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Saliva secretion in patients with arterial hypertension in the course of beta-blocker therapy

Arterial hypertension, as one of the diseases of the circulatory system, constitutes both medical and social problem in many countries. The etiology of the disease is complex. There is a number of factors coexisting here, beginning with genetic characteristics of the organism, lifestyle, nutrition habits or other co-occurring diseases.

The action of the medicines used in arterial hypertension treatment is based on the regulation of the volumes of circulating fluids and affecting the mechanisms responsible for arterial wall tone. The adequate choice of medicine depends on the type of hypertension, the disease progression and also possible complications and co-occurring diseases (14). Special indications to apply beta-blockers in monotherapy include young age, characteristics of hyperkinetic circulation and the lack of any other diseases implying secondary type of hypertension (3, 14).

Beta-adrenergic receptor blockers, similarly to other antihypertensive medicines, are not free from side-effects or even adverse ones. Adverse effects are the consequence of blocking beta-adrenergic receptors which are present in various organs of the organism.

Peristalsis and esophageal sphincter tonus are disturbed, constipations and dyspeptic disorders appear. Complaints connected with the first section of the alimentary tract can be particularly tiring for the patient (14). They can manifest themselves with dryness in the oral cavity and, quite often, gustatory sensibility disorders. Salivary gland tissues are abundantly equipped with beta-type adrenergic receptors, mainly $beta_1$ subtype (16). That fact allows to believe that the used beta-blockers are not without any effect on salivary gland physiology.

Saliva production and secretion are regulated by the autonomous nervous system (18, 22, 7). The process of saliva secretion is mainly controlled by the parasympathetic system. Nuclei of that system receive impulses from the sensory receptors of the tongue, oral cavity and from the centres converting olfactory, visual and acoustic stimuli (7, 18). Centrifugal fibres of the parasympathetic system lead to the parasympathetic ganglions: optic and submandibular ganglions. The postganglionic fibres of the submandibular ganglion supply secretion to submandibular and sublingual salivary glands through the facial nerve. The postganglionic fibres of the optic ganglion supply the parotid salivary gland through the glossopharyngeal nerve. Sympathetic innervation of all the salivary glands comes from the cervical ganglion of the sympathetic trunk. The role of the sympathetic system in increasing saliva secretion is considerably smaller than the one of the parasympathetic system. Stimulation of the sympathetic system has a larger impact on saliva composition than its amount. Stimulation of the sympathetic system results in a rise in noradrenaline secretion, which increases the secretion of

proteins, potassium and bicarbonate ions by salivary gland cells. Stimulation of the parasympathetic system causes a rise in acetylcholine secretion and, consequently, increased secretion of saliva rich in water and mineral elements (22).

The amount of secreted saliva varies individually. It is assumed that this value for unstimulated saliva should be at least 0.1 ml/min, for stimulated saliva, however, 0.2 ml/min. Any values below the ones above should be considered as hypofunction of the glands (8). In individual cases 50% reduction of saliva secretion should also be regarded as salivary gland insufficiency (7, 20). Mean volumes of saliva secreted within a minute are 0.3 ml/min, maximum secretion reaches 7 ml/min, and the total volume of saliva secreted during 16-hour activity is approximately 1500 ml.

A number of factors affect the amount and composition of produced saliva. The most crucial of them is the degree of the organism hydration. With the reduction of water content in human organism of about 8%, saliva secretion declines to zero. In the situation of overhydration saliva secretion increases. Another important factor is the body position. The more vertical it is the larger saliva secretion becomes. Light stimuli also have influence on the level of saliva secretion. In the dark the secretion falls by approx. 40%. 24-hour secretion rhythm is very characteristic. It changes within 24 hours according to the sinusoid. It reaches its minimum during sleep falling almost to zero, then gradually increases in the morning hours and reaches its maximum values in the afternoon hours (7). There was also observed a reduced saliva secretion connected with age, which is probably caused by morphological changes in large salivary glands related to ageing processes (10). A type of diet also affects the content of protein substances in saliva (11).

The amount of secreted saliva increases mainly in response to gustatory and mastication stimuli. Out of gustatory stimuli sour taste has the strongest action (e.g. 5% lemon acid increases saliva secretion to 7 ml/min) and it outdistances with its action power salty, bitter or sweet tastes (7). Mastication increases saliva secretion, simultaneously the secretion is larger when accompanied by gustatory stimuli. Salty taste increases protein content in parotid gland secretion, sour taste causes the production of saliva with more alkaline pH. Sublingual salivary glands, in which mucous cells prevail, secrete dense saliva, rich in glycoproteins. Parotid glands, with the prevalence of serous cells, mainly produce watery saliva, containing electrolytes, amylase and polypeptides. Submandibular salivary glands produce saliva with intermediate characteristics (7). The shares of particular salivary glands in saliva production are as follows: parotid glands – 20%, submandibular salivary glands – 65%, sublingual salivary glands – 7–8%, minor salivary glands of oral cavity about 7%.

Due to different compositions of saliva secreted in particular glands, an increase or decrease in saliva production by one of them automatically changes the composition of total saliva. In the situation of high saliva demand the dominating secretion role is taken over by the parotid gland, whose secretion share rises to approx. 50%, simultaneously the percentage content of organic substances in total saliva declines (7). Precise regulation of saliva composition and secretion in physiological conditions can be disturbed in salivary gland diseases and some other systemic diseases. Saliva composition and secretion can also be affected by some medicines.

Medical literature provides rather few reports on salivary glands functioning in patients with arterial hypertension before starting the therapy. Ben-Aryeh et al. (4, 21) report that saliva secretion in basic conditions in patients with arterial hypertension before the beginning of beta-blocker therapy is lower than in healthy people. The studies of van Hooffa et al. (23) imply that in arterial hypertension the influence of the parasympathetic system on salivary gland secretion is reduced. Some authors suppose that this could be the result of a reduced activity of the parasympathetic system in the pathogenesis of arterial hypertension (13, 19). These reports allow to suppose that all disturbances of the balance between the sympathetic and parasympathetic systems lead to disorders in saliva composition and secretion.

MATERIAL AND METHODS

The clinical examinations were conducted on a group of 76 people. The studied group comprised 44 patients treated for arterial hypertension with the selective beta-blocker *Metocard* produced by the company POLPHARMA. The patients diagnosed with no other systemic diseases apart from arterial hypertension were qualified for the study. The additional selection criterion was the monotherapy with the beta-blocker mentioned above and taking no other medications. All the patients received *Metocard* for the period of at least 6 months. The patients' average age was 27.4 years, the age range was from 19 to 38 years. During the study the control blood pressure measurements showed values ranging from 120 to 140 mm Hg for systolic pressure, and from 80 to 90 mm Hg for diastolic pressure, which implies the effective treatment of arterial hypertension.

The control group consisted of 32 healthy persons, aged from 20 to 36 years (on average 27.4), who were not on any form of medication, whose systolic pressure varied from 120 to 130 mm Hg, and diastolic pressure from 80 to 85 mm Hg, and these results were within the range of normal blood pressure values.

Saliva sampling. Saliva was collected into sterile disposable plastic test tubes in the conditions without stimulation, always between 9:00 and 11:00 hrs, but not earlier than 2 hours after the last meal. Before the test the patients rinsed their mouths with water. Saliva was collected into plastic graduated test tubes with the volume scale accuracy to 0.5 ml. The volumes of the collected saliva were recorded after 5 min.

Statistical analysis. Differences between variables were evaluated by means of Mann-Whitney non-parametric test. In the interpretation of statistical tests results 5% inference error was assumed. Consequently, relationships between variables were considered as statistically significant at the level of significance $p < 0.05$.

RESULTS

Mean results of determining saliva secretion rate in ml/min in the group of healthy people and patients with arterial hypertension treated with Metocard were presented in Table 1.

Table 1. Saliva secretion rate in the control group and studied group

Parameter	N	Control group	N	Studied group	p
		mean ± SD		mean ± SD	(Mann-Whitney test)
Secretion rate	32	0.867 ± 0.120	44	0.719 ± 0.211	p<0.001

As the table data imply, the rate of secreted saliva in the studied group was significantly lower than in healthy people. The results of saliva secretion rate measurements in both of the groups are illustrated by the diagram in Figure 1.

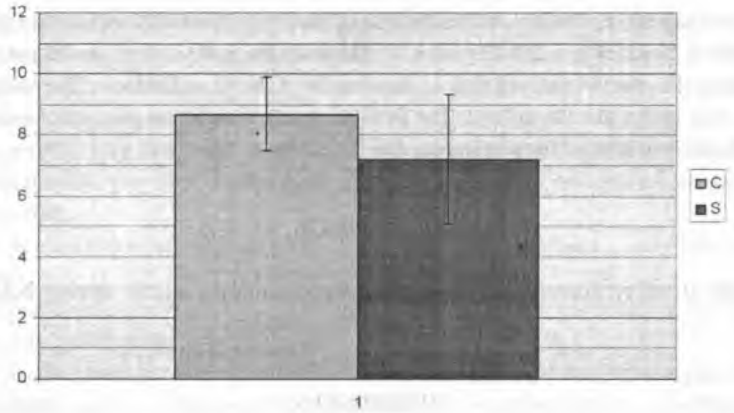

Fig. 1. Saliva secretion rate (ml/min) in control group (C) and studied group (S)

DISCUSSION

Appropriate composition and secretion of saliva are controlled by the autonomic (sympathetic and parasympathetic) nervous system, which innervates the salivary glands. Many diseases associated with the hyperfunction or hypofunction of the system, as well as medications affecting it, can have an effect on the composition and secretion of saliva. Salivary gland cells are equipped with beta-adrenergic receptors, mainly beta-1 subtype (5, 9, 16). These receptors are an action site of beta-adrenergic blockers used in the treatment of arterial hypertension.

The most frequently described side-effects of beta-blockers therapy are the disorders of the alimentary tract, especially of its first section, i.e. oral cavity. The disorders mainly affect the amount and, as it is supposed, composition of saliva. The parameter characterizing saliva secretion is its volume secreted within 1 minute. Most studies on the functioning of salivary glands in the course of beta-blocker therapy are based on experimental tests conducted on animals. Johnson and Cortez (12) report a reduced saliva secretion in rats during long-term metoprolol administration ($beta_1$-adrenergic antagonist). Similar conclusions result from the studies performed by Nederfors (15, 17) on the group of volunteers suffering from arterial hypertension and treated with beta-blocker. After the experimental cessation of drug administration the author describes an increase in the amount of secreted saliva to a level that remained the same for the following two weeks. Resuming of the drug administration resulted in a decrease in unstimulated saliva secretion from about 0.54 ml/min to approx. 0.46 ml/min.

In this study there was observed lower mean secretion of unstimulated saliva in comparison to the control group (0.72 ml/min and 0.87 ml/min). Perfect research conditions would be such conditions in which examined parameters could be compared in the same group before and after drug administration. Nevertheless, this study was conducted following the opinion and methodology accepted by Cowman et al. (6), Aarons (1) and Aarons et al. (2), who believe that in the case of patients already in treatment, cessation of drug administration is unacceptable for both ethical and medical reasons. Cowman et al. (6) conducted studies on the impact of beta-blockers on saliva secretion in relation to the patient's age. In the group of young people (aged 20–39) treated with selective beta-blocker they found a marked decrease in unstimulated saliva secretion by parotid glands as compared to the control group. As for submandibular salivary glands no similar relationships were observed. Adding up both test results one could expect a decline in the amount of secreted saliva in

relation to total saliva. The study was conducted on the group of patients and control group which were identical in terms of age (20–39 years). In this study the groups were considered as identical concerning age, the groups of young people, the same as in the quoted authors. The saliva analyzed in the study was total and unstimulated. The final results concerning the amount of secreted saliva correspond with the results of the presented authors.

CONCLUSION

The rate of saliva secretion is reduced at hypertention patients during beta-blockers treatment.

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SUMMARY

This study was an attempt to analyze the secretion rate of mixed saliva in patients with arterial hypertension, treated with beta-blocker. The study was conducted on a group of patients suffering from arterial hypertension, treated with the selective beta-blocker Metocard (the only medicine administered to the patients during the therapy). The study results were compared with the results of the control group which consisted of healthy individuals corresponding to the studied group in terms of sex and age. The people from the control group were not on any form of medication. A statistically significant decrease in saliva secretion rate was found in patients treated with beta-blocker.

Wydzielanie śliny u chorych na nadciśnienie tętnicze w przebiegu leczenia beta-blokerem

W pracy dokonano analizy szybkości wydzielania śliny mieszanej u osób chorych na nadciśnienie tętnicze, leczonych beta-blokerem. Badaniom poddano grupę chorych na nadciśnienie tętnicze, leczonych beta-blokerem selektywnym Metocard (jedyny lek stosowany przez chorych w trakcie terapii). Wyniki badań porównywano z wynikami badań grupy kontrolnej, którą stanowili ludzie zdrowi dobrani pod względem płci i wieku do grupy badanej. W grupie kontrolnej nie przyjmowano żadnych leków. Stwierdzono istotny statystycznie spadek szybkości wydzielania śliny u osób leczonych beta-blokerem.