ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LXI, N1, 89 SECTIO D 2006

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The adrenergic system and coronary risk factors

The aim of the paper was to show the place of the sympathoadrenergic mechanism among risk factors of coronary disease and the mutual relationship of coronary risk factors with the adrenergic nervous system.

The increased activity of the adrenergic nervous system, which was proved in many publications, is accompanied by risk factors of coronary artery disease such as arterial hypertension, disturbances of lipid and carbohydrate metabolism, cigarette smoking, lack of physical activity, obesity, metabolic syndrome, disturbances of coagulation, the climax in women, stress, depression. These clinical states are linked by the disturbance of the function of the endothelium, and the stimulation of the adrenergic system is here both the reason and the result. The increased activity of the adrenergic system can damage the function of the endothelium directly or indirectly by the influence on other risk factors of coronary artery disease (3, 4, 5). The activity of the adrenergic system can be evaluated on the basis of the level in the blood and the excretion of catecholamines and their metabolites in the urine, of density and sensitivity of the adrenergic receptors, and lately microneurography has been a method having advantage over other ones due to large repeatability of results in a given patient (11).

The adrenergic system and arterial hypertension Mutual relations of the adrenergic system and arterial hypertension are not explained and are still a subject of esearch, manifesting themselves in many pathogenetic mechanisms. The regulation of the cardiovascular system and the blood pressure by the adrenergic system takes place in a short and long-term way. The short-term stimulation of the sympathoadrenergic system by the activation of beta 1 adrenergic receptors leads to the acceleration of the heart action, and the stimulation of alfa 1 receptors causes the elevation of the blood pressure. In arterial hypertension in the adrenergic regulation the following factors are taken into consideration: 1. the disturbance of the central regulation of the blood pressure with the primary increase of the activity of the sympathetic system centers in the central nervous system; 2. the disturbance of the circumferential regulation as the effect of the damage to the function of baroreceptors, mechanoreceptors and chemoreceptors (15).

In the first period of the occurrence of hypertension haemodynamic changes consist in the increase of only the cardiac output (one-minute capacity of the heart), and the circumferential resistance remains normal. With the prolonged duration of hypertension the reactivity of beta 1 receptors in response to the increase of catecholamines and the adrenergic stimulation drops. The reactivity of alpha 1 receptors of the vessel's wall is not modified, that is why the circumferential resistance is high, and despite the decrease of cardiac output the blood pressure does not drop. Hypertension becomes consolidated and the wall of the vessel outgrows. In fixed hypertension, as the result of disturbances of adrenergic reaction, the circumferential resistance is constantly high, and the cardiac otput becomes normal or decreases. In a further stage overreactivity plays the main role in the reconstruction of walls of the vessels. Outgrown walls of the vessels become more sensitive and overreactive and shrink more easily although the activity of the sympathoadrenergic system declines (11).

Presented results show that the stimulation of the adrenergic system in hypertension causes damage to the vessels not only as the response to the rise of the blood pressure but is connected

with many humural mechanisms which act as a vicious circle.The damage to the function of the endothelium and remodelling of the blood vessel result from haemodynamic changes in arterial hypertension (15).

Stress as the reason for adrenergic stimulation Response to stress depends on such factors as: the level of the stimulation of the adrenergic system, individual sensitivity to stress, ability to cope with stress. Thus the influence of stress is connected both with environmental and genetic factors The fact that in young people with arterial hypertension in family anamnesis the rise of the blood pressure in response to stress is more frequent, e.g. overreaction to cooling proves the importance of the genetic factor.

Pathological mechanisms in response of the adrenergic system to a given impulse can manifest themselves as haemodynamic disturbances with the excessive perfusion in relation to current needs of the organism or as the rise of the perfusion in some organs at the cost of others. Supraventricular arrhythmias and dangerous for life ventricular arrhythmias can occur besides haemodynamic disturbances. Acute stress can be a factor leading to acute coronary episodes, which was proved by the occurrence of myocardial infarction without changes in the coronary vessels. Stress is thought to be a major factor of coronary risk, more frequently connected with worse socioeconomic conditions (6). Many authors observed that constant tension of the adrenergic system is connected with several times greater possibility of the development of arterial hypertension (6). Not only the recurrence of stress but also hyperreactivity of the sympathoadrenergic system play an important part in the maintenance of this tension (11, 15).

In the long-term reaction to stress in hypertension a certain part is played by the renin angiotensin–aldosterone system. The sympathetic stimulation by the stimulation of beta receptors of sympathoadrenergic system causes the increase of the secretion of renin and angiotensin II, and leads to the rise of the volume of the circulating blood and sensitivity of the vessel's wall to the pressor activity of catecholamines. Its central activity is shown by facilitation of conduction in the sympathetic ganglions, the increase of the synthesis and the ejection of norepinephrine, diminishing its manageable reuptake. Angiotensin II besides contraction of arteries and veins influences also the reconstruction of vessels. Damage to the function of the endothelium is the result of its activity (11, 15).

Disturbances of homeostasis. The increase of adrenaline concentration shows a pro- aggregation activity in connection with disturbances of the function of platelets. An intensive thrombotic activity during the adrenergic stimulation results from the increase of the aggregation and adherence of platelets to the endothelium, and a greater risk of ischaemic changes and myocardial infarction result from these changes (11).

Cigarette smoking and the adrenergic activity. There is a lot of evidence for the increase of the adrenergic activity in cigarette smokers. The relationship between values of blood pressure and indirect activity of nicotine was found. The mechanism of this rise can depend on activation of the sympathetic system in smokers, because elevated adrenaline and norepinephrines concentrations were observed in smokers and not in non-smokers. The level of catecholamines dropped when a person gave up smoking (1). Narkiewicz et al., evaluating adrenergic activity in microneurography in smokers, obtained similar results in his research on the activity of the adrenergic system (12). Nicotine besides the rise of the blood pressure causes also other changes in the circulatory system: accelerates the heart rate, increases platelet aggregation, and shows pro-inflammatory activity on the function of the endothelium. Cigarette smoking is accompanied by a higher level of LDL fraction and a low level of HDL (1). Many mechanisms of damage to the function of the endothelium in smokers can be deduced on the basis of that.

Obesity and the metabolic syndrome. Research on the sympathetic nerves in obese persons with and without hypertension showed that the activity of the sympathetic system was in obese persons twice bigger than in persons without obesity.

Chronic stress can lead, in a short time to the rise of the body mass. A stimulating influence of ingestion of food (fats, carbohydrates) on the activity of the sympathetic system in the central nervous system was shown A postprandial rise of glucose and insulin stimulates the metabolism of glucose in the hypothalamus cells which unblocks active pressurizing (pressor) canters of the

brainstem and increases the activity of the sympathetic system. The arteriospasm following this activation impairs the flow of the blood through the cells of the skeletal muscles and limits the use of glucose – causing the rise of resistance to insulin (9).

Disturbances of the diastolic function of blood-vessels of the skeletal muscles and blood-vessels of the skin in response to stress in obese persons without hypertension were described. Thus the rise of the circumferential resistance can occur in obesity (11). Insulin resistance and resulting hyperinsulinism can be responsible for the rise of the circumferential resistance in obesity. Hyperinsulinism increases sympathicotonia and catecholamine concentration which through the rise of resorption of sodium and the rise of volume of extracellular liquid and the rise of circumferential resistance contribute to the development of arterial hypertension.

The influence of insulin on the cardiovascular system depends however on the functional state of this system. In young persons with the preserved function of the endothelium insulin shows its own activity in reducing the circumferential resistance and then the blood pressure drops, whereas in older persons with impaired activity of the endothelium insulin causes the rise of the circumferential resistance and leads to proliferation of cells of the smooth muscles and contributes to the development of arterial hypertension (11, 15). Hyperinsulinism, by the adrenergic activetion, damages the function of the vascular endothelium, facilitates migration of lipids to the intima and cumulation of lipids, and also stimulates the synthesis of lipids in the cells of the smooth muscles of the arteries' walls (3).

Research on obesity contributed to the discovery of leptin whose receptors situated in the central nervous system, can have an influence on the regulation of the circulatory system. Administration of leptin causes the rise of the activity of the sympathetic system (15).

The adrenergic system and physical exercise. The equilibrium and a proper action of the sympathetic and parasympathetic parts of the nervous system determine the adaptation of the cardiovascular system to physical effort (exercise). Disturbances in both systems can cause dangerous for life cardiac arrhythmias. In the research of Krzemiński et al. a kind of physical effort (passive or active) did not influence the level of catecholamines but influenced haemodynamics of the cardiovascular system. During passive effort (exercise) the rise of the arterial blood pressure was observed, and during the dynamic one the rise of the cardiac output (8). Physiology of physical exercise reveals that the post-exercise period brings the fall of the level of catecholamines and of the blood pressure.

Estrogens and the adrenergic system. Research carried out by Stanosza et. al. (13) on 93 women with arterial hypertension in the menopause showed that before the menopause twenty-four hours (circadian) discharge of adrenaline and norepinephrines is characteristically higher, and after the menopause only twenty-four hours discharge of adrenaline is higher (13). It is known that arterial hypertension and coronary disease are more frequent in women after the menopause than before the menopause. Estrogens have an influence on the activity of the endothelium and vasodilatation, they modify the response to stress and the activity of the renin angiotensin aldosteron system, and also lipidogram (14).

The fact that clonidine was the medicine of choice in women with hypertension in the menopause which eliminated vasomotor symptoms, especially hot flush proves the importance of the adrenergic system in the climax.

Renal failure and the adrenergic activity. Renal failure is a factor that increases the risk of coronary heart disease. Stimulation of the adrenergic system manifesting itself in the rise of the concentration of adrenergic neuromediators in the blood and in the decrease of the density of alpha and beta adrenergic receptors in the heart was observed in renal failure.

Clinical symptoms which can be bound with the adrenergic stimulation are: arterial hypertension, myohypertrophy and the diminution of the contractility of the left ventricle. Some authors think that in renal failure a changed turnover of catecholamines is responsible for the disturbance of the adrenergic activity (7).

Age and the adrenergic activity. In the elderly mainly the concentration of the norepinephrine in the blood increases. It can be so not because of the growth of its production but because of its greater release to the circulation, diminished manageable escapement from the

adrenergic endings or diminished inactivation. Ng et al., by means of a microneurography method showed that the ageing process causes the rise of the activity of the adrenergic system regardless of coexisting diseases (10). The rise of the sympathetic activity leads to metabolic disturbances, the rise of the resistance to insulin and of the blood pressure (11).

Frequency of prevalence of arterial hypertension increases with age. Sixty percent of the elderly have elevated blood pressure. Hypertension predominates in men under the age of 60 and above 65 it occurs in women more frequently (2).

In older persons mainly the systolic pressure increases, the entire circumferential resistance also increases, whereas the susceptibility of large blood-vessels decreases. Research of many authors proved that the process of senescence is connected with the rise of the sympathetic activity, which is especially important because the vascular reactivity of beta receptors decreases and the function of alpha receptors causing the vasospasm remains normal. Norepinephrine released from the sympathetic endings is a growth factor and leads to the overgrowth of the muscular coat of the blood-vessel and the reconstruction of the blood-vessel with diminished susceptibility. The sympathetic stimulation simultaneously causes retention of sodium and elevates the blood pressure (2).

Function of the endothelium. The activity of the adrenergic system depends on the function of the endothelium. Nitrous oxide produced by the correct (normal) endothelium inhibits the sympathetic activity in the central nervous system. Experimental research showed the diminution of the production of nitrous oxide by the damaged endothelium. The damaged endothelium does not inhibit the sympathetic activity and a vicious circle is formed (3).

CONCLUSIONS

There are a lot of factors damaging the function of the endothelium and the sympathoadrenergic system acts in many directions and cooperates with all these factors. Catecholamines as growth factors, apart from the intensity of impairment of the endothelium by remaining risk factors can cause changes by themselves and effects of their cooperation depend on the functional state of the endothelium. To stop the vicious circle measures to fight coronary risk factors in order to improve the function of the endothelium are needed.

REFERENCES

1. Benowitz N.L., Gourlay S.G.: Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J. Am. Coll. Cardiol., 29, 1422, 1997.
2. Burt V.L. et al.: Prevalence of hypertension in US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension, 25, 305, 1995.
3. Facchini F.S. et al.: Enhanced sympathetic nervous system activity. The linchpin between insulin resistance, hyperinsulinemia and heart rate. J. Hypertens., 9, 1013, 1996.
4. Grundy S.M.: Obesity, metabolic syndrome, and coronary atherosclerosis. Circulation, 105, 2696, 2002.
5. Hjemam P.: Stress and the metabolic syndrome. An interesting but enigmatic association. Circulation, 19, 2634, 2002.
6. James G.D.I. et al.: Parity and perceived job stress elevate blood pressure in young normotensive working women. Am. J. Hypertens., 2, 37, 1989.
7. Książek A.: Znaczenie sympatycznego układu nerwowego w patogenezie zaburzeń sercowo-naczyniowych u pacjentów z przewlekłą niewydolnością nerek. Nefrol. i Dializ. Pol. 2001, 5 supl. 1, VII Zjazd Polskiego Towarzystwa Nefrologicznego, 45, bibliogr. sum. VII Zjazd Polskiego Towarzystwa Nefrologicznego, Kraków 2001.
8. Krzemiński K. et al.: Cardiovascular metabolic and plasma catecholamine responses to passive and active exercises. J. Physiol. Pharmacol., 51, 2, 267, 2000.

9. Landsberg L.: Insulin and sympathetic nervous system in the pahophysiology in hypertension. Blood Pressure, 5, Supl. II, 25, 1996.
10. Ng. A.V. et al.: Age and gender infuence muscle sympathetic nerve activity at rest in healthy humans. Hypertension, 21, 496, 1993.
11. Narkiewicz K.: Układ współczulny a nadciśnienie tętnicze. Via Medica, Gdańsk 2001.
12. Narkiewicz K. et al.: Cigarette smoking increases sympathetic outflow in humans. Circulation, 98, 528, 1998.
13. Stanosz S., Wasilewska E.: Stężenie katecholamin i aktywność układu reninowo-aldosteronowego u kobiet z nadciśnieniem tętniczym w okresie przed i pomenopauzalnym. Ginek. Pol., 63, 6, 300, 1992.
14. Sumino H. et al.: Hormone replacement therapy in postmenopausal women with essential hypertension increases circulating plasma levels of Bradykinin. Am. J. Hypertens., 12, 1044, 1999.
15. Wyrzykowski K.: Leki beta adrenolityczne w praktyce klinicznej. Via Medica, Gdańsk 2004.

SUMMARY

The aim of the paper was the presentation of the place of the adrenergic system among risk factors of coronary disease and their mutual relations. Experimental and clinical research shows that the increased activity of the adrenergic system is accompanied by risk factors of coronary artery disease such as: age, arterial hypertension, hyperlipidemia, diabetes, smoking of cigarettes, lack of physical activity, obesity, metabolic syndrome, disturbances of coagulation, the climax in women, stress, depression. These clinical states are linked by the disturbance of the function of the endothelium. Nitrous oxide produced by the correct endothelium inhibits the sympathetic activity, but the damaged endothelium does not inhibit the sympathetic activity. The increase of the adrenergic activity in turn causes the rise of the blood pressure, hyperglycaemia, lipid and metabolic disturbances, disturbances of coagulation and haemodynamics. Thus a vicious circle is formed, and the adrenergic system becomes the reason for and the result of the process that damages the endothelium.

Układ adrenergiczny a czynniki ryzyka wieńcowego

Celem pracy było przedstawienie miejsca układu adrenergicznego wśród czynników ryzyka choroby wieńcowej oraz ich wzajemnych relacji. Z badań doświadczalnych i klinicznych wynika, że zwiększona aktywność układu adrenergicznego towarzyszy czynnikom ryzyka choroby niedokrwiennej serca, takim jak wiek, nadciśnienie tętnicze, hyperlipidemia, cukrzyca, palenie papierosów, brak aktywności fizycznej, otyłość, zespół metaboliczny, zaburzenia układu krzepnięcia, okres przekwitania u kobiet, stres, depresja. Te stany kliniczne łączy za sobą zaburzenie funkcji śródbłonka. Produkowany przez prawidłowy śródbłonek, tlenek azotu hamuje aktywność współczulną. Uszkodzony śródbłonek natomiast nie hamuje tej aktywności. Zwiększona aktywność adrenergiczna powoduje zwyżki ciśnienia tętniczego krwi, hyperglikemię, zaburzenia lipidowe, metaboliczne, zaburzenia homeostazy, zaburzenia hemodynamiczne. Wytwarza się więc błędne koło, a układ adrenergiczny staje się przyczyną i skutkiem procesu uszkadzającego śródbłonek.