samples *t*-test; $p<0.001$ for all).

The decrease in systolic and diastolic blood pressures and pulse rate was similar for both drugs, and no significant difference was observed between Nebivolol and Metoprolol (Student's *t*-test; $p = 0.82, 0.19, 0.83$, respectively).

Blood pressures and pulse changes after four weeks of Nebivolol and Metoprolol treatments are shown in Table 1.

3.3. Effects on plasma nitric oxide levels

After 4 weeks of treatments, plasma NO levels did not change with Metoprolol while they increased with Nebivolol (Table 2). Plasma NO levels at baseline and at the end of the drugless period were similar.

Table 1
Blood pressures and pulse changes after Nebivolol and Metoprolol treatments.

	Basal andEnd of Drugless Period	Nebivolol 5 mg/day	Metoprolol 50 mg/day
Systolic BP (mmHg)	150.36 ± 12.16	140.16 ± 11.04 *	141.77 ± 10.51 *
Diastolic BP (mmHg)	96.72 ± 6.85	90.44 ± 6.76 *	91.04 ± 8.10 *
Pulse (min.)	74.95 ± 6.19	69.31 ± 5.60 *	69.18 ± 5.42 *

* paired samples *t*-test; $p<0.001$, paired samples *t*-test.

Table 2
Effects of Nebivolol and Metoprolol on NO plasma levels.

	Basal andEnd of drugless Period	After Nebivolol Treatment	After Metoprolol Treatment
Mean Plasma NO (μM)	20.55 ± 6.85	24.29 ± 7.68 ***(p<0.001)***	20.27 ± 6.46 *(p=0.268)*

(paired samples *t*-test).

3.4. Effects on sexual functions

After four weeks of Nebivolol and Metoprolol treatments, IIEF-5 score and SEP questions, which are indicators for sexual and erectile functions, were assessed.

In all 61 patients, IIEF-5 score was 15.52 ± 5.54 at the beginning and drugless period, while it was found to be 14.93 ± 5.04 after Nebivolol treatment and 11.31 ± 4.67 after Metoprolol treatment (paired samples *t*-test; p = 0,026, $p<0.001$, respectively) (Fig. 3). The decrease for Metoprolol was more than that for Nebivolol. IIEF-5 scores at baseline and at the end of the drugless period were similar.

The ratio of positive answer to the 3rd SEP question was decreased significantly after both Nebivolol and Metoprolol treatments.

The ratio of positive answer to the 3rd SEP question was 59% at the beginning and drugless period (36 patients out of 61), while this ratio was 52.4% after Nebivolol treatment (32 patients) and 24.5% after Metoprolol treatment (15 patients) (chi-square test; x^2=39.8, 13.8, respectively). The positive response rate was much more decreased with Metoprolol treatment as compared to that with Nebivolol (Fig. 4).

3.5. Subgroup analysis

When divided into subgroups, Nebivolol and Metoprolol significantly and similarly decreased systolic and diastolic blood pressures in all groups.

Plasma NO levels increased significantly only after Nebivolol treatment and did not change with Metoprolol treatment in all groups.

In non-ED group, IIEF-5 scores decreased with both Nebivolol and Metoprolol treatment, but the decrease in Metoprolol was much more pronounced (Wilcoxon signed ranks test; $p = 0.012$, $p = 0.001$).

In psychogenic, arteriogenic and venogenic ED groups, IIEF-5 scores were not decreased with Nebivolol, but the scores were significantly decreased with Metoprolol.

The changes in blood pressure, plasma NO and IIEF-5 in the non-ED group, psychogenic, arteriogenic and venogenic ED groups at baseline and after treatment are given in Table 3. Changes to IIEF-5 in the subgroups are also presented in Fig. 5.

3.6. Correlation analysis

A negative correlation was observed between age and plasma NO level. The plasma NO level decreased as the age of the patients increased (Pearson's correlation, $r = -0,265$, $p = 0,039$).

There was a positive correlation between plasma NO values and IIEF-5. (Pearson's correlation test, $r = 0,284$, $p = 0,026$). In other words, IIEF-5 score used for the assessment of sexual functions increased as the plasma NO level increased.

A negative correlation was observed between age and IIEF-5 (Pearson's correlation, $r= -0,412$, $p = 0,001$). IIEF-5 score decreased as the age increased.

4. Discussion

Beta blockers are drugs used not only for treating hypertension but also for treating heart failure, arrhythmia, myocardial infarction,

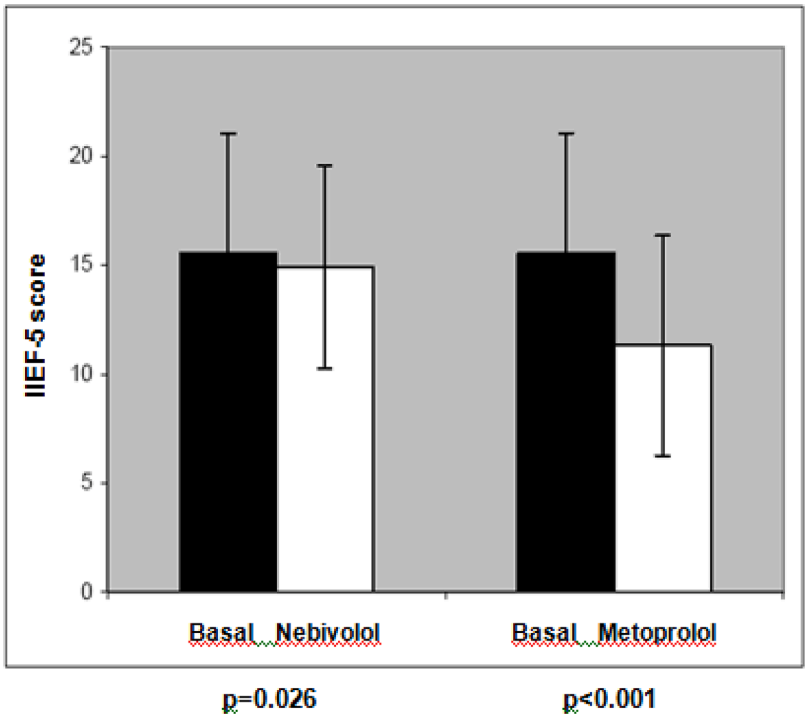

Fig. 3. IIEF-5 score changes post treatment.

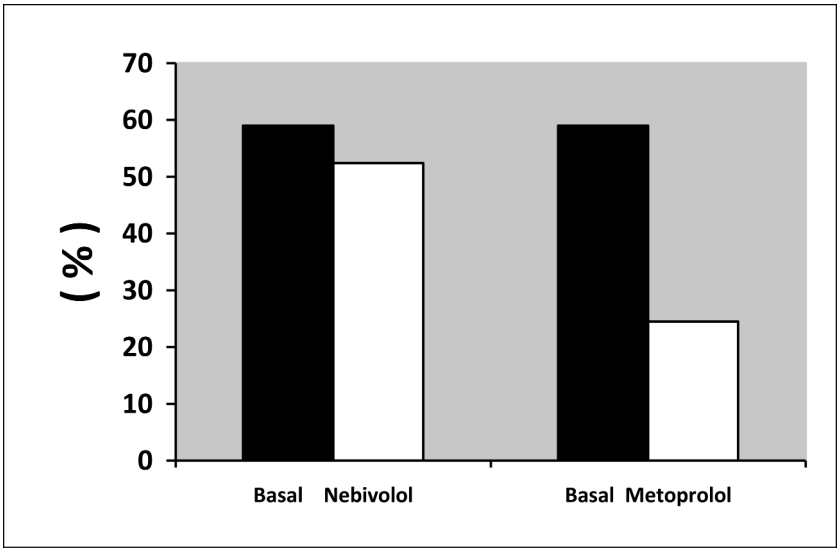

Fig. 4. Does your penis remain erect long enough to successfully complete your sexual intercourse?.

essential tremor, portal hypertension. One of the important side effects is ED, and this side effects may restrict their use [8]. Additionally, HT itself damages vascular relaxation stimulated by endothelia-dependent NO [19], causes microcirculatory changes [20], and damages penile vascular blood flow by preparing the ground for atherosclerotic changes, thus prevents tumescence by inhibiting blood flow to corpus cavernosum and may disrupt erection [21]. Since both HT and β-blocker drugs causes ED, this situation becomes even more important for hypertensive patients.

Because NO is known as the main neurotransmitter of erection [11–13], this study aimed to investigate the effects on erectile functions of Nebivolol, which increases the release of NO at penis corpus cavernous and penile smooth muscle cells [14], and of the widely used Metoprolol.

According to our results, both drugs caused significant and similar reductions in systolic and diastolic blood pressures and pulse rate in all patients and subgroups. There was no difference in antihypertensive efficacy. When IIEF-5 scores as an indicator of sexual functions were assessed, Metoprolol caused a significant decrease at IIEF-5 score in patients with psychogenic, arteriogenic, and venous failure related ED and non-ED. Nebivolol did not cause a significant decrease at IIEF-5 score in patients with psychogenic, arteriogenic and venous failure related ED. In the non-ED group, the IIEF-5 score decreased with Nebivolol. However, the decrease for Metoprolol was more than that for Nebivolol. According to these results, Nebivolol did not cause decrease in sexual functions to the same extent as Metoprolol.

Ratio of positively answering the 3rd question of the SEP questionnaire was decreased with both drugs as compared to the beginning.

Table 3
The changes in blood pressure, plasma NO and IIEF-5 in the subgroups.

Groups	Basal	Nebivolol	Metoprolol
Non-ED (n=13)			
IIEF-5	22.38 ± 1.12	20.07 ± 3.01 ***p=0.012***	16.61 ± 2.59 ***p<0.001***
Plasma NO	22.99 ± 4.84	26.59 ± 6.53 ***p=0.005***	22.74 ± 5.06 p=0.345
Systolic BP	147.92 ± 7.75	137.00 ± 7.64 ***p=0.001***	139.69 ± 6.21 ***p=0.002***
Diastolic BP	94.30 ± 6.93	88.38 ± 6.39 ***p=0.002***	87.53 ± 6.66 ***p=0.001***
Psychogenic ED (n=27)			
IIEF-5	14.62 ± 4.86	14.96 ± 4.52 *P=0.201*	11.18 ± 3.98 ***P<0.001***
Plasma NO	20.69 ± 7.01	25.10 ± 6.99 ***p<0.001***	20.61 ± 6.24 *p=0.719*
Systolic BP	150.25 ± 11.18	140.62 ± 11.93 ***P<0.001***	142.07 ± 12.14 ***p<0.001***
Diastolic BP	96.62 ± 6.88	91.00 ± 6.55 ***p<0.001***	92.48 ± 8.18 ***p<0.001***
Arteriogenic ED (n=10)			
IIEF-5	13.40± 4.14	13.10 ± 3.81 *p=0.598*	8.80 ± 3.96 ***p=0.004***
Plasma NO	17.88± 8.89	20.16 ± 10.21 ***p=0.013***	16.79 ± 7.87 *p=0.41*
Systolic BP	156.90± 19.89	140.70 ± 14.04 ***p=0.005***	144.20 ± 1.39 ***p= 0.008***
Diastolic BP	99.90 ±5.70	92.20 ± 7.28 ***p=0.005***	93.20 ± 10.43 ***p=0.028***
Venous Failure Related ED (n=11)			
IIEF-5	11.54 ± 4.59	10.45± 3.95 *p=0.08*	7.63 ± 3.13 ***p= 0.005***
Plasma NO	19.75 ± 6.24	23.36 ± 7.40 ***p=0.016***	19.68 ± 6.50 *p=0.790*
Systolic BP	147.54 ± 8.61	142.27± 9.73 ***p=0.041***	141.27± 10.20 ***p=0.03***
Diastolic BP	96.90 ± 7.32	89.90 ± 7.48 ***p=0.005***	89.72 ± 6.40 ***p=0.003***

Wilcoxon signed rank test.

However, the positive response rate was much more decreased with Metoprolol compared to Nebivolol. The effects of Nebivolol and Metoprolol treatmentson sexual activity were independent of their antihypertensive effects.

Nebivolol causes less decrease in sexual functions compared to Metoprolol or even no decrease in ED subgroups. This can be explained by the fact that the negative effect caused by beta-blocking is compensated by the increase in NO release observed with Nebivolol, and thus the erectile functions are preserved. The increase in plasma NO achieved with Nebivolol was not observed with Metoprolol. Moreover, a positive correlation was observed between plasma NO levels and IIEF-5 score. Sexual functions increased as plasma NO level increased. Our results support the idea that Nebivolol can improve erectile functions by increasing NO level.

Sivestri et al. suggested that knowing that they are being treated with a beta-blocker drug may lead to ED as a result of anxiety and psychological influence in patients [22]. The authors reported that the knowledge and prejudice about side effects of beta-blockers can produce anxiety, which may cause erectile dysfunction. In our study, which was designed as a cross-over, we announced to our patients that their sexual functions could be assessed in each control and both drugs could have effects on sexual performance. Thus, the dispersion of any psychological influence on our patients using both drugs was equal. Although it was thought that such an effect would be more in the psychogenic ED group, the results in this group were also similar to the other ED groups. Hence, it was concluded that the difference between Nebivolol and Metoprolol on sexual activity was caused by the pharmacology of drugs.

Other studies have supported that Nebivolol has more positive effects on sexual activity. Boydak et al., in their multi-centered, randomized study, found that Nebivolol did not cause a negative effect on sexual activity and commented that Nebivolol improves erectile functions by NO release [23]. In another study comparing Nebivolol and Metoprolol, the authors reported that despite the similar antihypertensive efficacy of Nebivolol and Metoprolol, Nebivolol may offer additional benefits by avoiding erectile dysfunction in male hypertensive patients on long-term beta-adrenoceptor antagonist therapy [24]. In males who have undergone coronary artery bypass surgery, Aldemir M et al. found that Nebivolol exerts protective effects on erectile function against the disruptive effects of cardiopulmonary bypass when compared to Metoprolol [25].

There are important differences between our study and other studies. First, we checked whether the patients were affected with ED, and the cause of ED was then investigated. The drug effects were examined separately in both non-ED and all subgroups of ED. Second, by

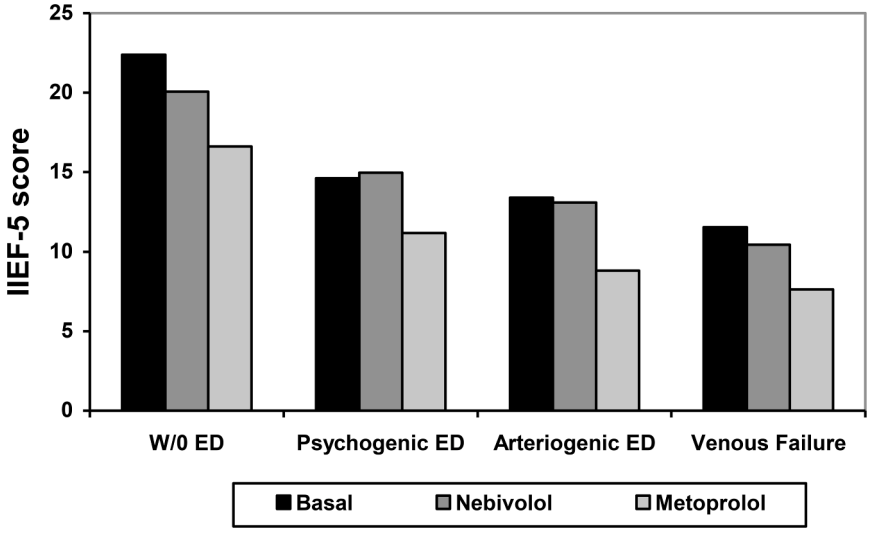

Fig. 5. IIEF-5 changes in the sub-groups.

measuring both sexual functions and plasma NO, the sexual function advantages obtained with Nebivolol were shown to be correlated with increased plasma NO levels.

The number of patients was over 50 (61 patients who completed the study) in our study. We used the paired samples *t*-test in all patients without subgrouping for the changes in blood pressure, heart rate, and IIEF-5 score before and after medication because of dependent variables. In subgroups, we used the Wilcoxon signed rank test. Nevertheless, the sample size was relatively small, and the paired samples *t*-test in this sample may have limitations.

5. Conclusions

Considering all these results, although Nebivolol and Metoprolol have similar antihypertensive effects, Nebivolol may be advantageous in terms of preserving sexual functions because of increasing NO. Nebivolol can be preferred for life quality and adherence to treatment in eligible hypertensive male patients.

CRediT authorship contribution statement

Gokhan Gungor: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing. **Hakki Perk:** Conceptualization, Methodology, Supervision. **Sedat Soyupek:** Conceptualization, Methodology, Formal analysis, Investigation, Resources. **Bahattin Baykal:** Conceptualization, Methodology, Investigation, Resources. **Murat Demir:** Conceptualization, Investigation. **Mehmet Tugrul Sezer:** Conceptualization, Methodology, Formal analysis, Investigation, Supervision, Project administration.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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