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Features of blood pressure variability and arterial stiffness in hypertensive men with androgen deficiency

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Key words: *Hypertension, Testosterone, Arterial Stiffness.*

Male sex has long been argued as a strong risk factor for arterial hypertension. Noteworthy is that available data support the negative impact of low testosterone on male cardiovascular health.

Objective. This study was designed to assess characteristics of circadian blood pressure and arterial stiffness in hypertensive men with and without testosterone deficiency.

Materials and methods. A total of 60 male hypertensive patients aged above 45 years were screened on androgen deficiency symptoms via Male andropause symptoms self-assessment questionnaire (MASSQ). 42 subjects with suspected low testosterone level were recruited into the study for subsequent total testosterone (TT) measurement. 24 h BP monitoring was carried out for all participants. Aortic stiffness was assessed using BPLab Vasotens System (cuff-based oscillometry method).

Results. 43 % of patients had biochemically confirmed low testosterone level. The total score of MASSQ in this group was significantly higher compared to patients with normal testosterone. The decreasing of TT concentration with age was detected. The low TT group was characterized by significantly higher values of 24 h systolic blood pressure (SBP) and pulse pressure (PP) values. The lower testosterone appears to be associated with prevalence of "non-dipper" pattern. The results of the multiple regression analysis revealed the relationship between plasma testosterone levels and SBP values in both study groups, while the relationship between testosterone and DBP values was not significant. A significant relationship was also found in each group between TT and PWV.

Conclusion. The study revealed the high prevalence of androgen deficiency among hypertensive middle-aged men. These patients are characterized by higher BP values compared to those with normal TT levels in the same age range. Low TT concentration may be considered also as the contributor of increased arterial stiffness in hypertensive males.

Особливості варіабельності артеріального тиску та жорсткості артерій у чоловіків із гіпертонічною хворобою II стадії на тлі андрогенного дефіциту

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Чоловіча стать розглядається як незалежний фактор ризику розвитку артеріальної гіпертензії. Наявні дані свідчать про негативний вплив низького рівня тестостерону на розвиток та прогресування серцево-судинних захворювань у чоловіків.

Мета роботи – оцінювання параметрів добового профілю артеріального тиску та жорсткості артерій у чоловіків із гіпертонічною хворобою II стадії на тлі андрогенного дефіциту або за нормального рівня тестостерону.

Матеріали та методи. Обстежили 60 пацієнтів чоловічої статі з гіпертонічною хворобою II стадії віком старше за 45 років щодо андрогенного дефіциту за допомогою опитувальника симптомів чоловічої андропаузи (MASSQ). 42 пацієнти, загальна кількість балів яких, згідно з опитувальником, відповідала наявності симптомів зниження тестостерону, були включені в дослідження для дальшого визначення загального тестостерону (ЗТ). Усім досліджуваним здійснили добове моніторування артеріального тиску (ДМАТ) та оцінювання жорсткості артерій за допомогою системи BPLab Vasotens (осцилометричним методом).

Результати. 43 % пацієнтів мали біохімічно підтверджений низький рівень тестостерону. Загальний бал MASSQ у цій групі виявився значно вищим порівняно з досліджуваними з нормальним рівнем тестостерону. Спостерігалося зниження концентрації ЗТ із віком. Група хворих із низьким рівнем ЗТ характеризувалася значно вищими значеннями систолічного артеріального тиску (САТ) і пульсового артеріального тиску (ПАТ) за даними ДМАТ. Добовий профіль АТ у групі андрогенного дефіциту характеризувався переважанням «non-dipper». Результати множинного регресійного аналізу показали взаємозв'язок між рівнем тестостерону та значеннями САТ в обох групах, водночас як зв'язок між тестостероном і значеннями діастолічного АТ не був статистично значущим. Сильним виявився зв'язок у кожній групі між ЗТ і швидкістю поширення пульсової хвилі.

Висновки. Дослідження продемонструвало високу поширеність андрогенного дефіциту серед чоловіків середнього віку з гіпертонічною хворобою II стадії. Ці пацієнти характеризуються вищими значеннями АТ порівняно з такими тієї самої вікової групи, але з нормальним рівнем ЗТ. Зниження рівня ЗТ може розглядатися як один із факторів підвищеної жорсткості артерій за наявності гіпертонічної хвороби.

Ключові слова: *гіпертонічна хвороба, тестостерон, жорсткість артерій.*

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Особенности вариабельности артериального давления и жёсткости артерий у мужчин с гипертонической болезнью II стадии на фоне андрогенного дефицита

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Мужской пол рассматривается как независимый фактор риска развития артериальной гипертензии. Имеющиеся данные свидетельствуют о негативном влиянии низкого уровня тестостерона на развитие и прогрессирование сердечно-сосудистых заболеваний у мужчин.

Цель работы – оценка параметров суточного профиля артериального давления и жёсткости артерий у мужчин с гипертонической болезнью II стадии на фоне андрогенного дефицита и при нормальном уровне тестостерона.

Материалы и методы. Обследовано 60 пациентов мужского пола с гипертонической болезнью II стадии в возрасте старше 45 лет на предмет андрогенного дефицита с помощью опросника симптомов мужской андропаузы (MASSQ). 42 пациента, у которых общее количество баллов, согласно опроснику, соответствовало наличию симптомов снижения тестостерона, были включены в исследование

для дальнейшего определения общего тестостерона (ОТ). Всем испытуемым проведено суточное мониторирование артериального давления (СМАД) и оценка жёсткости артерий с помощью системы BPLab Vasotens (осциллометрическим методом).

Результаты. 43 % пациентов имели биохимически подтверждённый низкий уровень тестостерона. Общий балл MASSQ в этой группе оказался значительно выше по сравнению с обследуемыми с нормальным уровнем тестостерона. Наблюдалось снижение концентрации ОТ с возрастом. Группа больных с низким уровнем ОТ характеризовалась существенно более высокими значениями систолического артериального давления (САД) и пульсового артериального давления (ПАД) по данным СМАД. Суточный профиль АД в группе андрогенного дефицита характеризовался преобладанием «non-dipper». Результаты множественного регрессионного анализа показали взаимосвязь между уровнем тестостерона и значениями САД в обеих группах, в то время как связь между тестостероном и значениями диастолического АД не была статистически значимой. Сильной оказался связь в каждой группе между ОТ и скоростью распространения пульсовой волны.

Выводы. Исследование продемонстрировало высокую распространённость андрогенного дефицита среди мужчин среднего возраста с гипертонической болезнью II стадии. Эти пациенты характеризуются более высокими значениями АД по сравнению с таковыми той же возрастной группы, но с нормальным уровнем ОТ. Снижение уровня ОТ может рассматриваться как один из факторов повышенной жёсткости артерий при наличии гипертонической болезни.

Ключевые слова: *гипертоническая болезнь, тестостерон, жёсткость артерий.*

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Last years the interest to the problem of hormonal changes in the development of cardiovascular disorders markedly increased. Male sex has long been argued as a strong risk factor for arterial hypertension. The functional activity of the entire endocrine system changes with aging, and it is of interest to study the male age-related androgen deficiency syndrome in cardiovascular diseases (CVD). However serum testosterone level is not accepted as a traditional risk factor, the natural aging process faces with gradual decreasing of androgen concentration [14]. Baltimore Aging Study has shown that 20 % of men over 60 years, 30 % over 70 years and 50 % over 80 years have low level of total testosterone [8].

There is an increasing number of evidence regarding the negative impact of low testosterone on male cardiovascular health [2]. Testosterone may act as a biomarker of general health disorders, similar to other hormones that are biomarkers of illness, such as thyroid hormone, which declines with illness severity and predicts mortality [12,13]. Many co-morbidities and prescribed medications can affect testosterone levels resulting in a wide range of nonspecific clinical signs and symptoms of androgen deficiency [3]. Nowadays there is thoroughly studied the role of androgenic status in the maintenance of cardiovascular health in adult male. Higher physiological testosterone levels are now getting attention as a beneficial modulator of traditional cardiovascular risk factors [5,10].

Within the last decade the prospective population-based studies demonstrated the association of low testosterone levels with an increased risk of major coronary events and significant correlation between poor androgenic status and cardiovascular mortality [4]. Despite the growing number of observations of the impact of low androgens levels to development, progressing and outcomes of CVD the controversies regarding the exact laboratory definition of testosterone deficiency still exist.

A large number of researches have shown the crucial role of preclinical organ damage to determine individual cardiovascular risk. Accelerated arterial stiffness is considered as a novel predictor of cardiovascular events and all-cause mortality, and can be evaluated with pulse wave velocity (PWV) [6], ambulatory arterial stiffness index (AASI) [1] and augmentation index (AIx) [11]. Cause-and-affect relationship between testosterone level and arterial stiffness is yet to be established. Numerous studies describe arterial stiffness in various subpopulations, but there are no evaluations of PWV, AASI, and AIx in hypertensive patients according to androgenic status.

Objective

This study was designed to assess characteristics of circadian blood pressure and arterial stiffness in hypertensive men with and without testosterone deficiency.

Materials and methods

A total of 60 male hypertensive patients aged above 45 years were exposed to perform Male andropause symptoms self-assessment questionnaire (MASSQ) [9]. 42 subjects with more then 40 points of MASSQ were supposed to have mild-to-moderate androgen deficiency and were recruited into the study. Patients with BMI >28 kg/m^2, prior history of hypogonadism, medical or surgical treatment for any prostatic disease, major cardiovascular events and diabetes mellitus were excluded. Signed informed consent was obtained from all patients. The subsequent total testosterone (TT) concentration was evaluated using immunoassay. TT was measured in the morning (between 7 a. m. and 11 a. m.) after an overnight fast. As the cut-off the value of 350 ng/dL was used to define androgen deficiency [7]. The patients with TT levels below 230 ng/dL were not included into this study because of requirement of testosterone replacement therapy. 24 h BP monitoring was carried out for all participants. Aortic stiffness was assessed using BPLab Vasotens System (cuff-based oscillometry method). Pulse wave analysis was evaluated due to the non-invasive measurement of aortic pulse wave velocity (PWVao), augmentation index (AIx) adjusted to the 75 beats per minute of heart rate and subendocardial viability ratio (SEVR).

Statistical analysis of the data was performed using Statistica 6.0 for Windows. Multiple regression analysis was used to assess the causality of androgen deficiency in hypertension and changes of arterial stiffness. The results are expressed as means±SD. The level of significance was taken as $p<0.05$.

Results

The general characteristics of the two groups are shown in *Table 1*.

Eighteen patients (43 %) had biochemically confirmed low testosterone level. Furthermore, the total score of MASSQ in participants of this group was significantly higher compared to patients with normal testosterone. The most usual manifestations

Table 1

Main characteristics of the study population

Data, unit	Low TT patients, n=18	Normal TT patients, n=24
Age, years	64±5.87	53±6.06
MASSQ, total score	64.3±9.71*	46.4±5.68
24 h SBP, mm Hg	141.5±11.44*	133.8±9.62
24 h DBP, mm Hg	87.25±6.41	85.62±7.14
24 h PP, mm Hg	63.53±6.71*	54.27±5.24
Total testosterone, ng/dL	327±17.29*	408±29.98
PWVao, m/s	10.9±2.14*	9.1±3.25
ASI, mm Hg	181.5±14.54	164.5±16.72
Pulse pressure amplification (PPA), %	144.6±9.62	133.3±8.14
Subendocardial viability ratio (SEVR), %	75.4±8.72*	84.6±9.45

Note: * – p≤0.05 between groups with and without androgen deficiency.

of androgen decline were physical exhaustion and decrease in ability to perform sexually.

Patients with testosterone deficiency were more aged. The TT level seemed to be lower with increasing of age, and this decline becomes evident after the age of 64. The decreasing of TT concentration with age is shown in *Fig. 1*.

The low TT group was characterized with significantly higher values of 24 h systolic blood pressure (SBP) and pulse pressure (PP) values. Therewith it was noticed that the difference in SBP was more representative for values SBP during the active period. The difference between diastolic blood pressure (DBP) values between groups was non-significant. The circadian BP profile of non-dipper was prevalent in androgen deficient patients (51 %).

The pulse wave form assessment showed that pulse pressure amplification tends to be higher and wave reflection tends to be lower in participants with testosterone insufficiency (*Fig. 2*).

Linear statistical analysis revealed that PWV and PP were positively correlated with age and both SBP and DBP. TT levels were inversely related to PWV ($r=-0.66$; $P<0.005$), AIx ($r=-0.51$; $P<0.05$), SBP ($r=-0.64$; $P<0.05$). Correlation between TT and DBP was proved as insignificant.

Based on the idea that testosterone deficiency can affect BP and arterial stiffness and although on the possibility of reverse causality multiple regression analysis was performed with testosterone as an independent variable and BP and arterial stiffness parameters as dependent variables.

The results of the multiple regression analysis using TT as an independent variable and SBP, DBP, PWV and SEVR as dependent variables are demonstrated in *Table 2*. This analysis revealed the relationship between plasma testosterone levels and SBP values in both study groups, while the relationship between testosterone and DBP values was not significant. A significant relationship was also found in each group between TT and PWV.

Discussion. The present research demonstrated the prevalence of androgen deficiency among male patients with arterial hypertension and confirmed the gradual decline of TT level with increasing of age. These findings are in accordance to

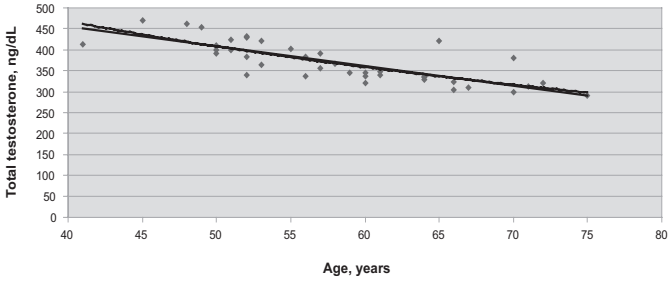

Fig. 1. The distribution of TT concentration according to the age.

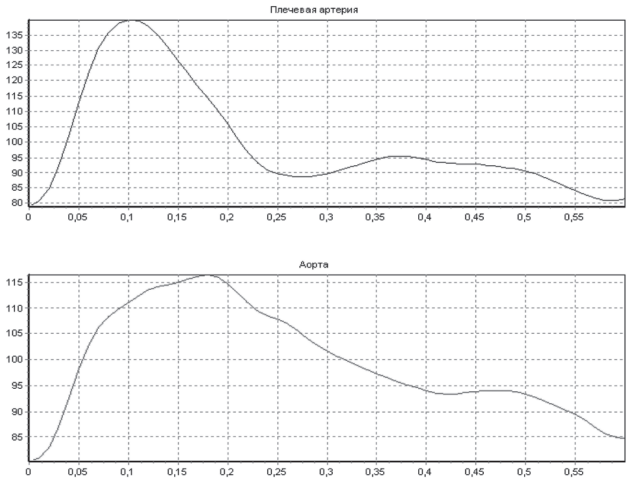

Fig. 2. Measured brachial artery (top) and aortic pressure (bottom) waves recorded in hypertensive patient with androgen deficiency (56 years old).

many prospective cross-sectional and longitudinal studies, such as Massachusetts Male Aging Study that also indicated a decrease of TT in the process of aging [10]. Hypertensive patients with low TT level are characterized by higher 24 h SBP and PP; herewith the most prevalent circadian BP profile is non-dipper. At the same time, the assessment of aortic stiffness parameters has shown the significant relationship

Table 2

Multiple regression analysis of arterial stiffness parameters in hypertensive patients

Data, unit	Patients with low TT		Patients with normal TT	
TT, r^2=0.6, ng/dL	F value	P	F value	P
Age, years	29.46	0.37	32.8	0.14
SBP, mm Hg	2.47	0.014	2.21	0.01
DBP, mm Hg	0.23	0.62	0.18	0.66
PWV, m/s	71.85	0.053	65.69	0.01
SEVR, %	12.61	0.001	14.33	0.0005

between androgenic status and PWV and SEVR. The study design reflects the actual interest to non-invasive evaluation of central hemodynamics in hypertension with considering of hormonal changes while aging.

Limitations to the present study should be noted. Measures of aortic BP and AIx were noninvasively and automatically calculated from peripheral pressure waveforms. The sample population size is small and the ability to generalize the findings is limited.

Conclusion

The study revealed the high prevalence of androgen deficiency among hypertensive middle-aged men. These patients are characterized by higher BP values compared to those with normal TT levels in the same age range. Low TT concentration may be considered also as the contributor of increased arterial stiffness in hypertensive males.

Conflicts of interest: authors have no conflict of interest to declare.

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