DAHİLİ BİLİMLER / *MEDICAL SCIENCES*
Araştırma Makalesi / Research Article

Endothelial Dysfunction In Patients With Chronic Heart Failure And Its Correction Methods.

Kronik Kalp Yetmezlikli Hastalarda Endotel Disfonksiyonu ve Bunu Doğrulayan Yöntemler

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Background: Beta-blockers are commonly used to improve endothelial function in patients with chronic heart failure (CHF), however, comparative effectiveness of bisoprolol and carvedilol remains to be clarified.

Objective: The purpose of this study was to evaluate the functional state of endothelium in patients with chronic heart failure and the comparative effectiveness of long-term treatment with bisoprolol and carvedilol.

Methods: In 100 patients, men (age: 38-60) with myocardial infarction history, complicated by chronic heart failure, we determined vasomotor endothelial function of the brachial artery by assessing endothelium dependant and independent vasodilation, von Willebrand factor (vWf) level. Patients were assigned in two groups both against the background of standard therapy: 1 – 51 receiving bisoprolol, 2 – 49 receiving carvedilol.

Results: Against the background of standard therapy with bisoprolol and carvedilol after 6 months, endothelium dependant vasodilation increased significantly, in NYHA Class I by 18,3 and 38,8%; in Class II by 11,1 and 35,7%; in Class III by 34 and 60%, in the 1st and 2nd groups, respectively. Von Willebrand factor levels were depressed by 4,1 and 10% in NYHA Class I, by 15,3 and 23,3% in Class II. Analyzing vWf level in Class III patients, we observed increased this index by 3,2 with bisoprolol and 25,8% by carvedilol.

Conclusion: Depending on the NYHA Classes, endothelial dysfunction exaggerates: reduces endothelium dependant vasodilation, speed characteristics of blood flow, vascular tone and sensitivity of the brachial artery to the shear stress, increases the secretion of von Willebrand factor. In patients with expressed heart failure signs, NYHA Class III, carvedilol demonstrated high efficacy, markedly improving the functional state of the endothelium, positively affecting the functional and humoral markers of endothelial dysfunction.

Key Words : ***Endothelium dependant vasodilation, Endothelium independent vasodilation, Von Willebrand factor, Carvedilol, Bisoprolol.***

Ön bilgi: Kronik kalp yetmezlikli hastalarda endotel disfonksiyonunun düzeltilmesinde betablokerler yaygın olarak kullamlmaktadır, bununla birlikte karvedilol ve bisoprololün karşılaştırılmah etkinliğinin açıklığa kavuşması gerekmektedir.

Amaç: Bu çalışmada amaç kronik kalp yetmezlikli hastalarda endotelin fonksiyonel durumunu değerlendirmek ve uzun süreli bisoprolol ve karvedilol tedavisinin etkinliğini karşılaştırmak

Metodlar: Kronik kalp yetmezlikli myokard infarktüsü öyküsü olan yaşları 38-60 arasında olan 100 erkek hastada, von Willebrand factor(vWf) seviyesi, endotele bağımlı olan ve olmayan vasodilatasyonu değerlendirerek brakial arterin vasomotor endotel fonksiyonlarını tespit ettik. Hastalar (I-51) bisoprolol ve (2-49)karvedilol alan iki gruba ayrıldı.

Sonuçlar: 6 ay sonunda standart tedaviye ek olarak bisoprolol ve karvedilol alanlarda endotel bağımlı vasodilatasyonun anlamlı derecede arttığı sırasıyla birinci ve ikinci grup için: NYHA sınıf 1 için %18,3 ve %38,8, sınıf 2 için %11,1 ve %35,7, sınıf 3 için %34 ve %60 , vWf seviyeleri ise azalmıştır sırasıyla sınıf 1 de %4,1 ve %10 , sınıf 2 de %15,3 ve %23,3, sımf 3 de bisoprolol ile %3,2, karvedilol ile % 25,8 artış izlenmiştir.

Tartışma: NYHA smıfına bağlı olarak, endotel disfonksiyomı artar: endotele bağlı vasodilatasyon, kan akımının hız karakteristiği, vasküler tonus, shear strese karşı brakial arterin duyarlıhğı azalır, von vvillebrand faktörün sekresyonu artar. Kalp yetmezliği bulguları belirgin olan NYHA sımf 3 hastalarda karvedilolün endotelin fonksiyonel durumunu belirgin derecede düzelttiğini, endotel disfonksiyononun fonksiyonel ve humoral belirteçlerini pozitif yönde etkilediğini göstermiştir.

Anahtar Sözcükler: ***Endotele bağlı vasodilatasyon, endotelden bağımsız vasodilatasyon, Von Willebrand factor, karvedilol, bisoprolol***

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From the beginning of XXI century, a new direction was clearly marked out, which focused clinicians' attention on the role of endothelial dysfunction (ED) in the formation of chronic heart failure (CHF) (1,2,3). It is commonly known that in the pathogenesis of chronic heart failure, along with neuroendocrine regulation disorders – activation of the sympathoadrenal system (SAS) and renin - angiotensin - aldosterone system (RAAS), endothelial dysfunction plays an important role (4,5), which is characterized by reduced dilation of blood vessels and enhanced vasoconstriction as a result of depressed NO formation, activation of cytokine systems and disorders of vascular wall thrombo - resistance. At present, it is proven that reduced endothelium - dependent vasodilation of vessels, changes in the content of humoral markers of blood, such as von Willebrand factor (VWF), tumor necrosis factor, cytokine and endothelin serve as markers of endothelial dysfunction (6,7).

To date, beta-blockers (BAB), along with angiotensin converting enzyme inhibitors are the primary means of CHF treatment. At present, it is established that BABs have a blocking effect not only on the SAS, but also on several other neurohormonal systems responsible for the progression of heart failure, including - RAAS, endothelin and cytokine systems (8,9,10).

Methods

We examined 52 patients with postinfarction cardiosclerosis, complicated by chronic heart failure - men aged 38-60 years at the Tashkent Medical Academy, I Clinic, Cardiology Department. Following written informed consent, patients having myocardial infarction with Q wave within 2 months – 3 years were randomly assigned to receive bisoprolol or carvedilol. NYHA classes were determined analyzing six-minute walk test (6′WT)and the scale of assessment of clinical status (SACS). The study did not include patients with diabetes mellitus, cardiac arrhythmias, and chronic obstructive pulmonary disease. All the patients were divided into two groups: 1 - 51 patients treated on basic therapy (ACE inhibitors, spironolactone, nitrates, aspirin, if necessary, loop diuretics) – and highly selective BAB - bisoprolol ("Concor" Company « Nycomed », Germany); 2 - 49 patients treated on basic therapy and BAB, which has α1-, β1-and β2 - blocking properties - carvedilol ("Dilatrend" Company « Roche », Switzerland). BAB titration was performed from 1.25 to 10 mg / day assigned dose for - bisoprolol and 3,125 to 25-50 mg / day assigned dose for - carvedilol. Control group consisted of 20 healthy volunteers.

The study was approved by the local Ethics Committee.

Vasomotor endothelial function of the brachial artery was assessed by Doppler screening on the unit - Acuson 128 (U.S.) with 7 MHz linear transducer. Brachial artery (BA) was visualized in the longitudinal section, 2-5 cm proximal to the elbow. Blood vessel regulating function of endothelium was studied by assessing endothelium dependant and endothelium independent vasodilation (EDVD and EIVD). Von Willebrand factor in blood plasma was determined by enzyme-linked immunosorbent assay (ELISA) using reagents of the company "RENAM" analyzer - "Vidas" (France).

Statistical processing of research results was performed on a personal computer type IBM PC / AT using a spreadsheet package EXCEL 6,0 Windows-95. Parameters were described in the form of: arithmetic mean ± standard deviation (M ± SD).

Results

Baseline 6′WT performance showed that all patients, regardless of NYHA Classes of CHF, had low tolerance to physical load. Patients of the first and second groups with NYHA Class II of CHF had less tolerance by 1,4 and 1,3 times, respectively, compared to Class I, while Class III - by 2,0 and 2,1 times. Evaluation of the clinical status of examined patients by SACS showed that patients in the first group with Class I CHF had this index as 3,4 ± 0,31 points and in the second group - 3,5 ± 0,26 points, respectively. The study revealed increasing SACS indices along with progression of chronic heart failure: its indices were higher by 58.8% and 147% in patients of the first group with Classes II and III CHF, respectively, compared to the datum of patients with Class I CHF.

After 3 months of observation, 6′WT results showed a significant increase in the distance in all patients, after 6 months this index was normalized in patients with Class I CHF, while Classes II and III CHF had increased walked distances by 29.5 and 30.3% (P <0.001) in the first group and 35,7 and 40,1% (P < 0,001) - in the second group. Initial SACS results showed that the patients of the first and second groups had 3,4 ± 1,08 and 3,5 ± 0,90 points, respectively. And it increased with the progression of chronic heart failure: it exceeded Class I CHF by 58.8 and 147% (P <0.001) and by 57 and 142% (P <0.001) in Classes II and III CHF, respectively. Three and six months of bisoprolol treatment improved the clinical status of the patients, the indices of the baseline SACS decreased by 20,5 and 35,2% (P <0.01), 12,9 and 35,2%, 15% and 30.9% (P < 0,001) in respective Classes I-III CHF. At the same time, complex treatment with carvedilol also significantly improved the clinical status of the patients. The studied indices decreased from baseline in Classes I-III CHF by 31 and 51.4% (P <0.001), 25.4 and 45% (P <0.001), 21.2 and 40% (P <0.001), in respective 3 and 6 months of observation.

To assess the vasodilating function of endothelium, the examined patients had the parameters of blood flow studied in the brachial artery by evaluating EDVD and EIVD. In patients with Class I CHF, BA diameter was less compared to the control group by

2,4 and 4,8%. Systolic blood velocity (Vs) in BA was significantly decelerated by 19.5 and 18.4% (P <0.01) and diastolic velocity (Vd) bvy 35% and 38.8% in the first and second groups compared to the control group (P <0.01). Analysis of baseline datum of the resistive index (Ri) - reflecting the state of blood flow resistance, distal to the site of measurement, showed that in patients with Class I CHF, it was significantly higher compared to the control group by 8,8 and 11,7% (P <0.01). Pulse index, indirectly reflecting the vessel tonus, exceeded the indices of the control group by 14.4 and 18.3% (P <0.01). In the control group, EDVD was 11,4 ± 1,7%, while patients with Class I CHF in both groups had decreased indices by 23,6 and 25,4%, respectively, compared to the control group. Patients with Class II CHF in both groups had shortened diameter of the BA by 7,3 and 4,9%, decelerated systolic blood velocity in the BA by 27.4% and 26.4%, and diastolic blood velocity by 49.7 and 52 4% (P <0.01) in the first and second groups, respectively, compared to the control group. Average blood velocity was decelerated in patients of the first and second groups with Class II CHF by 32,6 and 32,4% compared to the datum of healthy individuals. These patients had significant higher resistive index compared to the control group by 14.7 and 16.2%, and pulse index by 23.3 and 25.9% (P <0.01) in the first and second groups, respectively. Lessening of EDVD was observed by 36.8 and 38.6%, and the sensitivity index of the BA to the shear stress by 28,5 and 35,7% in patients with Class II CHF compared to the control group.

In patients with Class III CHF in both groups, there were serious disorders of EDVD, indicating a sharp aggravation of endothelial functional state: in the first group, 68% of patients had lessened EDVD, 30% - pathological vasoconstriction was identified and only 2% - it was preserved; in the second group, 70% of patients had lessened EDVD, 27% - pathological vasoconstriction and only 3% had preserved EDVD. The first and second groups had significant decelerations in systolic blood velocity by 28.2 and 27.3%, diastolic by 62 and 62.2% (P<0.01), respectively, compared to the control group. Decelerated average blood velocity was observed in patients with first and second groups with Class III CHF by 36,2 and 35,6% compared to healthy individuals, making up 38,7 ± 1,84 and 39,1 ± 1,1 cm/s, respectively . The diameter of the BA was shortened by 19.5 and 17.1% in patients of groups 1 and 2. In Class III CHF, EDVD was 5 ± 3,9 and 4,8 ± 4,5%, respectively, vs. 11,4 ± 1,7% in healthy individuals, that is, depression of this index by 56.5 and 58.2% (P<0.001) was observed. Initial pulse indices of patients with Class III CHF exceeded the indices of the control group by 36.5 and 38.4% (P<0.01). Analysis of the resistive index datum showed that these indices were elevated by 29.6 and 31.2% (P<0.05) in the first and second groups, respectively, compared to the control group. Index of BA sensitivity to the shear stress was decreased by 64.3% (P<0.001) compared to the control group. Changes in the diameter of the BA after nitroglycerine test represent a functional - morphological substrate of endothelium-independent vasodilation (EIVD). Thus, all patients had almost identical reaction to vasodilation. In the first group, EIVD indices were 14 ± 2,29; 14,2 ± 4,5 and 15,8 ± 5,2% and second -15,8 ± 1,66; 15,3 ± 3,6 and 15 2 ± 4,54% in respective NYHA Classes I-III CHF. It may be related to the processes of vascular remodeling in CHF: the predominance of vasoconstrictor reactions during reactive hyperemia test and the consequent reduction of NO formation. And the administration of exogenous NO filled in its deficiency, increasing vasodilation during nitroglycerine testing (9,10).

Against the background of complex treatment with bisoprolol and carvedilol in patients of first and second groups with Class I CHF after 6 months, EDVD increased significantly - by 18,3 and 38,8% (P <0.05), respectively. Noted an increase in the diameter of the BA by 4,6 and 11,9% (P <0.005) on the background of bisoprolol and carvedilol. Systolic blood velocity accelerated by 3.6 and 12.8%, and diastolic by 10.5 and 55%. Average blood flow velocity accelerated significantly from initial by 4,9 and 20,9% (P <0.001). Resistive index decreased by 1.3 and 11.8%, pulse index by - 4,2 and 17,8%. The sensitivity of the BA to the shear stress increased significantly by 30 and 40% (P <0.005), in the first and second groups, respectively. Long-term bisoprolol therapy in patients with Class II CHF promoted an increase of EDVD by only 11,1%, when after carvedilol, it increased significantly - 35.7% (P <0.05), the diameter of BA increased as well: after bisoprolol by 10,5%, and carvedilol by 12.8% (P <0.001). Systolic blood velocity accelerated by 1,4 and 7,9%, diastolic - 13,5 and 35,4%, the average flow velocity accelerated by 3,6 and 12,6% (P <0.001) from the initial. Resistive index decreased by 3,8 and 6,3%, pulse index by 5,4 and 10,6%. The sensitivity of the BA to the shear stress in the first group is almost unchanged, while in the second group it increased by 33.3% (P <0.001). Against the background of complex treatment with bisoprolol and carvedilol in patients with Class III CHF after 6 months, EDVD increased by 34 and 60.4% (P <0.02), respectively, compared to the initial datum. The diameter of the BA lengthened by 6 and 8.8%, respectively (P <0.01). Systolic blood velocity accelerated by 2,7 and 2,9%, diastolic by 15.2 and 30%, the average flow velocity by 4,6% and 6,7% (P <0.01) after administration of bisoprolol and carvedilol, respectively,.

Changes in levels of von Willebrand factor is experimentally and clinically proven marker, reflecting the functional state of the endothelium (12,13). Studying baseline levels of VWF in patients with Class I CHF noted elevation by 11,7% and 14,5%, compared to the control group, making up 125,6 ± 5,3% and 128,7 ± 7,32% in the first and second

groups, respectively, vs. 112 ± 13,9% in healthy individuals. In patients with Class II CHF, initial VWF levels were 158 ± 3,46% and 157,3 ± 3,09% in the first and second groups, respectively, that is, significant increase in this index by 40,5% and 39,9% compared the control group. In patients with Class III, VWF was significantly elevated by 51.4% and 56.3% (P <0.001) compared to healthy individuals, making up 170,2 ± 6,37% and 175,7 ± 6,37 % in patients of the first and second groups, respectively. The level of VWF, determined in blood plasma of patients with chronic heart failure depends on the degree of functional class, the largest of its value was observed in patients with Class III CHF. After treatment with bisoprolol and carvedilol, VWF levels were depressed by 4,1% and 10% (P <0.05) in Class I CHF, by 15,3 and 23,3% (P <0.05) in Class II CHF. In patients with Class III CHF, tendency to elevate VWF level by 3,2% was observed on the background of bisoprolol and a significant increase in this index by 25,8% (P <0.05) compared to the initial state on the background of carvedilol.

Thus, in patients with CHF, depending on the severity of CHF, endothelial dysfunction enhances: reduces EIVD, speed characteristics of blood flow, vascular tone and sensitivity of the BA to the shear stress, increases the secretion of von Willebrand factor, which was more expressed in patients with Class III CHF. Comprehensive long-term therapy with bisoprolol and carvedilol in patients with Classes I-II CHF showed improvement of clinical status of patients: lengthened distance of SMWT, improved SACS indices; functional state of the endothelium: an increase in the diameter and velocity of blood flow indices, the sensitivity of the BA to the shear stress, reduced VWF level. In patients with expressed HF signs with Class III CHF, carvedilol demonstrated high efficacy, significantly improving the functional state of the endothelium, positively affecting the functional and humoral markers of endothelial dysfunction. The positive effect of carvedilol in patients with Class III CHF on the parameters of endothelial dysfunction is associated with its additional α1-adrenoblocking, and antioxidant properties of the drug and conforms to datum of other researchers (13,14).

Conclusions

Long-term therapy with carvedilol and bisoprolol promotes correction of endothelial dysfunction, expressing as improving endothelium - dependent vasodilation, reducing vascular tone, accelerating blood velocity, reducing von Willebrand factor in patients with NHYA Classes I-II of CHF. In patients with Class III CHF, six-month carvedilol therapy significantly improves endothelium-dependent vasodilation, reduces vascular tone, functional activity of platelets and von Willebrand factor level.

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