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Atenolol in Dilated Cardiomyopathy: A Clinical Instrumental Study

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Summary. **The usefulness of beta blockers in the treatment of congestive heart failure has been questioned. We selected 11 patients, mean age 47.1 ± 13.8, affected by dilated cardiomyopathy in NYHA class III, who had been taking digoxin and diuretics for a long time. Atenolol 50 mg was added to conventional therapy. Both before and 3 months after treatment a clinical evaluation, chest x-ray, an exercise test, and an echocardiogram were performed. We observed an improvement of NYHA class in five patients. However, the exercise test showed no improvement: 2310 ± 1299 vs. 2902 ± 983 total kgm (ns). The echocardiogram showed improvements of the end-systolic diameter (from 6.3 ± 1 cm to 5.9 ± 0.8 cm; $p < 0.02$), the fractional shortening (from 13.6 ± 6.3% to 15.2 ± 5.6%; $p < 0.05$) the radius/thickness ratio (from 4.14 ± 0.5 to 3.5 ± 0.5; $p < 0.05$), and the wall stress (from 208.4 ± 49 g/cm^2 to 163.5 ± 41 g/cm^2; $p < 0.02$). The inotropic state index did not show any changes. We conclude that in some patients with dilated cardiomyopathy beta blockers may improve the clinical status and left ventricular performance.**

Key Words. **congestive heart failure, beta blockers, dilated cardiomyopathy, atenolol.**

During heart failure a prolonged and intense adrenergic stimulation can be observed, which consequently reduces the density of beta-adrenergic receptors [1]. This loss of receptors is accompanied by a proportional decrease in the activity of adenylate cyclase in muscle stimulated with agonists [2]. A similar reduction in the density of beta receptors has been observed in peripheral lymphocytes of patients with cardiac failure [3,4]. In ventricular myocardium, this down regulation of receptors appear to selectively affect the beta-$_1$ receptors [5,6]. It is thought that down-regulation acts as a protection against the endogenous catecholamines.

To ascertain the possible protective action of beta blockers during heart failure, we used atenolol to treat a cohort of patients presenting with dilated cardiomyopathy.

Methods

We studied ten males and one female, mean age 47.1 ± 13.8 (SD) years. All were affected by idiopathic dilated cardiomyopathy, in NYHA class III, and had been taking digoxin and diuretics for a long time. The treatment was not modified during the period of observation, and the digoxin plasma level was periodically checked. Coronary artery, pericardial, valvular, and congenital heart disease were excluded by right and left heart catheterization, angiocardiography, and selective coronary angiography. The diagnosis of idiopathic dilated cardiomyopathy was therefore possible. At the moment of selection, the patients underwent standard chest x-rays, an M-mode and 2D echocardiogram, an exercise stress test, and routine laboratory investigations. These tests were repeated after 3 months of treatment with the beta blocker, atenolol, at 25 mg/day for 7 days. We chose atenolol, which has never previously been mentioned in the literature, because of its characteristics of cardioselectivity and the absence of intrinsic sympathetic activity. After this the dose was raised to 50 mg. None of the patients had any obstructive airways disease. Chest x-rays was performed with the patient in a standing position and a film focus distance of 180 cm with front-back projection. The cardiothoracic index was calculated following Keats [7].

The echocardiogram was performed with a commercially available ATL 300 C instrument, which is able to record a complete one- and two-dimensional examination. Blood pressure was always recorded at the same time as the echo. Derived echocardiographic parameters were: the end-diastolic (EDD) and end-systolic (ESD) diameters of the left ventricle and the average end-diastolic and end-systolic wall thickness. Three cardiac cycles were averaged when the patient was in sinus rhythm, five when the patient was in atrial fibrillation. These values were then used to derive the fractional shortening (FS), the index of hypertrophy or end-diastolic radius/thickness ratio

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Table 1. Some clinical and functional data before and after treatment with beta blockade

	Basal values	Beta blockers	p
H.R. (beats/min)	78 ± 15.1	69 ± 4	< 0.05
B.P. (mmHg)	131 ± 19	120 ± 12	< 0.01
ET (kgm)	2310 ± 1299	2902 ± 983	ns
C.T.	0.58 ± 0.04	0.57 ± 0.05	ns

Mean and standard deviation.
H.R. = heart rate; B.P. = blood pressure; E.T. = exercise test; C/T = cardio/thoracic index.

(r/th), the end-systolic meridional wall stress (ESS), the pressure/dimension ratio (P/D), the pressure/volume ratio (P/V), and FS/ESS amongst the pump/stress indexes. All the echocardiograms were individually evaluated, measured, and processed by two different echocardiographers.

The exercise test was always carried out at the same time of day, the patient having previously been fasted for at least 4 hours. The test was performed on a cycloergometer equipped for a continual increase in workload. The initial load was 30 watts, increased by 10 watts per minute until limited symptoms were observed. The electrocardiogram and blood pressure were monitored during the entire exercise. Statistical calculations were carried out using Student's t test for paired data.

Results

General data (table 1)

The heart rate decreased from 78 ± 15.1 beats/min to 69 ± 4, a statistically significant beats/min difference ($p < 0.05$). The maximum blood pressure decreased from 131 ± 19 mmHg to 120 ± 12 mmHg ($p < 0.01$).

The exercise test, evaluated in total kilogram meters, was equal to 2310 ± 1299 kgm on selection and 2902 ± 983 after 3 months of treatment. The difference was not statistically significant. The cardiothoracic index was 0.58 ± 0.04 before and 0.57 ± 0.05 after 3 months of treatment with beta blockers.

Historical "control" group

Eleven patients, 10 males and 1 female, mean age 50 ± 8.7 years, presenting with dilated cardiomyopathy have been considered as a retrospective historical "control group." All the patients were in NYHA class III and were receiving digoxin and diuretics for many years. The cardiothoracic index, echocardiogram, and exercise tolerance test were evaluated at a first visit and 3 months later and the results were compared. We did not observe any changes in the various parameters, except for end-diastolic diameter and r/th ratio, which increased from 6.7 to 7.1 cm ($p < 0.01$) and from 3.5 to 4.6 ($p < 0.05$), respectively.

Table 2. Echocardiographic data before and after treatment

	Basal values	Beta blockers	p
EDD (cm)	7.16 ± 0.9	6.9 ± 0.7	ns
ESD (cm)	6.2 ± 1	5.9 ± 0.8	< 0.02
ESS (g/cm^2)	203.4 ± 49	163.5 ± 41	< 0.01
FS (%)	13.6 ± 6.3	15.9 ± 5.6	< 0.05
r/th	4.14 ± 0.9	3.5 ± 0.5	ns
P/D (g/cm^3)	29.2 ± 10	27.5 ± 7.3	ns
P/V (mmHg)/ml)	0.76 ± 0.9	0.73 ± 0.75	ns

Mean and Standard Deviation.
EDD = end-diastolic diameter; ESD = end-systolic diameter; ESS = end-systolic meridional wall stress; FS = fractional shortening; r/th = end-diastolic radius/thickness ratio; P/D = end-systolic pressure/diameter ratio; P/V = end-systolic pressure/volume ratio; FS/ESS = fractional shortening/stress ratio.

Echocardiographic data (table 2)

The end-diastolic diameter was not reduced after treatment. However, the end-systolic diameter significantly decreased ($p < 0.02$). The improvement in the performance parameters could well be attributed to this reduction, combined with the ESS decrease (from 203.4 ± 49 to 163.5 ± 41 g/cm^2 ($p < 0.01$)) and the drop in mean blood pressure. In particular, FS increased from 13.6 ± 6.3% to 15.9 ± 5.6% ($p < 0.05$) and the hypertrophy index (R/th) was consequently reduced from 4.14 ± 0.9 to 3.5 ± 0.5. The pure inotropic indexes (P/D, P/V, FS/ESS) were not modified, possibly even showing moderate deterioration.

Discussion

Results obtained by administering beta blockers to patients with chronic congestive heart failure are reported in the literature and seem to be contradictory. Some authors observed an improvement in the exercise time [8–11] and the ejection fraction [9,10,12], while others reported, in general, completely negative results [13,14]. We observed an improvement in some echocardiographic indexes, whilst the inotropic parameters, such as the exercise time and the cardiothoracic index, remained unchanged.

A dramatic improvement in clinical condition was also observed by the Swedish group [15], with several changes from NYHA class IV to class I. All of the positive and some of the negative reports [14] illustrated individual cases of clear clinical improvement. According to Alderman and Grossman [16], this fact would suggest the existence of a subpopulation of patients with dilated cardiomyopathy in whom prolonged treatment with beta blockers leads to an im-

provement in the cardiac function and a lengthening of life.

The limitation of our report lies in the control group, since we have compared our data with a historical control group. We tried to select a control group that was as similar as possible to the patient group with regard to functional and hemodynamic indexes.

In our study we saw a reduction in heart rate, a phenomenon also seen in certain other studies. Bradycardia is able to eliminate the left ventricular dysfunction induced by exercise [16], to reduce the increase in left ventricular end-diastolic pressure induced by tachycardia [17], and to have a positive effect on diastolic function [18,19]. Besides these and other effects, Packer's suggestion [6] that spontaneous downregulation protects against the endogenous catecholamines circulating in excess during heart failure should not be neglected.

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