# The prognostic value of the cardiopulmonary exercise test in patients with heart failure who have been treated with beta-blockers

## Beta-blokerlerle tedavi edilmekte olan kalp yetersizlikli hastalarda kardiyopulmoner egzersiz testinin prognostik değeri

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## ABSTRACT

***Objectives:*** The prevalence of chronic heart failure and a reduced ejection fraction (CHF-REF) has increased over the last decade. The cardiopulmonary exercise test (CPET) is an established tool for managing these patients. For patients who are administered beta-blockers, its predictive value is debated. The aim of this study was to assess the prognostic values of several parameters in patients with CHF-REF who were on beta-blockers.

***Study design:*** 390 patients with CHF-REF underwent CPET after cardiac rehabilitation and were followed for two years.

***Results:*** The primary endpoints were all-cause mortality, cardiac-related mortality and major cardiovascular events (hospitalization for HF, heart transplantation and acute coronary syndrome or arrhythmia). The mean beta-blockers dosage was 68.9% of the target dose. The two-year mortality rate was 13%, while the mean age of the population was 57.1 years. In addition, most of the patients were men (85.5% *vs.* 14.5%). The resting LVEF was 35.7±9.4 and the maximal oxygen uptake (peak $VO_2$) was 19.5 ml/kg/min. The peak $VO_2$, $VE/VCO_2$ slope and circulatory power were significant predictors of risk. The prognosis was better when the initial linear $VE/VCO_2$ slope was lower than 30, and the final steeper $VE/VCO_2$ slope was lower than 32. There was no difference between the two slopes. The oxygen uptake efficiency slope, oxygen uptake, heart rate recovery, $VE/VCO_2/VO_2$ index and ventilatory threshold had no prognostic value.

***Conclusion:*** The peak $VO_2$, circulatory power and $VE/VCO_2$ slope were prognostic indicators for patients with CHF-REF who were on beta-blockers.

## ÖZET

***Amaç:*** Son on yılda kronik kalp yetersizliği ve azalmış ejeksiyon fraksiyonu (KKY-AEF) prevalansı son on yılda artmıştır. Kardiyopulmoner egzersiz testi (KPE) bu hastaların yönlendirilmesinde yeri iyi bilinen bir yöntemdir. Beta-bloker kullanan hastalarda testin öngördürücü değeri tartışmalıdır. Bu çalışmanın amacı beta-bloker almakta olan KKY-AEF'si olan hastalarda birkaç parametrenin prognostik değerini değerlendirmekti.

***Çalışma planı:*** KKH-AEF'si olan ve kardiyak rehabilitasyondan sonra KPE uygulanmış 390 hasta 2 yıl boyunca takip edildi.

***Bulgular:*** Birincil son noktalar tüm nedenlere bağlı ve kalp nedenli ölüm ve önemli kardiyovasküler olaylar (kalp yetersizliği için hastaneye yatış, kalp nakli, akut koroner sendrom veya aritmi) idi. Ortalama beta-bloker dozu hedeflenen dozun %68.9'u idi. İki yıllık mortalite oranı %13, hasta popülasyonunun yaş ortalaması ise 57.1 yıl idi. Ek olarak hastaların çoğu erkek idi (%14.5 ve %85.5). İstirahatte sol ventrikül EF 35.7±9.4 ve maksimum oksijen alımı (pik $VO_2$) 19.5 ml/kg/dk idi. Pik $VO_2$, $VE/VCO_2$ eğrisi ve kan dolaşımının yeterliliği riskin önemli öngördürücüleriydi. Başlangıç doğrusal $VE/VCO_2$ eğrisi 30'dan az, nihai daha dik eğri 32'den aşağı olduğunda prognoz daha iyi idi. İki eğri arasında hiçbir fark yoktu. Oksijen alım etkinliği eğrisi, oksijen alımı, kalp hızı toparlanması, $VE/VCO_2/VO_2$ indeksi ve solunum eşiği herhangi bir prognostik değere sahip değildi.

***Sonuç:*** Pik $VO_2$, kan dolaşımının yeterliliği ve $VE/VCO_2$ eğrisi beta-bloker almakta olan KKY-AEF'si olan hastaların prognostik göstergeleriydi.

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The prevalence of chronic heart failure (CHF) and a reduced ejection fraction (REF) has increased over the last decade and is between 2-3% of the European population.[1] Therefore, estimating the prognosis of patients with this condition is one of the most important challenges that clinicians who treat CHF-REF face. Exercise testing with ventilator-expired gas analysis provides valuable information. Peak exercise oxygen uptake plays an important role in the risk stratification and selection of heart transplant candidates from patients with CHF-REF.[2,3] Recently, the slope of the increase in ventilation (VE) relative to carbon dioxide production ($VCO_2$) during exercise, which reflects increased ventilatory drive, has been theorized as a new potent predictor of outcomes. Similarly, it is believed to have a similar or greater prognostic value than peak $VO_2$.[4-6] Indeed, a variety of prognostic markers have been identified from these studies. Circulatory power (CP) can be used to assess cardiac pump function and has prognostic value.[7] The oxygen uptake efficiency slope (OUES), oxygen uptake, heart rate recovery (HRR), $VE/VCO_2/VO_2$ index and ventilatory threshold are other parameters. Eventually, investigators would like to identify which of these prognostic parameters is related to patients' outcomes. Furthermore, the predictive value of the cardiopulmonary exercise test (CPET) is debated in patients who are administered beta-blockers. Also, in most studies, not all patients were receiving beta-blocker therapy. In Lund's study,[8] about 65% of patients were given beta-blockers.

The aim of this study was to assess the prognostic values of several parameters in patients with CHF-REF who were on beta-blockers.

## PATIENTS AND METHODS

### Study population

Patients with stable CHF-REF secondary to left-ventricular systolic dysfunction (a left-ventricular ejection fraction [LVEF] less than 45% with optimal treatment and after cardiac rehabilitation) who underwent an exercise test between January 1, 2000 and December 31, 2004 were retrospectively included. All patients were taking beta-blockers. In this cardiac rehabilitation (cardiologic center Trouville/mer), patients were hospitalized for 3 weeks. The rehabilitation included medical supervision, exercise training for 5 sessions/week (continue training at ventilatory anaerobic threshold (VAT) on treadmill and/or bicycle and gymnastics) and multidisciplinary management (therapeutic education from dieticians, cardiologists, nurses and psychologists). They consulted with a cardiologist, which included a physical examination, electrocardiogram, echocardiogram and CPET at the beginning and at the end of the study.

**Abbreviations:**

| | |
|---|---|
| *CHF* | *Chronic heart failure* |
| *CP* | *Circulatory power* |
| *CPET* | *Cardiopulmonary exercise test* |
| *HRR* | *Heart rate recovery* |
| *LVEF* | *Left-ventricular ejection fraction* |
| *OUES* | *Oxygen uptake efficiency slope* |
| *REF* | *Reduced ejection fraction* |
| *ROC* | *Receiver operating characteristic* |
| *$VCO_2$* | *Carbon dioxide production* |
| *VAT* | *Ventilatory anaerobic threshold* |
| *VE* | *Minute ventilation* |

All tests were conducted on an outpatient basis, with a mean follow-up of two years. The primary endpoint was a composite endpoint that included both the all-cause mortality and major cardiovascular events (cardiac related-mortality, heart transplantation, acute heart failure, acute coronary syndromes and arrhythmia).

### Cardiopulmonary exercise test

Exercise was performed on a bicycle (Corival Lode, Groninger, Holland) until maximal exhaustion (10-Watts/minute or 15-Watts/minute protocols). The oxygen consumption ($VO_2$), carbon dioxide production ($VCO_2$) and minute ventilation (VE) were measured on a breath-by-breath basis using ergospirometry (Metasys TR-M Brainware, la Valette du Var, France). The investigated parameters included the exercise time (min), the maximum workload (W) and the maximal heart rate (beats/min).

The $VE/VCO_2$ slope was first calculated using linear regression throughout the entire exercise period or calculated from the initial slope (at the level of the respiratory compensation point).[9] The oxygen pulse was calculated as the peak $VO_2$ divided by the maximal heart rate, and anaerobic ventilatory threshold was defined using the V-slope method.[10] The peak $VO_2$ was defined as the highest $VO_2$ that was reached in the final 30 seconds of the exercise. The percentage of predicted peak $VO_2$ was calculated as the peak $VO_2$ divided by the maximal predicted $VO_2$.[11] Two other variables included the recovery half-time of the $VO_2$ ($T1/2\ VO_2$) and the recovery half time of the heart rate ($T_{1/2}$ HR). The CP was calculated as the product of

**Table 1.** **Population characteristics**

| | Population | | |
|---|---|---|---|
| | n | % | Mean±SD |
| Age (years) | 390 | | 57.1±11.8 |
| Men | 390 | 85.6 | |
| HBP | 390 | 33.6 | |
| Diabetes | 389 | 30.8 | |
| Smokers | 390 | 61.0 | |
| Hyperlipidemia | 390 | 47.7 | |
| Family history | 390 | 21.8 | |
| BMI >25 | 390 | 59.3 | |
| BMI (kg/cm²) | 390 | | 26.4±4.8 |
| LVEF | 376 | | 35.7±9.4 |
| BNP (pg/ml) | 135 | | 530.3±705.2 |
| Max workload (W) | 391 | | 104.65±41.81 |
| NYHA | 270 | | |
| I | | 3.3 | |
| II | | 68.8 | |
| III | | 27.7 | |
| Ischemic cardiopathy | | 49 | |
| Dilated cardiomyopathy | | 30 | |
| Toxic cardiopathy | | 12 | |
| Rythmic cardiopathy | | 4 | |
| Mixed cardiopathy | | 5 | |

BMI: Body mass index; HBP: High blood pressure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association function class; SD: Standard deviation.

the peak $VO_2$ and the maximal arterial systolic blood pressure or the product of the peak $VO_2$ and the mean arterial blood pressure.[7,12] HRR was defined as the heart rate 1 minute after the CPET subtracted from the maximal heart rate during the exercise test.[13] The OUES, which is a non-linear description of the ventilatory response to exercise, was defined as the regression slope *"a"* in the equation $VO_2 = a \log VE + b$.[14] The $VE/VCO_2/VO_2$ index was the ratio of the $VE/VCO_2$ slope across the entire exercise period to the peak $VO_2$.[15]

### Statistical methods

A statistical software program was used for the data analysis (SPSS 12.0 for Windows, Chicago, Illinois, USA). The continuous variables are presented as means ± standard deviations (SD), and the categorical variables are presented as percentages. Student's t-test and the Mann-Whitney U-test were used to compare the means of the two groups. The chi-square test was used to compare the categorical variables. Linear regression analysis was based on the least-squares method. A receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value. P values of 0.05 or less denote statistically significant differences.

## RESULTS

A total of 390 patients (334 men, 56 women) with a mean age of 57.1 years participated in this study. The patients were in NYHA class II of the NYHA functional classification (68.8%). The mean LVEF was 35.7±9.4%. The heart failure aetiologies were ischemia (49%), dilated cardiomyopathy (30%) and toxic cardiomyopathy (12%) (Table 1). The mean dose of beta-blocker therapy was 68.9% of the target dose. 82.9% of patients were taking angiotensin converting enzyme inhibitors and 16.4% were taking angiotensin II receptor blockers. The patient's treatments' are showed in Figure 1. A total of 51 patients had deceased by the time of the 2-year follow-up, with a death rate of 13%. Also, 29% of the patients had one or more events within 2 years. None of the patients were lost at follow up. The mean maximal oxygen uptake (peak $VO_2$) was 19.5±6.2 ml/kg/min, the mean value of the $VE/VCO_2$ slope (calculated during the entire exercise

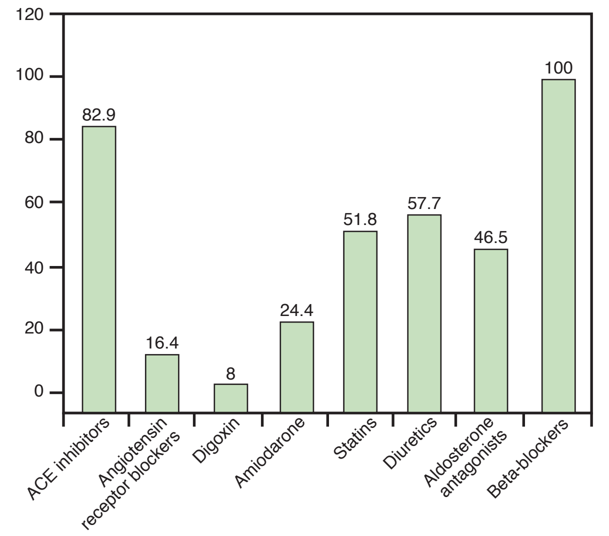


**Figure 1.** Subject treatment (All patients were taking beta-blockers, and 82.9% were taking ACE inhibitors). ACE: Angiotensin converting enzyme.

period) was 32.3±5.9, and the mean respiratory exchange ratio (RER) was 1.2±0.1, suggesting that most of the patients performed maximal exercise. The mean percentage of the maximum predicted heart rate was 73.3%, confirming the effect of beta-blockers on heart rate. The following factors were significant determinants of an adverse prognosis within 2 years in a univariate analysis model: $VE/VCO_2$ slope, peak $VO_2$, CP, time of exercise and maximum workload. These parameters have prognostic value for both all-cause mortality (Table 2) and major cardiovascular events (Table 3). Using the ROC curve, we determined the threshold of the $VE/VCO_2$ slope. For the initial $VE/VCO_2$ slope (up to 30), patients had worse prognoses for all-cause mortality within 2 years (odds ratio = 6.327, $p<0.001$). For the overall $VE/VCO_2$ slope (up to 32), patients had worse prognoses for all-cause mortality (odds ratio = 2.701, $p<0.041$). Based on a multivariate Cox analysis using a model that included the $VE/VCO_2$ slope, peak $VO_2$, CP and maximum workload, the maximum workload appeared to have a better prognostic value (95% confidence interval: 0.98 [0.96-0.99], p=0.005).

## DISCUSSION

In patients taking beta-blockers, the prognostic values of CPET parameters are still debated. In this study, we confirmed that peak $VO_2$ is still the gold standard, even in patients who receive beta-blocker therapy. In Zugck's[16] study, 408 patients with HF and a LVEF ≤45% were included and separated into 2 groups (with or without beta-blocker treatment). There was no significant difference in the peak $VO_2$; however, the patients who were treated with beta-blockers had the best prognoses, suggesting that beta-blockers influenced the peak $VO_2$. In the beta-blocker group, the patients who had lower peak $VO_2$ values had worse prognoses.

Lund et al.[8] studied 221 patients with HF, of which 144 were treated with beta-blockers. In this group, the

**Table 2. The prognostic values of the cardiopulmonary exercise test parameters after two years in patients alive and in patients dead**

| | Patients alive (Mean±SD) | Patients dead (Mean±SD) | *p* |
|---|---|---|---|
| Time (min) | 10.3±2.8 | 8.5±2.5 | **<0.001** |
| Max workload (W) | 107.7±42.2 | 78.4±26.2 | **<0.001** |
| Initial $VE/VCO_2$ | 29.0±6.5 | 32.3±7.6 | 0.029 |
| Overall $VE/VCO_2$ | 32.0±5.8 | 35.6±6.0 | 0.007 |
| Peak $VO_2$ (mL/kg) | 1.5±0.6 | 1.1±0.4 | **<0.001** |
| Peak $VO_2$ % predicted | 71.3±19.7 | 58.5±16.2 | **<0.001** |
| Peak $VO_2$ (mL/kg/min) | 20.0±6.2 | 15.5±4.4 | **<0.001** |
| Circulatory power (MAP x peak $VO_2$) | 2.0±0.7 | 1.4±0.4 | **<0.001** |
| Circulatory power (SAP max x peak $VO_2$) | 2942±1166 | 2104±778 | **<0.001** |
| $O_2$ pulse | 13.1±4.9 | 11.8±4.1 | 0.13 |
| VAT (mL/kg/min) | 12.5±3.8 | 10.8±3.9 | 0.08 |
| Oxygen uptake efficiency slope | 1.9±1.8 | 1.4±0.4 | 0.288 |
| $VE/VCO_2/VO_2$ index | 1.8±1.3 | 2.3±0.9 | 0.097 |
| $T_{½}$ $VO_2$ (min) | 1.3±0.4 | 1.2±0.4 | 0.662 |
| $T_{½}$ HR (min) | 2.4±9.3 | 1.6±0.8 | 0.676 |
| HRR (HR max-HR 1 min) | 14.7±10.8 | 11.4±12.6 | 0.18 |
| RER | 1.2±0.1 | 1.1±0.1 | 0.529 |

$VE/VCO_2$: Ventilation minute/carbon dioxide; MAP: Mean arterial pressure; SAP: Systolic arterial pressure; $O_2$: Oxygen; VAT: Ventilatory anaerobic thresthold; $T_{1/2}$ $VO_2$: Recovery half time of the $VO_2$; $T_{1/2}$ HR: Recovery half time of the heart rate; HRR: Heart rate recovery; RER: Respiratory exchange ratio; SD: Standard deviation.

**Table 3. The prognostic values of the cardiopulmonary exercise test parameters for major cardiovascular events over two years**

| | *p* |
|---|---|
| Time (min) | **<0.001** |
| Max workload (W) | **<0.001** |
| Initial $VE/VCO_2$ | 0.024 |
| Overall $VE/VCO_2$ | 0.031 |
| Peak $VO_2$ (mL/kg) | **<0.001** |
| Peak $VO_2$ % (predicted) | **<0.001** |
| Peak $VO_2$ (mL/kg/min) | **<0.001** |
| Circulatory power (MAP x Peak $VO_2$) | **<0.001** |
| Circulatory power (SAP max x Peak $VO_2$) | **<0.001** |
| $O_2$ pulse | 0.18 |
| VAT (mL/kg/min) | 0.375 |
| Oxygen uptake efficiency slope | 0.149 |
| VE / $VCO_2$ / $VO_2$ index | 0.286 |
| $T_{½}$ $VO_2$ (min) | 0.987 |
| $T_{½}$ HR (min) | 0.549 |
| HRR (HR max-HR 1 min) | 0.08 |
| RER | 0.529 |

$VE/VCO_2$: Ventilation minute/carbon dioxide; MAP: Mean arterial pressure; SAP: Systolic arterial pressure; VAT: Ventilatory anaerobic threstold; $T_{1/2}VO_2$: Recovery half time of the $VO_2$; $T_{1/2}$HR: Recovery half time of the heart rate; HRR: Heart rate recovery; RER: Respiratory exchange ratio.

patients had the same becoming regardless of whether they were above or below the peak $VO_2$ value of 14 mL/kg/min. This result can be explained by the small number of patients. Indeed, in Peterson's[17] study with 369 patients, the peak $VO_2$ had prognostic value, which is in contrast with the results of Pohwani's[18] study (55 patients). Another possible explanation (according to a study by Mancini and Myers[19]) is there is no absolute threshold value. Instead, there may be a continuous relationship between a patient's outcome and his peak $VO_2$. Moreover, the threshold value of 14 mL/kg/min can be criticized because it was validated before the widespread use of the beta-blockers. Shakar's[20] study seems to confirm this issue.

Corrà et al.[21] showed that peak $VO_2$ has prognostic value if it was less than 10 mL/kg/min, in a study with 236 patients who were being treated with beta-blockers. Up to this threshold, there is no link between peak $VO_2$ and a patient's outcome. O'Neill et al.[22] studied 2105 patients, of whom 43% were taking beta-blockers. In this group, peak $VO_2$ had prognostic value that was better than those in the other groups. This data seems to confirm the prognostic value of peak $VO_2$ in patients being treated with beta-blockers; however, the threshold was not determined in our work. Peak $VO_2$ is a continuous variable, and lower values indicate poorer outcomes.

Circulatory power is another prognostic marker. Cohen-Solal[7] was the first to determine the prognostic value of CP; however, in his study only 12% of 179 patients with HF were taking beta-blockers. He considered the CP to be a new global index instead of an index of cardiac power (cardiac output x MAP). This new index could reflect the arterial/venous $O_2$ (A-V $O_2$), heart rate, systolic ejection volume or blood pressure response. All of these parameters have prognostic value.

In a study by Williams et al.,[12] CP was a predictor of survival; however, we do not know if beta-blockers were used in that study. Scharf et al.[23] also determined the prognostic value of CP, although only 31% of the included 154 patients were on beta-blockers in that study. In this study, CP was a much stronger marker than the peak $VO_2$. Scharf explained that the peak $VO_2$ actually ignores the after-load, and cardiac input completely depends on the latter parameter. With a high after-load (due to an adrenergic tonus, for example), the peak $VO_2$ can collapse, whereas the cardiac pump will remain efficacious, and *vice versa*. The CP, which is a noninvasive parameter, reflects cardiac input during exercise and the after-load that is measured by the arterial systolic blood pressure. In Scharf's study, beta-blockers did not modify the prognostic value of CP because they improved the cardiac pump capacity, peak $VO_2$ and blood pressure.

Tabet et al.[24] compared two populations of patients with HF who were receiving (255 patients) or were not receiving (147 patients) beta-blocker therapy. The mortality rates were comparable, which could be explained by the fact that patients who were being treated with beta-blockers had more severe HF. In this group, CP had the best prognostic value, behind the $VE/VCO_2$ slope and the peak $VO_2$. It is possible that both the arterial systolic blood pressure and exercise increased with better systolic function and a decreased heart rate, which is similar to the effects of beta-blockers. Arterial systolic blood pressure is not affected by muscle function in contrast to the peak $VO_2$. Andersson et al.[25] found an increased peak SBP with the use of beta-blockers.

In the literature, some studies[5,26,27] have shown that the $VE/VCO_2$ slope is a powerful prognostic marker and provides information other than peak $VO_2$. In work by Francis et al.,[5] the peak $VO_2$ and the $VE/VCO_2$ slope were highly significant prognostic indicators. In a multivariate analysis using a forward-backward method, only the peak $VO_2$, age and the LVEF were retained. CHF-REF is also characterized by an increased respiratory response to exercise. There are also pathophysiological abnormalities in CHF-REF, such as increased anatomical and physiological dead spaces, a ventilation-perfusion mismatch, abnormal pulmonary vascular hemodynamics and disordered ventilator reflex control. Accordingly, the $VE/VCO_2$ slope is less susceptible to the vagaries of CHF-REF (such as irregular breathing and early subjective fatigue) that may sometimes interfere with the determination of peak $VO_2$. In 2004, Arena et al.[4] studied 213 patients (of which 89 were taking beta-blockers) who underwent CPET. The peak $VO_2$ and $VE/VCO_2$ slope were independent prognostic indicators of cardiac mortality and hospitalization. The peak $VO_2$ depends on the effort of the subject, whereas the $VE/VCO_2$ slope preserves its prognostic value during submaximal effort.[9] The peak $VO_2$ also depends on the contribution of the peripheral metabolism. Two patients with HF who have similar heart function but different skeletal muscle function and exert maximal effort may have different peak $VO_2$ values. Only about one-third of patients were taking beta-blockers in most of the studies. Arena[28] compared two groups of patients with CHF-REF who were receiving (167) or were not receiving (300) beta-blocker treatment. In a multivariate analysis, the $VE/VCO_2$ slope was the strongest predictor of mortality in the two groups. The threshold value was 34.3 for the group that was taking beta-blockers, which was less than that of the other group (36). In a study by Ponikowski et al.,[27] the $VE/VCO_2$ slope was identified as a prognostic marker of mortality in patients with CHF-REF and preserved exercise tolerance, whereas the peak $VO_2$ was not. Arena et al.[29] compared two $VE/VCO_2$ slope calculations. The calculation that used all data points from rest to peak exercise had a greater prognostic power in patients with HF. Tabet's[9] study confirmed this result. In our work, it could not be determined.

## Limitations

This study was retrospective and monocentric with its known limitations. In our study, we did not use a control group (patients that were not taking beta-blockers). Therefore, the results may not be applicable to all CHF-REF patients. Our population was well treated, with regular follow-ups occurring after cardiac rehabilitation. Also, the genders were not balanced in our study, and HF in the context of a preserved ejection fraction was not studied. Finally, we have not determined cut off values for several parameters, which may be useful in practice.

Peak $VO_2$, $VE/VCO_2$ slope and CP are prognostic markers for patients with CHF REF who were being treated with beta-blockers. The threshold value of peak $VO_2$ is still discussed in favor of its continuous relationship with peak $VO_2$ and patient outcomes. These three parameters provide different information, and all are useful for performing a prognostic evaluation, especially for the assessment of candidates for heart transplantation. A multivariable score with several variables (clinical, echocardiographic, biological and functional) should be evaluated.

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*Key words:* Adrenergic beta-antagonists/therapeutic use; heart failure/drug therapy; oxygen consumption/physiology; predictive value of tests; prognosis.

*Anahtar sözcükler:* Adrenerjik beta-antagonist/terapötik kullanım; kalp yetersizliği/ilaç tedavisi; oksijen tüketimi/fizyoloji; testlerin öngördürücü değeri; prognoz.