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Dihydrotestosterone treatment in men with coronary artery disease. II. Influence on myocardial ischemia and left ventricle

The discovery of androgen receptors in cardiomyocytes has shown evidence of direct influence of androgens on the heart. Chimpanzee studies suggest that circulating dihydrotestosterone (DHT), but not testosterone (T), is the androgenic hormone affecting cardiovascular system (11). However, T treatment has been reported to increase a diameter of coronary arteries, improve coronary blood flow and reduce myocardial ischemia at exercise (4,9,13). Since the effect of T therapy may be related to its conversion to estrogens, in this study we focused our attention on DHT – a non-aromatizable androgen, resistant to estrogen transformation.

The purpose of the study was to evaluate the effects of transdermal DHT on the result of treadmill stress test, left ventricle mass as well as its systolic and diastolic function in males with coronary artery disease.

MATERIAL AND METHODS

The enrolment criteria and clinical characteristics of the study group are described in the first part of this paper.

Symptom limited electrocardiografic (ECG) stress tests according to Cornell protocol were performed early in the morning on computerized treadmill MAX-1 from Marquette Electronics. ST segment depression was measured 80 ms after J point. Time to 1 mm ST depression and ST depression at peak exercise were noted. According to the changes of heart rate (HR) and ST depression, the value of ST/HR slope for each electrocardiographic lead was calculated automatically. The highest ST/HR slope from each ECG stress test was used for further calculations. Moreover, total exercise time, maximum workload in metabolic equivalents (MET) and time to the onset of angina were recorded.

Transthoracic echocardiography was performed using a Hitachi EUB-450 ultrasonograph with 3.5 MHz transducer. In M-mode presentation of parasternal long-axis view, left ventricular end-diastolic diameter (LVEDD), interventricular septum (IVS), left ventricular posterior wall (LVPW) and left ventricular end-systolic diameter (LVESD) were measured. M-mode images were also used to estimate shortening fraction (FS) and ejection fraction (EF). EF, left ventricular diastolic (LVEDV) and systolic (LVESV) volumes were measured according to the Teicholz method. Left ventricular mass (LVM) was calculated according to the Devereux formula (3): $LVM\ (g) = 1.04*[(LVEDD + IVS + LVPW)^3 - (LVEDD)^3] - 14$. LVM was indexed by the

body surface area (LVMI, g/m^2). Stroke volume (SV) and cardiac output (CO) were calculated according to the following formulas: LVEDV-LVESV and HR*SV, respectively.

Then, from the apical four or five chamber view, isovolumetric relaxation time (IVRT) and parameters of left ventricular diastolic filling were assessed. The Doppler sample volume was positioned just below the level of the mitral annulus and the velocity curve was used to calculate the maximum early diastolic flow velocity (E), maximum atrial diastolic flow velocity (A), their ratio (E/A) and atrial-filling fraction (AFF). IVRT was measured from the five-chamber view with the Doppler sample positioned in the midway between left ventricle outflow and anterior leaflet of mitral valve. Time from the end of aortic outflow to the onset of mitral inflow was considered IVRT.

The differences between normally distributed variables were assessed by Student's paired t test and not normally distributed data by Wilcoxon matched pairs test. The relations among variables were evaluated by Spearman`s rank correlation test. A p value < 0.05 was considered statistically significant.

RESULTS

Table 1. Echocardiographic evaluation of left ventricle in DHT and placebo group. All values are expressed as (mean ± SD)

	DHT		Placebo	
	before	after	before	after
HR (beat/min)	56.5 ± 5.9	59.4 ± 10.3	73.9 ± 14.1	73.8 ± 10.7
EF (%)	58.1 ± 14.2	59.1 ± 12.2	58.5 ± 7.1	54.8 ± 9.8
FS (%)	31.9 ± 9.3	32.3 ± 8.0	31.5 ± 5.0	29.4 ± 5.4
LVM (g)	258.8 ± 70.7	275.3 ± 88.8	272.2 ± 78.5	275.7 ± 113.6
LVMI (g/m^2)	134.0 ± 34.5	141.8 ± 44.2	138.7 ± 40.6	138.9 ± 56.3
LVEDV (ml)	186.6 ± 77.8	176.9 ± 75.6	161.0 ± 33.9	155.5 ± 36.2
CO (l/min)	5.7 ± 1.5	5.6 ± 1.6	6.8 ± 1.4	6.2 ± 1.4
IVRT (s)	0.150 ± 0.037	0.135 ± 0.03 *	0.144 ± 0.022	0.140 ± 0.032
E (cm/s)	0.578 ± 0.143	0.550 ± 0.172	0.611 ± 0.120	0.598 ± 0.132
A (cm/s)	0.584 ± 0.149	0.574 ± 0.150	0.610 ± 0.124	0.603 ± 0.130
E/A	1.04 ± 0.34	1.04 ± 0.46	1.03 ± 0.27	1.01 ± 0.23
AFF	0.41 ± 0.09	0.41 ± 0.12	0.42 ± 0.09	0.41 ± 0.09

*$P < 0.05$

The results of echocardiographic examination in the DHT group and Placebo are shown in Table 1. Three months' DHT treatment did not affect systolic function of left ventricle. However, the significant decrease in IVRT in this group may indicate the improvement of diastolic function of left ventricle. DHT treatment was also associated with the slight increase in parameters of left ventricle mass (LVM and LVMI), but the finding did not reach the level of statistical significance. Other echocardiographic parameters remained unchanged during DHT treatment. There were no significant differences in any parameter under evaluation in patients receiving Placebo.

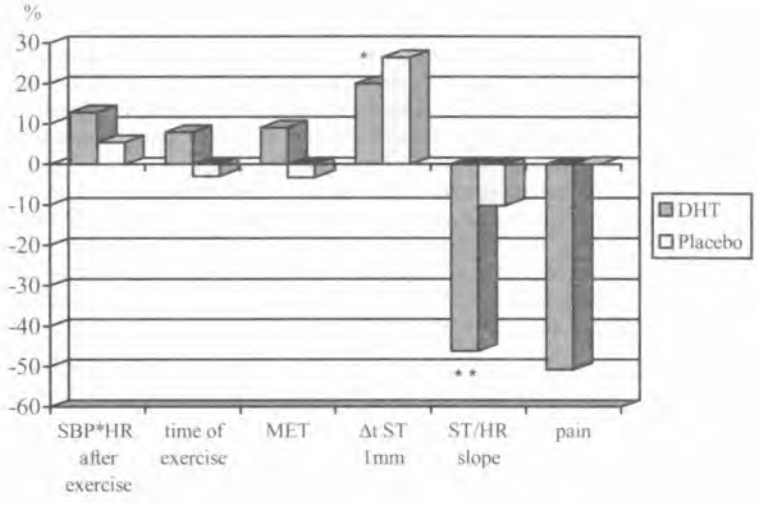

Fig. 1. Changes in selected parameters of ECG stress test in DHT (dark) and placebo group (light bar). Bars represent percent changes of the parameters; * P<0.05; ** p <0.01

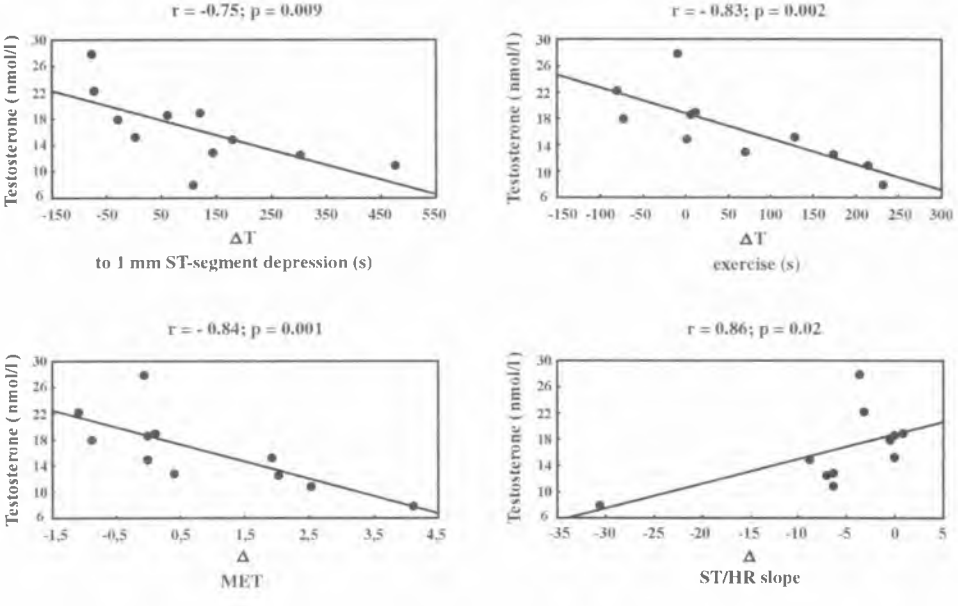

Fig. 2. Spearmans' correlation coefficients between baseline total testosteron level and changes in selected parameters of ECG stress test

The percent changes of the parameters of ECG stress test in the subgroups are presented in Figure 1. DHT treatment resulted in significant prolongation of the time to 1 mm ST segment depression, decrease in the ST/HR slope value and reduction of the frequency of exercise induced chest pain. There was also a trend toward longer total exercise time in this group. The other parameters, including heart rate, blood pressure, double product (heart rate * systolic blood pressure) remained unchanged after DHT treatment. There were no significant differences in ECG stress test results between the DHT group and Placebo.

Figure 2 shows correlation coefficients between total T concentration at the beginning of the study and differences in selected parameters of ECG stress test observed before and after 3 months of DHT treatment. Lower T level at baseline was associated with more pronounced improvement of myocardial ischemia assessed by changes in total exercise time ($r=-0.83$, $p=0.002$), maximum workload ($r=-0.84$, $p=0.001$), time to the onset of 1 mm ST depression ($r=-0.75$, $p=0.009$) and ST/HR slope ($r=0.68$, $p=0.02$).

DISCUSSION

The echocardiographic examination revealed that three months' DHT treatment did not significantly affect left ventricle mass and its systolic function. A decrease in IVRT observed in this group suggests the improvement of left ventricle diastolic function.

Unlike studies on estrogen effects on left ventricle in postmenopausal women, the available data on the effects of androgens on left ventricle function in men are limited. Most of the studies focused on young body builders and athletes abusing anabolic steroids. Their results are inconsistent. Some revealed no effects of steroids on left ventricular mass (12), others showed thickening of an interventricular septum with concomitant increase of left ventricular mass (10). However, no study proved effect of androgens on a systolic function of left ventricle.

A diastolic function depends both on elastic properties of myocardial wall (6) and, as an active process, also on the availability of calcium ions within myocytes (1). Aging is associated with decreased compliance and increased stiffness of myocardium resulting in reduction of early filling and enhancement of atrial filling of left ventricle (2). In early stages of ischemic heart disease early filling due to impairment of relaxation is decreased (6). A prolonged relaxation observed in these patients is considered a compensatory mechanism, which decreases myocardial ischemia, mainly in subendocardium (7). Late stages of ischemic heart disease, associated with scaring, fibrosis and ventricular remodeling, are characterized by late filling abnormalities (6).

Shortening of IVRT observed in our patients indicates the improvement of diastolic function of left ventricle. This effect may be related to calcium channels inhibition mediated by DHT, subsequently leading to decrease in calcium ion influx to cardiomyocytes (8). Shorter relaxation time may also be associated with increased coronary flow (7), and this mechanism is supported by the results of stress test in our patients.

We found that DHT treatment markedly improved coronary reserve assessed by ECG treadmill stress test. Active treatment was associated with increased time to 1 mm ST segment depression, decreased ST/HR slope value and reduced frequency of chest pain during exercise. These findings suggest direct vasodilatation exerted by DHT. Similar effects were observed in males treated with transdermal and parenteral T (5,9,13). Intracoronary T administration in males with coronary artery disease induced rapid improvement of coronary flow (14). In many studies there were made attempts to assess T treatment in males with coronary artery disease (5,9,13,14,15). Since T is converted to E_2 in peripheral tissues, many authors attributed vasodilatory effect of T to E_2 potent vascular effects of which were described in animal and clinical studies. Increased levels of E_2 in the course of T treatment supported the theory. However, the latest study revealed that low, substitutive doses of T reduced myocardial ischemia without E_2 elevation (4). The latter study, like our results, confirms direct vasodilatory effect of androgens.

DHT is a non-aromatizable androgen and its beneficial effects cannot be attributed to conversion to E_2. Moreover, we observed decreased levels of E_2 after DHT treatment. Also, an experimental study in animals revealed that DHT may directly relax arteries (8).

The beneficial effects of DHT on myocardial ischemia were more pronounced in patients with lower baseline levels of T. The same phenomenon was observed by Rosano et al. They found that T therapy was more effective in males with coronary artery disease and lower T levels (9).

In the light of the available data the future role of selective modulators of androgen receptors in the treatment of coronary artery disease seems promising.

CONCLUSION

DHT therapy in males with coronary artery disease decreases myocardial ischemia and improves diastolic function of left ventricle.

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SUMMARY

The effect of transdermal dihydrotestosterone on left ventricle mass and its systolic and diastolic function as well as on the results of treadmill stress test was assessed in eleven males with coronary artery disease. DHT treatment for 3 months resulted in significant decrease in isovolumetric relaxation time (0.150 ± 0.37 s vs. 0.135 ± 0.03 s; $p < 0.05$) indicating the improvement of left ventricle diastolic function. Left ventricle mass and systolic function indices remained unchanged. There was improvement in myocardial ischemia, time to 1 mm ST segment depression increased ($p < 0.05$) and ST/HR slope decreased ($p < 0.01$). Correlation coefficients between testosterone concentration at the beginning of the study and differences in selected parameters of ECG stress test were as follows: for T and increased total exercise time (r=-0.83, p=0.002), for T and increased maximum workload (r=-0.84, p=0.001), for T and increased time to 1 mm ST segment depression (r=-0.75, p=0.009) and for T and decreased ST/HR slope (r=0.68, p=0.02).

Wpływ leczenia dihydrotestosteronem u mężczyzn z chorobą wieńcową
II. Wpływ na niedokrwienie mięśnia serca i czynność lewej komory

Oceniano wpływ przezskórnego podawania dihydrotestosteronu na masę oraz wskaźniki czynności skurczowej i rozkurczowej lewej komory serca oraz na wyniki testu wysiłkowego na bieżni ruchomej u 11 mężczyzn w chorobą wieńcową. W wyniku 3-miesięcznego stosowania DHT skróceniu uległ czas rozkurczu izowolumetrycznego (0.150 ± 0.37 s vs. 0.135 ± 0.03 s; $p < 0.05$), świadcząc o poprawie czynności rozkurczowej lewej komory serca. Masa lewej komory i wskaźniki czynności skurczowej nie uległy zmianie. Zmniejszyły się natomiast cechy niedokrwienia w próbie wysiłkowej na bieżni ruchomej, wydłużył się czas do obniżenia odcinka ST o 1 mm ($p < 0.05$), skróceniu uległ wskaźnik ST/HR slope ($p < 0.01$). Poprawa była tym większa, im niższy był wyjściowy poziom testosteronu. Współczynniki korelacji wynosiły odpowiednio: pomiędzy T a wydłużeniem czasu badania (r=-0.83, p=0.002), pomiędzy T a zwiększeniem maksymalnego obciążenia w MET (r=-0.84, p=0.001), pomiędzy T a wydłużeniem czasu do obniżenia odcinka ST o 1 mm (r=-0.75, p=0.009), pomiędzy T a skróceniem wskaźnika ST/HR slope (r=0.68, p=0.02).