The effect of carvedilol therapy on coronary flow reserve in patients with idiopathic dilated cardiomyopathy

İdiyopatik dilate kardiyomiyopatili hastalarda karvedilol tedavisinin koroner akım rezervine etkisi

Mustafa Çalışkan, M.D., Özgür Çiftçi, M.D., Hakan Güllü, M.D., Haldun Müderrisoğlu, M.D.[1]

Department of Cardiology, Medicine Faculty of Başkent University, Konya and [1]Ankara

Objectives: We evaluated the effect of carvedilol, a nonselective beta-blocker with vasodilating action, on coronary flow reserve (CFR) in patients with idiopathic dilated cardiomyopathy (IDC).

Study design: Twenty-four patients (17 males, 7 females; mean age 57±11 years) with IDC were consecutively enrolled. After obtaining clinical and hemodynamic stabilization, transthoracic echocardiography was performed including CFR measurement and carvedilol therapy was initiated with 3.125 mg twice daily and titrated to a target dose of 25 mg twice daily. Twenty-three patients reached the target dose in a mean of 11±3 weeks. The mean duration of carvedilol therapy was 19±3 weeks, after which echocardiography was repeated and findings were recorded at baseline and after dipyridamole infusion. Clinical and echocardiographic findings were compared with those of 23 age- and sex-matched patients (13 males, 10 females; mean age 55±4 years) with atypical chest pain.

Results: Compared to the control group, left ventricular end-diastolic and end-systolic volumes, left ventricular mass index, and isovolumic relaxation time were significantly higher and ejection fraction was significantly lower in the IDC group. Before carvedilol therapy, patients with IDC had a significantly higher baseline diastolic peak flow velocity (DPFV) and a significantly lower CFR; however, hyperemic DPFV was similar in the two groups. After carvedilol therapy, left ventricular end-systolic volume decreased significantly and ejection fraction increased significantly. Decreases in baseline DPFV and hyperemic DPFV were slight and there was no improvement in CFR. Even after elimination of the confounding effect of rate-pressure product using analysis of covariance, pre- and post-treatment CFR remained similar.

Conclusion: Carvedilol therapy does not improve coronary microvascular functions in patients with IDC.

Key words: Blood flow velocity/drug effects; carbazoles/therapeutic use; cardiomyopathy, dilated/drug therapy; coronary circulation/drug effects; echocardiography.

Amaç: İdiyopatik dilate kardiyomiyopatili (İDK) hastalarda, vazodilatatör etkili, selektif olmayan bir beta-bloker olan karvedilolun koroner akım rezervine (KAR) etkisi araştırıldı.

Çalışma planı: Çalışmada İDK'li ardışık 24 hasta (17 erkek, 7 kadın; ort. yaş 57±11) değerlendirildi. Klinik ve hemodinamik stabilizasyonun sağlanmasının ardından, her hastada transtorasik ekokardiyografi ve KAR ölçümleri yapıldı ve karvedilol tedavisine (günde 2 kez 3.125 mg) başlanarak hedef doz olan günde iki kez 25 mg'ye çıkıldı. Yirmi üç hastada ortalama 11±3 hafta içinde hedef doza ulaşıldı. Ortalama 19±3 hafta uygulanan karvedilol tedavisinden sonra ekokardiyografi tekrarlandı ve başlangıçtaki ve dipiridamol infüzyonu sonrasındaki bulgular kaydedildi. Elde edilen klinik ve ekokardiyografik bulgular, atipik göğüs ağrısı nedeniyle incelenen 23 hastadan (13 erkek, 10 kadın; ort. yaş 55±4) oluşan kontrol grubuyla karşılaştırıldı.

Bulgular: Kontrol grubuyla karşılaştırıldığında, İDK'li grupta sol ventrikül diyastol sonu ve sistol sonu hacimleri, sol ventrikül kütle indeksi ve izovolümik gevşeme zamanı anlamlı derecede yüksek, ejeksiyon fraksiyonu anlamlı derecede düşük bulundu. Karvedilol tedavisinden önce, İDK'li grupta başlangıç diyastolik zirve akım hızı (DZAH) anlamlı derecede yüksek, KAR anlamlı derecede düşük idi; hiperemik DZAH ise iki grupta benzerdi. Karvedilol tedavisinden sonra sol ventrikül sistol sonu volümü anlamlı düşüş, ejeksiyon fraksiyonu anlamlı artış gösterdi. Başlangıç ve hiperemik DZAH değerlerinde görülen hafif düşüş anlamlı değildi; KAR'da ise düzelme görülmedi. Sonucu etkilemesi olası hız-basınç ürünü değerleri kovaryans analiziyle etkisizleştirilmesine rağmen, tedavi öncesi ve sonrası KAR değerlerinde değişme olmadı.

Sonuç: Karvedilol tedavisinin İDK'li hastalarda koroner mikrovasküler fonksiyonları düzeltici etkisi yoktur.

Anahtar sözcükler: Kan akım hızı/ilaç etkisi; karbazol/terapötik kullanım; kardiyomiyopati, dilate/ilaç tedavisi; koroner dolaşım/ilaç etkisi; ekokardiyografi.

Received: December 28, 2007 *Accepted:* June 10, 2006

Correspondence: Dr. Özgür Çiftçi. Başkent Üniversitesi Tıp Fakültesi, Konya Araştırma ve Uygulama Merkezi, 42080 Selçuklu, Konya, Turkey. Tel: +90 332 - 257 06 06 / 2111 Fax: +90 332 - 257 06 37 e-mail: ozgurciftci@baskent-kon.edu.tr

Attenuated coronary flow reserve (CFR) has been reported in patients with idiopathic dilated cardiomyopathy (IDC).[1] Structural changes in coronary microvasculature[2] and changes in coronary vasoreactivity[3] have been implicated in the development of myocardial ischemia and possibly progressive left ventricular dysfunction in patients with IDC.[3] Carvedilol is a nonselective beta-blocker with vasodilating and some adrenoceptor-blocking actions.[4] Antioxidant and free radical scavenging effects of carvedilol were previously reported.[4,5] Additionally, carvedilol decreases oxidative stress in patients with heart failure.[6,7] These favorable effects of carvedilol are possibly associated with increased nitric oxide (NO) bioavailability.[6]

Pharmacological stress transthoracic Doppler echocardiography is currently a useful and highly reproducible tool in evaluating CFR, whose feasibility has been validated in several studies.[8,9]

Based on our hypothesis that carvedilol may reverse coronary microvascular dysfunction and, therefore, improve CFR, we designed a prospective, single-blind study to evaluate the effect of carvedilol on CFR in patients with IDC.

PATIENTS AND METHODS

Thirty patients with IDC were consecutively enrolled. Inclusion criteria were age 18 to 75 years, left ventricular ejection fraction of less than 45%, and the presence of angiographically normal coronary arteries. Exclusion criteria were the following: any identifiable reason that might cause dilated cardiomyopathy, the presence of diabetes mellitus, hypertension, any valvular disease more severe than mild-to-moderate degree, cardiac rhythm other than sinus, angiographically proven coronary artery disease including wall irregularities, serum creatinine level of >1.8 mg/dl, smoking, alcohol usage, and being on beta-blocker therapy for any reason.

During the study period, one patient died of sudden death without presenting to the hospital, atrial fibrillation developed in two patients, and three patients refused to continue participating in the study. Therefore, with the exclusion of six patients, the study was completed with 24 patients (17 males, 7 females; mean age 57±11 years) and the results were expressed accordingly.

Study design. After obtaining clinical and hemodynamic stabilization of each patient with IDC, medical therapy was started with digoxin 0.125-0.25 mg five times a week, and daily administration of lisinopril 5 mg, spironolactone 25 mg, ferosemide 40 mg, and aspirin 100-300 mg. Then, if tolerated, lisinopril was upward titrated over two weeks to 20 mg/day with 5 mg increments, and the therapy was continued for eight weeks. Then, each subject underwent echocardiographic examination including CFR measurement and carvedilol therapy was initiated with 3.125 mg twice daily for two weeks. Carvedilol therapy was then increased at two-week intervals (if tolerated) first to 6.25 mg, then to 12.5 mg, and finally to a target dose of 25 mg twice daily. Clinical examinations were performed weekly and carvedilol was titrated according to the patient's clinical and symptomatic status. Of 24 IDC patients, carvedilol therapy was increased to the target dose in 23 patients. In only one patient, upward titration was stopped at 12.5 mg twice daily and carvedilol was continued without further titration. In nine patients, titration to the target dose was achieved at the end of eight weeks. Other patients needed more time to reach the target dose. The mean time to the target dose was 11±3 weeks. After reaching the target dose, carvedilol therapy was continued for an additional eight weeks. Thus, till the second echocardiographic examination including CFR measurement, the mean duration of carvedilol therapy was 19±3 weeks.

All echocardiographic examinations were performed by the same investigator who was blind to the patients' data. Two echocardiographers separately made off-line measurements on videotape records. The study was conducted according to the recommendations set forth by the Declaration of Helsinki on biomedical research involving human subjects. Written informed consent was obtained from each subject and the study protocol was approved by the institutional ethics committee.

Clinical and echocardiographic findings of the study group were compared with those of a control group consisting of 23 consecutive, age- and sex-matched patients (13 males, 10 females; mean age 55±4 years) who underwent coronary angiography because of atypical chest discomfort.

Measurement of coronary flow reserve. Each subject was examined using an Acuson Sequoia C256 echocardiography system equipped with a 3V2c broadband and a 5V2c high-resolution transducer with second harmonic capability (Acuson Corp, Mountain View, CA, USA). Visualization of the distal left anterior descending (LAD) coronary artery was performed using a modified, foreshortened, 2-cham-

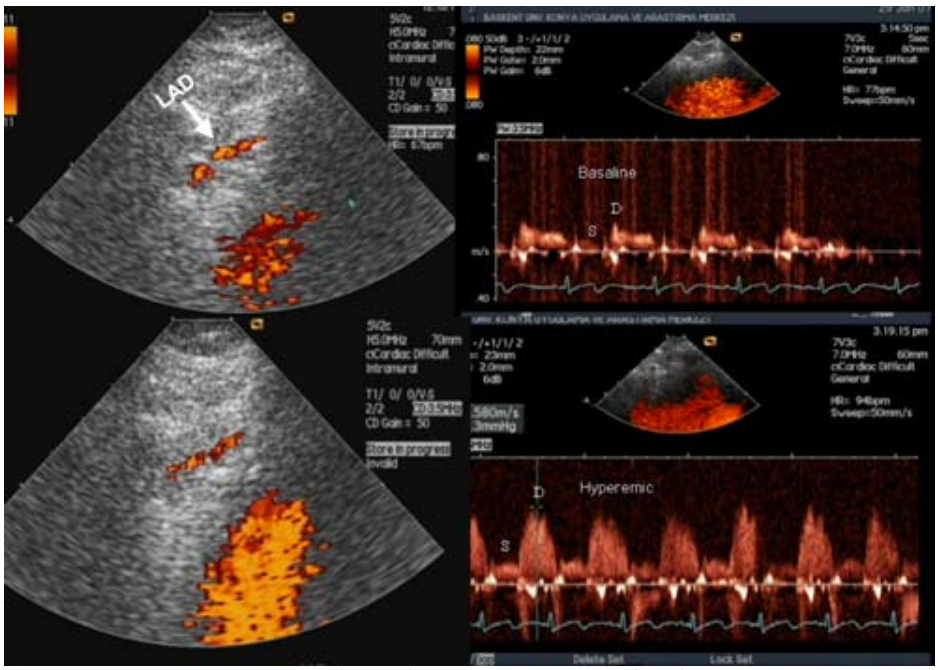

Figure 1. Mid to distal segment of the left anterior descending (LAD) coronary artery in color-coded transthoracic Doppler echocardiography. Spectral Doppler coronary blood flow by sampling of mid to distal segment of LAD. LV: Left ventricle; LAD: Left anterior descending artery; S: Systole; D: Diastole.

ber view obtained by sliding the transducer on the upper part and medially from an apical 2-chamber view to reach the best alignment to the interventricular sulcus. Subsequently, coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall, with the color Doppler velocity range 8.9 cm/sec to 24.0 cm/sec (Fig. 1). The color gain was adjusted to provide optimal images. The acoustic window was around the midclavicular line, in the fourth and fifth intercostal spaces, with the subject in the left lateral decubitus position.[8] The left ventricle was imaged on the long-axis cross-section and the ultrasound beam was then inclined laterally. Next, coronary blood flow in the LAD (middle to distal) was searched by color Doppler flow mapping. All subjects had Doppler recordings of the LAD during dipyridamole infusion at a rate of 0.56 mg/kg over six minutes. All subjects had continuous heart rate and electrocardiographic monitoring as well as blood pressure recording at baseline, during dipyridamole infusion and at recovery. By placing the sample volume on the color signal, spectral Doppler of the LAD showed the characteristic biphasic flow pattern with larger diastolic and smaller systolic components (Fig 1). Coronary diastolic peak velocities were measured at baseline and after dipyridamole by averaging the highest three Doppler signals for each measurement. Coronary flow reserve was defined as the ratio of hyperemic to baseline diastolic peak velocities. For reproducibility analysis, CFR measurement was repeated in 10 control subjects 10 days after the first evaluation. The intraobserver intraclass correlation coefficient for CFR measurement was 0.952.

Statistical analyses. All analyses were performed using SPSS 9.0 statistical software package. Data were expressed as mean ± standard deviation. Independent t-test was used for comparisons between the study and control groups, and paired t-test for repeated measures of the study group. To reduce the contribution of decreased rate-pressure product to CFR after carvedilol therapy, we performed the analysis of covariance. A p value of less than 0.05 was considered significant.

RESULTS

Patients with IDC exhibited similar clinical characteristics compared to the control group with regard to age, sex, body mass index, systolic and diastolic blood pressure, triglyceride and glucose levels. However, total cholesterol, HDL-cholesterol, and LDL-cholesterol levels were significantly lower and high-sensitivity C-reactive protein level was significantly higher in patients with IDC (Table 1).

Left ventricular end-diastolic and end-systolic volumes, left ventricular mass index, and isovolumic

Table 1. Clinical and echocardiographic characteristics of the patient and control groups

		Study group			
	Control group	Before carvedilol	After carvedilol	*p**	*p***
Clinical and laboratory findings					
Body mass index (kg/m^2)	27.7±3.4	28.1±5.8		.NS	
Systolic blood pressure (mmHg)	122.2±11.2	121.5±13.1		.NS	
Diastolic blood pressure (mmHg)	76.1±6.4	77.1±8.6		.NS	
Heart rate (beat/min)	70.1±9.4	71.6±15.0		.NS	
Total cholesterol (mg/dl)	207.7±26.9	173.2±34.6		<0.01	
HDL-cholesterol (mg/dl)	50.1±11.6	42.5±7.7		<0.005	
LDL-cholesterol (mg/dl)	110.0±10.0	93.3±6.7		<0.01	
Triglyceride (mg/dl)	141.6±61.9	132.7±44.2		.NS	
High-sensitivity C-reactive protein (mg/l)	2.3±1.5	4.7±4.0		<0.005	
Glucose (mg/dl)	93.7±7.2	97.3±12.6		.NS	
Echocardiographic findings					
Left ventricular end-diastolic volume (ml)	90.5±12.6	207.6±69.5	195.6±61.0	<0.001	.NS
Left ventricular end-systolic volume (ml)	30.4±5.5	133.9±54.5	122.9±46.7	<0.001	<0.05
Ejection fraction (%)	67.1±2.2	35.5±6.4	38.1±7.3	<0.001	<0.001
Left ventricular mass index (g/m^2)	82.6±14.1	153.7±32.7	148.6±32.7	<0.001	.NS
Mitral E-wave max (cm/sec)	71.1±13.3	74.3±28.1	67.4±24.8	.NS	.NS
Mitral A-wave max (cm/sec)	64.8±12.9	67.1±28.4	72.1±28.4	.NS	.NS
E/A ratio	1.1±0.2	1.6±1.5	1.1±1.0	.NS	.NS
Mitral E-wave deceleration time (msec)	193.4±14.7	210.7±76.9	210.2±69.8	.NS	.NS
Isovolumic relaxation time (msec)	88.0±12.6	111.5±18.2	117.2±21.6	<0.001	.NS
Coronary flow reserve	2.48±0.39	2.14±0.41	2.09±0.42	<0.05	.NS

*Versus the control group; **Before and after carvedilol treatment; NS: Not significant.

relaxation time were significantly increased in the IDC group (Table 1). Left ventricular ejection fraction was 35.5±6.4 in the IDC group, and 67.1±2.2 in the control group (p<0.00l).

Compared to controls, baseline diastolic peak flow velocity (DPFV) was significantly higher and CFR was significantly lower in the IDC group (p<0.05); however, hyperemic DPFV was similar in the two groups (Table 2).

After carvedilol therapy, left ventricular end-systolic volume decreased significantly (p<0.05) and left ventricular ejection fraction increased significantly (p<0.001). Decrease in the left ventricular mass index was slight and not significant (Table 1). Changes in mitral E and A velocities, E/A ratio, mitral E wave deceleration time, and left ventricular isovolumic relaxation time were not significant. Systolic and diastolic blood pressures decreased slightly but not significantly. Heart rate decreased significantly after carvedilol therapy (Table 2).

Following carvedilol treatment, baseline DPFV, hyperemic DPFV, and CFR slightly decreased (p>0.05). Considering the fact that CFR might have been affected by rate-pressure product values, analysis of covariance was used to reduce the effect of rate-pressure product on CFR. After reducing its contribu-

Table 2. Hemodynamic and echocardiographic findings before and during dipyridamole infusion

		Study group			
	Control group	Before carvedilol	After carvedilol	*p**	*p***
Baseline heart rate (beat/min)	74.3.4±10.0	70.9±14.8	64.4±11.5	.NS	<0.05
Peak heart rate (beat/min)	89.4±20.8	88.0±17.0	80.1±12.7	.NS	<0.01
Baseline systolic blood pressure (mmHg)	122.6±11.3	115.3±11.2	106.2±12.5	.NS	.NS
Peak systolic blood pressure (mmHg)	116.5±8.8	113.3±25.6	118.3±10.5	.NS	.NS
Baseline diastolic blood pressure (mmHg)	75.7±6.4	72.3±8.5	70.1±8.4	.NS	.NS
Peak diastolic blood pressure (mmHg)	70.4±7.0	74.6±6.6	73.7±7.1	.NS	.NS
Baseline diastolic peak flow velocity (cm/sec)	22.2±4.3	26.9±8.2	25.2±4.8	<0.05	.NS
Hyperemic diastolic peak flow velocity (cm/sec)	55.1±14.3	56.2±15.3	51.8±9.8	.NS	.NS
Baseline rate-pressure product (beat/min x mmHg/100)		8.61±1.87	7.80±1.50	.	<0.05
Peak rate-pressure product (beat/min x mmHg/100)		10.00±3.03	9.55±1.53	.	.NS

*Versus the control group; **Before and after carvedilol treatment; NS: Not significant.

tion, pre- and post-treatment CFR values remained similar (p=0.984).

DISCUSSION

Despite angiographically normal coronary arteries, CFR is impaired in patients with IDC because of coronary microvascular dysfunction.[1,10] Compared to the control group, our study demonstrated impaired coronary microvascular functions and CFR in patients with IDC. Carvedilol is used in patients with IDC due to its favorable effects that have not been yet clearly explained. Additionally, there is a general expectation that patients with IDC may benefit from its vasodilator effect.[11] Release of NO in the resistance vasculature could account for the vasodilator effect of carvedilol administered therapeutically to IDC patients. However, in our study, therapy with carvedilol did not improve CFR in patients with IDC. Dipyridamole-induced coronary flow change predominantly reflects coronary microvascular functions. To date, it has been shown that carvedilol favorably affects endothelial functions rather than coronary microvascular functions.[11] This observation was validated by our findings showing no improvement in CFR and coronary microvascular functions following the use of dipyridamole in IDC patients receiving carvedilol.

To our knowledge, there is only one study in the literature investigating the effect of carvedilol on CFR in patients with IDC. Sugioka et al.[12] reported that carvedilol therapy remarkably increased CFR in nine patients with IDC. These authors measured CFR after one and six months of carvedilol therapy with a mean dose of 14±7 mg per day and found that baseline DPFV did not change, but hyperemic DPFV increased significantly and CFR improved from 2.6±0.9 to 3.5±0.7 after the first month and to 3.75±0.6 after the sixth month. However, our results were remarkably different. In our study, despite a larger sample size, administration of maximal doses of carvedilol, elimination of favorable effects of ACE inhibitors by starting carvedilol therapy at least one month after optimization with ACE inhibitor therapy, and elimination of any confounding effect of rate-pressure product in analysis of covariance, carvedilol therapy was not associated with any beneficial effect on CFR. The favorable effect of ACE inhibitors on coronary flow was not eliminated in the above-mentioned study.

Coronary flow is largely regulated by the myocardial oxygen demand,[13] and beta-blockers reduce myocardial oxygen consumption, resulting in decreased coronary flow.[14] In our study carvedilol treatment resulted in a decrease in rate-pressure product and a decrease in baseline DPFV as expected. However, after dipyridamole infusion hyperemic DPFV decreased significantly and, therefore, CFR did not change. After adjustment for rate-pressure product values, pre- and post-treatment CFR values remained similar.

Our findings suggest that carvedilol therapy does not improve myocardial blood supply and beneficial effects of carvedilol in patients with IDC cannot be explained by its effect on the coronary microvasculature.

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