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Evaluation of Nebivolol Therapy in Patients with Heart Failure on Exercise Tissue Doppler Echocardiographic Parameters

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Research Article

History

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ABSTRACT

Objective: Heart failure is one of the most important disease which threats population's health. Its prevalance increases both in our country and in the world in years. Nebivolol is a molecule which is proved its efficacy in the treatment of heart failure. The aim of this study was to evaluate the changes in echocardiographic parameters such as tissue doppler imaging and myocardial performance index (MPI) after 6 months of nebivolol treatment in patients with heart failure.

Method: 20 patients with heart failure were enrolled to the study The average age was 59.8 ± 8.4 years (15 men, 5 women). During rest and exercise (cycle ergometer) we recorded conventional and tissue doppler parameters. In the first examination we recorded basal measurements. Then nebivolol treatment was administered. After 6 months nebivolol treatment we measured again same echocardiographic parameters.

Results: The average Ejection fraction (EF) of patients with heart failure in this study was %38.85 ± 6.45 in the first examination. The average EF was increased to %40.95 ± 5.47 in the end of the study ($p<0.05$). After 6 months nebivolol treatment both during rest and exercise we found significant improvements in the tissue doppler parameters and MPI.

Conclusions: Nebivolol is associated with significant improvements in EF in the patients with heart failure. In addition, both during rest and exercise, it's associated with improvements in tissue doppler parameters which can show beneficial effect on the prognosis of this group of patients.

Keywords: β blockers, heart failure, nebivolol, stress echocardiography, tissue doppler imaging.

Kalp Yetmezliği Olan Hastalarda Nebivolol Tedavisinin Egzersiz Doku Doppler Ekokardiyografik Parametrelerle Değerlendirilmesi

ÖZ

Amaç: Kalp yetersizliği, toplum sağlığını tehdit eden en önemli hastalıklardan birisidir. Prevalansı hem ülkemizde hem de dünyada yıllar içerisinde artmaktadır. Nebivolol, etkinliğini kalp yeterszliği tedavisinde kanıtlamış bir moleküldür. Bu çalışmanın amacı, kalp yetmezliği olan hastalarda 6 aylık nebivolol tedavisi sonrası doku doppler görüntüleme ve miyokard performans indeksi (MPI) gibi ekokardiyografik parametrelerdeki değişiklikleri değerlendirmektir.

Yöntem: Kalp yetersizlikli 20 hasta çalışmaya dahil edildi. Ortalama yaş 59.8 ± 8.4 idi (15 erkek, 5 kadın). Dinlenme ve egzersiz (Bisiklet ergometrisi) sırasında konvansiyonel ve doku doppler ekokardiyografik parametrelerin kaydı alındı. İlk muayenede bazal ölçümler kaydedildi. Daha sonra nebivolol tedavisi başlandı. Nebivolol tedavisinden 6 ay sonra aynı ekokardiyografik parametreler tekrar ölçüldü.

Bulgular: İlk muayenede çalışmadaki kalp yetersizlikli hastaların ortalama ejeksiyon fraksiyonu (EF) %38.85 ± 6.45 idi. Ortalama EF, çalışma sonunda %40.95 ± 5.47'e yükseldi ($p<0.05$). 6 aylık nebivolol tedavisi sonrası hem dinlenme, hem de egzersiz sırasında doku doppler parametreleri ve MPI'da anlamlı iyileşmeler saptadık.

Sonuç: Nebivolol, kalp yetersizlikli hastalarda EF'de anlamlı iyileşmelerle ilişkilidir. Ek olarak, hem dinlenim hem de egzersiz sırasında, bu hasta grubunda prognoz üzerine faydalı etkisi olabilecegini gösteren doku doppler parametrelerinde iyileşmeler ile ilişkilidir.

Süreç

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Anahtar sözcükler: β bloker, doku doppler görüntüleme, kalp yetersizliği, nebivolol, stres ekokardiyografi.

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Introduction

Heart failure (HF) is a syndrome associated with the inability of the heart to pump enough blood into the systemic circulation to meet the body's metabolic needs. This syndrome continues to be a health problem with a poor prognosis, which is common all over the world and its frequency is increasing day by day. Despite advances in its treatment, its mortality is still high. The main physiopathological event in heart failure is the activation of the neurohormonal system. Due to the low cardiac output and low arterial perfusion pressure due to cardiac dysfunction, the continuous activation of the neurohormonal system, which is initially a compensatory mechanism, leads to serious and undesirable effects in the long term. Today, it is known that the sympathetic nervous system (CNS) plays a very important role in direct toxic effects on the myocardium, myocardial remodeling and life-threatening arrhythmias in HF progression. It is known that β-blocker therapy reduces mortality in patients with HF by decreasing CNS activation and positively affects long-term outcomes.

Evaluation of cardiac function with tissue doppler parameters is a method that has been increasingly used in recent years and its effectiveness has been demonstrated by many studies. Stress echocardiography is a frequently used method in cardiology practice, especially in the investigation of ischemia and viability, but it has not been used to evaluate the response to treatment with tissue doppler parameters in HF patients. In our study, we aimed to investigate the changes in tissue doppler parameters with stress echocardiography (Bicycle ergometry) before and after β-blocker therapy in patients with HF.

Material and Methods

Twenty patients who applied to the Cardiology Polyclinic of Mustafa Kemal University Medical Faculty Hospital between 24.04.2008 and 15.12.2009 and were diagnosed HF were included in the study. The patients included in the study were selected from patients who had previously been treated with HF, but did not use β-blockers. Echocardiographic parameters of the patients before and six months after treatment were compared. Anamnesis of the patients was taken and physical examinations were made. Patients who did not meet the exclusion criteria in the electrocardiography (ECG) and exercise test were included in the study, and conventional, tissue doppler recordings at rest and during stress (cycling ergometry) were taken. The patients were followed up with nebivolol treatment monthly and evaluated for drug side effects, blood pressure monitoring and drug use. Echocardiographic parameters of the patients during rest and stress were re-evaluated and recorded at the end of the sixth month. Patients with hypertrophic cardiomyopathy (HCMP), atrial fibrillation, left ventricular hypertrophy (LVH) due to aortic stenosis, thyroid dysfunction, orthopedic problems that effects echocardiographic images, and patients with pacemakers were not included in the evaluation. In the first evaluation, normal echocardiographic parameters of the patients were taken, and tissue doppler parameters were evaluated from four cardiac walls (anterior, inferior, lateral, septal) during rest and after cycling ergometry. Control tissue doppler parameters were taken again from patients who completed the study 6 months later. During a 6-month period, blood pressure and heart rate were monitored and the dose of nebivolol was tried to be increased up to a maximum of 10 mg. Written consent approved by the ethics committee of our hospital. All of the patients were informed about the study.

Echocardiographic Methods: Echocardiographic examinations 2-dimensional, M-mode, tissue doppler echocardiographic parameters were obtained using a 2.5 MHz, Vivid 7 Digital ultrasound device (Horten, Norway, GE). Echocardiographic evaluation was performed from parasternal and apical views with the patients lying in the left lateral position, patients with technical inadequacy were not included in the study, and measurements and recordings were made at the end of normal inspiration and expiration. Parasternal long and short axis, apical four-chamber, apical five-chamber and apical two-chamber views were used to evaluate LV and valve functions during stress (cycling ergometry). The measurement of echocardiographic parameters was recorded at rest and during cycling exercise, and the exercise test was divided into two-minute intervals. ECG and blood pressure monitoring were performed and blood pressure was measured at rest and at the end of the test, and echocardiographic data were correlated until the subjects' heart rate reached 100/min in submaximal exercise. By using longitudinal tissue Doppler from the septal, lateral, anterior and inferior myocardium, systolic (Sm) and diastolic function (Em and Am) parameters, isovolumetric contraction time (IVCT), contraction time (CT), isovolumetric relaxation time (IVRT) were determined. MPI was calculated for the evaluation of global ventricular function using parameters obtained from doppler. As a result of our research, we could not find any study evaluating the effects of nebivolol treatment on echocardiographic and tissue doppler longitudinal systolic and diastolic function and MPI parameters during supine cycling exercise in patients with heart failure. Therefore, in our study, we planned to determine the values of these parameters after 6 months of nebivolol treatment and to compare them with the values before the treatment.

Statistical analyzes of the obtained data were performed with the Statistical Package for Social Sciences (SPSS) for Windows 16.0 program. Paired-Samples T test was used to compare the pre-treatment and post-treatment values of the patients. Descriptive statistical results of study data were expressed as mean ± standard deviation. In the results obtained from statistical tests, a p value below 0.05 (5%) with a 95% confidence interval was considered significant.

Results

We included 20 patients (15 males, 5 females) with a mean age of 59.8 ± 8.4 years in our study. The mean EF of the patients at the first examination was %38.85 ± 6.45. After 6 months of nebivolol treatment, mean EF values increased to %40.95 ± 5.47. During the study, 18 patients (90%) received 10 mg nebivolol treatment, while 2 (10%) patients received 5 mg nebivolol treatment. The dose was not increased because the patients who received 5 mg nebivolol treatment had blood pressure values of 90/60 and complained of fatigue.

The mean S wave velocity taken from the lateral wall before the treatment was 4.95 ± 1.19 cm/sec, the mean E wave velocity was 6.3 ± 2.05 cm/sec, the mean A wave velocity was 5.60 ± 1.75 cm/sec, the isovolumetric contraction time was 84.60 ± 14.86 ms, the contraction time was 277.80 ± 44.62 ms, isovolumetric relaxation time 83.35 ± 20.46 ms, and mean MPI value was 83.65 ± 20.43.

After nebivolol treatment, there was a significant increase in the S and E waves taken from the lateral wall during exercise, while no significant decrease was found in the A wave. While a significant decrease was found in IVCT and IVRT values, a significant increase was found in CT values (p<0.05). MPI values decreased significantly (p<0.05). (Table 1)

The mean S wave velocity taken from the septal wall before the treatment was 4.95 ± 0.94 cm/sec, the mean E wave velocity was 5.90 ± 1.74 cm/sec, the mean A wave velocity was 6.55 ± 2.06 cm/sec, the isovolumetric contraction time was 80.0 ± 12.14 ms, the contraction time was 259.60 ms. It was ± 34.30 ms, isovolumetric relaxation time 81.15 ± 18.42 ms, and mean MPI value was 81.46 ± 18.42.

While there was a significant increase in the S and E waves taken from the septal wall during exercise after nebivolol treatment (p<0.05), no statistically significant change was found in the A wave. While a significant decrease was found in IVCT and IVRT values, a significant increase was found in CT values (p<0.05). MPI values decreased significantly (p<0.05). (Table 2)

Anterior Wall Tissue Doppler The mean S wave velocity taken from the anterior wall before the treatment was 4.90 ± 1.02 cm/sec, the mean E wave velocity was 6.70 ± 3.04 cm/sec, the mean A wave velocity was 5.70 ± 1.49 cm/sec, the isovolumetric contraction time was 80.90 ± 14.26 ms, the contraction time was 265.50 ms on average. It was ± 29.30 ms, isovolumetric relaxation time 81.35 ± 10.94 ms, and mean MPI value was 81.65 ± 10.96

A significant increase was detected in the S, E, and A waves taken from the anterior wall after nebivolol treatment. While a significant decrease was found in IVCT and IVRT values, a significant increase was found in CT values (p<0.05). MPI values decreased significantly (p<0.05).

After nebivolol treatment, there was a significant increase in the S and E waves taken from the anterior wall during exercise (p<0.05), but no significant change was found in the A wave. While a significant decrease was found in IVCT and IVRT values, a significant increase was found in CT values (p<0.05). MPI values decreased significantly (p<0.05).(Table 3)

Inferior Wall Tissue Doppler The mean S wave velocity taken from the inferior wall before the treatment is 5.45 ± 0.88 cm/sec, the mean E wave velocity is 6.45 ± 2.25 cm/sec, the mean A wave velocity is 7.10 ± 2.10 cm/sec, the isovolumetric contraction time is 80.55 ± 14.61 ms, the contraction time is 281.90 ms, mean. It was ± 26.14 ms, isovolumetric relaxation time 84.10 ± 18.16 ms, and mean MPI value was 84.38 ± 18.15.

Table 1. Tissue Doppler parameters taken from the lateral wall during exercise

Dinlenme	0.Ay	6.Ay	P değeri
S(cm/sec)	5.35 ± 1.30	6.10 ± 0.96	p<0.05
E(cm/sec)	6.90 ± 2.02	7.75 ± 2.12	p<0.05
A(cm/sec)	6.00 ± 1.58	6.0 ± 1.07	p>0.05*
IVCT(ms)	77.10 ± 13.59	70.60 ± 10.10	p<0.05
CT(ms)	267.55 ± 38.20	284.55 ± 36.64	p<0.05
IVRT(ms)	72.90 ± 14.28	64.95 ± 11.47	p<0.05
MPI	73.19 ± 14.27	69.20 ± 11.84	p<0.05

Systolic (S) and diastolic function (E and A) parameters, isovolumetric contraction time (IVCT), contraction time (CT), isovolumetric relaxation time (IVRT), Myocardial perfusion index (MPI)

Table 2. Tissue Doppler parameters taken from the septal wall during exercise

Dinlenme	0.Ay	6.Ay	P değeri
S(cm/sec)	5.35 ± 1.03	5.90 ± 0.91	p<0.05
E(cm/sec)	5.80 ± 1.82	6.80 ± 1.47	p<0.05
A(cm/sec)	6.45 ± 2.28	6.55 ± 1.63	p>0.05*
IVKZ(ms)	76.40 ± 10.17	69.00 ± 10.29	p<0.05
KZ(ms)	255.30 ± 35.87	271.30 ± 34.09	p<0.05
IVGZ(ms)	73.50 ± 12.76	68.70 ± 9.31	p<0.05
MPI	73.80 ± 12.76	68.97 ± 9.29	p<0.05

Systolic (S) and diastolic function (E and A) parameters, isovolumetric contraction time (IVCT), contraction time (CT), isovolumetric relaxation time (IVRT), Myocardial perfusion index (MPI)

Table 3. Tissue Doppler parameters taken from the anterior wall during exercise

Dinlenme	0.Ay	6.Ay	P değeri
S(cm/sec)	5.35 ± 1.03	5.90 ± 0.85	p<0.05
E(cm/sec)	6.40 ± 2.34	7.75 ± 2.35	p<0.05
A(cm/sec)	6.15 ± 1.59	6.45 ± 1.50	p>0.05*
IVKZ(ms)	83.30 ± 19.17	72.05 ± 8.23	p<0.05
KZ(ms)	258.20 ± 33.93	271.50 ± 33.42	p<0.05
IVGZ(ms)	79.60 ± 17.42	71.55 ± 8.91	p<0.05
MPI	79.91 ± 17.42	71.82 ± 8.89	p<0.05

Systolic (S) and diastolic function (E and A) parameters, isovolumic contraction time (IVCT), contraction time (CT), isovolumic relaxation time (IVRT), Myocardial perfusion index (MPI)

Table 4. Tissue Doppler parameters taken from the inferior wall during exercise

Dinlenme	0.Ay	6.Ay	P değeri
S(cm/sec)	5.80 ± 0.69	6.25 ± 0.63	p<0.05
E(cm/sec)	6.40 ± 1.39	7.50 ± 1.60	p<0.05
A(cm/sec)	7.50 ± 1.87	6.90 ± 1.88	p>0.05*
IVKZ(ms)	76.95 ± 12.46	71.00 ± 9.23	p<0.05
KZ(ms)	265.55 ± 31.52	277.50 ± 28.58	p<0.05
IVGZ(ms)	74.70 ± 14.44	67.30 ± 12.07	p<0.05
MPI	74.99 ± 14.43	71.86 ± 9.99	p<0.05

Systolic (S) and diastolic function (E and A) parameters, isovolumic contraction time (IVCT), contraction time (CT), isovolumic relaxation time (IVRT), Myocardial perfusion index (MPI)

After nebivolol treatment, there was a significant increase in S and E waves taken from the inferior wall during exercise (p<0.05). There was no statistically significant change in A waves (p>0.05). While a significant decrease was found in IVCT and IVRT values, a significant increase was found in CT values (p<0.05). MPI values decreased significantly (p<0.05). (Table 4)

Discussion

β-blockers, previously contraindicated in the treatment of heart failure, are now a cornerstone of heart failure therapy . This information has been widely accepted and used in different studies with different β-blockers. In the SENIORS study (Study of the Effects of Nebivolol Intervention on Outcomes and Hospitalisation in Seniors with heart failure), the effects of the selective β1 blocker nebivolol, which also has vasodilator properties, were evaluated in elderly patients with heart failure. In this study, it has been shown that nebivolol reduces all-cause mortality and cardiovascular hospitalization, regardless of the initial ejection fraction. The SENIORS study was an international, double-blind, placebo-controlled study. 2128 heart failure patients were assigned to the nebivolol or placebo group. Patients included in the study were over 70 years of age, with a diagnosis of heart failure for at least 12 months, and with EF ≤35%. The initial dose of nebivolol was 1.25 mg/day as a single dose, followed by 2.5-5 at 1-2 week intervals and the target dose 10 mg, or the maximum tolerated dose in 16 weeks. There was a 14% reduction in all-cause death or cardiovascular hospitalization, a 16% reduction in cardiovascular death or hospitalization, and a 38% reduction in the risk of sudden death. In previous studies with β-blockers in heart failure, the mean patient age was 63 years, compared to 76 years in the SENIORS study. This is closer to the mean age of patients with heart failure treated in the real population. In addition, while the mean EF of the patients included in the SENIORS study was 36%, this value was 25% in the other heart failure patient studies. In this respect, the SENIORS study patient group is closer to the average population values of the patients we treated.

In this study, the mean EF of the patients we recruited was %38.85 ± 6.45. After 6 months of nebivolol treatment, the mean EF values increased to %40.95 ± 5.47 (p<0.05). The EF values we found were consistent with the results in the SENIORS study. There are studies showing the beneficial effects of β-blockers in improving LV function in systolic heart failure patients. In addition to the beneficial effects of nebivolol similar to other β-blockers, in addition to the increased beneficial effects, nebivolol has vasodilator activity associated with increased nitric oxide release. In this study, nebivolol was found to be associated with positive improvements in myocardial tissue doppler parameters and EF, similar to previous β-blocker studies in heart failure patients.

The prognostic value of tissue doppler imaging has been demonstrated in various studies and in various cardiac diseases. Tissue doppler parameters are important in the evaluation of cardiac functions in these patients, since it has been shown that Sm is well associated with EF and the diagnostic power of these parameters in patients with heart failure and their relationship with mortality. In recent studies, the use of Sm velocity in the early diagnosis and follow-up of heart failure has been found to be superior to conventional echocardiographic evaluations. In patients with heart failure, since its relationship with prognosis and mortality has been shown in many studies, systolic functions are evaluated with EF and diastolic functions with mitral flow velocities in daily practice. However, there are many

difficulties in obtaining and interpreting these parameters, especially in patients with impaired ventricular functions. Evaluation of EF is affected by ventricular geometry and image quality. In addition, since measuring EF from two and four chambers as standard in practical applications is a time-consuming process, EF is not calculated and is often estimated based on the experience of the echocardiographer. As a result, the variability within and between observers varies considerably Mitral flow velocities are affected by load increases, left atrial pressure and ventricular relaxation. Since these disadvantages are prominent in patients with heart failure, difficulties are often encountered in the evaluation of cardiac functions with these parameters in daily practice in these patients.

Tissue Doppler parameters, which are easily obtained and relatively less affected by image quality, have been successfully used in the evaluation of ventricular functions in different cardiac diseases . In recent years, it has been shown that Sm is well associated with EF, Em and Am are relatively less affected by load increases and left atrial pressure, and most importantly, the diagnostic power of these parameters and their relationship with mortality in patients with HF have been shown to improve cardiac function in HF patients. has increased the importance of tissue doppler parameters in the evaluation. The findings obtained in our study suggest that myocardial velocities and especially Sm can be used in clinical follow-up as well as in the evaluation of cardiac functions in HF patients, considering the advantages of tissue doppler parameters. Interobserver and intraobserver variability of Sm measurements is between 4-8% . The advantages of tissue doppler echocardiography in clinical use can provide a better evaluation opportunity, especially in cases with insufficient images due to echogenicity.

More quantitative values can be obtained than conventional methods. Ventricular functions can be evaluated both globally and regionally. It shows a correlation (Sm) with functional capacity at least as much as, perhaps better than, conventional parameters. In this study, when tissue doppler Sm velocities were compared at 0 and 6 months in the state of rest and exercise, a significant increase was found in line with the increase of EF. This finding was correlated with the results recorded after the use of β-blockers in patients with HF. Early diastole mitral annular velocity provides important predictive information in terms of cardiac mortality in individuals with heart disease. While survival is better especially in patients with Em velocity >5 cm/s, the prognosis is worse in patients with <3 cm/s. In this study, Em velocity at rest was associated with significant increase values when compared to control values after 6 months. Our findings are associated with increased prognosis expectancy with the use of nebivolol, which overlaps with previous studies when considered together with increases in EF. When the pre- and post-exercise values were compared.

Em velocities from the lateral, septal, inferior and anterior walls were associated with significant increases when compared to 0 and 6-month values. While Am values alone did not show a statistically significant change in measurements taken from the septal wall during exercise, the Am wave obtained from the anterior wall during exercise increased contrary to expectations. This may be because this parameter is affected by the preload. Another reason may be the inadequacy of the number of patients to reveal statistical significance.

MPI; It is calculated by dividing the sum of IVCT and IVRT by CT. In studies conducted, this index dp/dt evaluated with cardiac catheterization showed a close relationship with the tau constant. This index has been found to be associated with the severity of symptoms in patients with heart failure. MPI is an important method in regional systolic and diastolic evaluation. Many studies have shown the diagnostic and prognostic reliability of MPI in different clinical situations. Transmitral parameters are generally load dependent and vary with sample volume, rhythm, and heart rate. Whereas, MPI is a reliable parameter in providing information about systolic and diastolic functions without being affected by LV geometry, heart rate or blood pressure. But preload and afterload can affect time intervals. In this study, the use of nebivolol was found to be associated with a significant decrease in MPI values, similar to previous studies of β-blockers in patients with heart failure. This is associated with an increase in myocardial contractility and an improvement in the prognosis of patients. After 6 months of treatment, a significant improvement was found in MPI values taken both at rest and during exercise compared to baseline values.

Significant decreases were found in the IVRT and IVCT values of the patients, both at rest and during exercise, when the values before the use of nebivolol were compared with the ones after. Conversely, Deceleration time(DT) durations increased statistically significantly. This was found to be associated with the improvement of the relaxation-contraction relationship, which was impaired in HF patients, with nebivolol. The improvement in all tissue doppler parameters taken from the lateral, septal, anterior, and inferior wall indicates that the use of nebivolol in patients with heart failure is associated with a global rather than a regional improvement. Stress echocardiography is an increasingly popular method in cardiology practice. It is especially used to detect ischemia in stable coronary artery disease, to distinguish high-risk patients who require invasive intervention, to identify patients who will benefit from revascularization by detecting viable tissue and ischemia in the region where myocardial infarction developed after MI, and to evaluate patients with cardiac risk who will undergo noncardiac surgery. The test can be administered with dobutamine or exercise. Both can be preferred according to the clinical condition of the patient. Dobutamine stress echocardiography can be performed on patients who cannot exercise for any reason. If the patient can do it, exercise echocardiography should be preferred to avoid drug side effects, if possible. In our literature review, we could not find any study in which stress echocardiography

and tissue Doppler examination were performed in patients with heart failure after β-blocker therapy. We chose our patient preference especially among patients who could complete the exertion test.

Conclusion

In conclusion, nebivolol is associated with improved cardiac performance and systolic-diastolic functions in patients with heart failure. In our study; similar to previous studies, we found improvements in tissue doppler parameters after nebivolol treatment. These effects are associated with an increase in the EF, in long-term regular use, and significant clinical improvement such as a decrease in the symptoms of patients with HF and an increase in exercise capacity. Evaluation of tissue doppler parameters with both resting and stress echocardiography provides additional and early information compared to conventional echocardiographic evaluation in terms of improvement in cardiac functions and patient prognosis.

Conflict of interest

There is not a conflict of interest

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