Hypertension treatment in the young age and in the elderly

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Abstract
The review assesses the current guidelines of hypertension treatment in different age groups and pathophysiology of hypertension according to age. Specific questions concerning prevention of cognitive decline in the elderly are also discussed as well as target blood pressure levels and side effects of the drugs.
Key words: hypertension, elderly, cognitive dysfunction, candesartan.

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Молодой и пожилой пациент с артериальной гипертензией: особенности лечения

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Резюме
В обзоре приводятся данные современных рекомендаций по лечению артериальной гипертензии у пациентов различного возраста, а также патогенетические основы повышения артериального давления в зависимости от возраста. Помимо этого обсуждаются специфические

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проблемы целевых уровней артериального давления, профилактика когнитивных нарушений у пожилых, особенности побочных эффектов лекарств в различном возрасте.

Ключевые слова: артериальная гипертензия, возраст, когнитивная дисфункция, пожилые, кандесартан.

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Background

Worldwide efforts directed towards the elimination of negative demographic trends, aim, on one hand, at the birth rate increase, and, on the other hand — at mortality reduction, especially cardiovascular death rate. The control of the main cardiovascular risk factor in the elderly — hypertension (HTN) — is not only medical, but also a social issue. Preventive strategies are much less effective in elderly than in young persons. The high cost of therapy may be a barrier for successful risk factor control; therefore any recommendations for the treatment in the elderly patients should be verified regarding their cost and therapy effectiveness. On the contrary, young hypertensive patient is a candidate for lifelong treatment, therefore the long-term effects, including effect on target organs, treatment acceptability become the most important factors. In special sections of the recent European guidelines HTN management in young patients and patients with cognitive dysfunction, which include vast majority of the elderly, is discussed [1].

Hypertension epidemiology and the age

The prevalence of hypertension progressively increases with the age. Among adolescents and persons under 30 years, hypertension is more common in males, while in elder people, hypertension prevalence increases among women. People from 40 to 59 years old have at least twice lower prevalence of hypertension than the elderly [2]. According to the last data HTN is detected in two-thirds of the population older than 60 years and three-quarters of the population older than 75 years [3]. Isolated systolic hypertension (ISAH) has the biggest impact because of pathophysiological mechanisms: impaired baroreflex (regulator of blood pressure and vascular reactivity, and renal mechanisms) plays the leading role in blood pressure (BP) elevation in young age. In the older age, the main mechanisms include changes in vascular wall — reduction of elasticity and increase of rigidity. This leads to an increase in systolic BP (SBP), as well as to diastolic BP decrease (DBP), resulting in the increased pulse pressure, which is an independent cardiovascular risk factor [4].

The mortality rate from coronary heart disease in older patients with HTN is three times higher than in normotensive patients of the same age [5]. Undiagnosed myocardial infarctions are most often observed in the elderly patients, and the most typical — in patients with HTN. Thus, electrocardiography should be performed annually in the elderly people with HTN [6]. In elderly people, as well as in general population of hypertensive patients, left ventricular hypertrophy (LVH) is an independent risk factor, which is also partly due to the high pulse BP and its negative effects on the myocardium [7, 8].

Target organ damage, including renal function disorders, silent myocardial infarction, transitory ischemic attack, retinopathy, usually is found in elderly hypertensive patients. According to the Framingham study, at least 60% of older men and 50% of women of the same age, has at least one of these complications [9]. Thus, they should be at once referred as a high-risk group, and require intensive therapy. In addition, HTN itself can lead to encephalopathy and acute heart failure. Isolated HTN is observed in less than 20% patients. In the elderly HTN often is a component of metabolic syndrome also leading to the increased risk and requiring special treatment approach [10].

Pathophysiology of hypertension in different age groups

The elasticity of the arteries is determined by media layer. There is an interaction between

elastic membrane and smooth muscles in media of the aorta and its major branches. Thus, the resulted elastic-contractile elements can develop maximal resistance in response for vascular stretching. Abdominal aorta contains more elastin than collagen, but moving along the vascular tree towards smaller arterial branches collagen becomes predominant. At each systole, SBP tension goes down from aorta to peripheral vessels.

Elastin is the most stable protein — its half-life period is about 40 years. Despite its stability, 2 billion heartbeats during 60 years of human life cause gradual fragmentation of elastin fibers and laminae, which is accompanied by changes in extracellular matrix, in particular, collagen production and calcium deposits. This diffuse degenerative process leads to an increase in vascular stiffness and enlarged pulse pressure [11].

Hemodynamics in young hypertensive subjects is characterized by initial high cardiac output (CO) with the subsequent development of persistent increase in peripheral resistance. In contrast, in the elderly patients with HTN, normal or even low CO is combined with a slight increase in the peripheral resistance and significant increase in aorta stiffness. The main differences in HTN pathogenesis between young and elder patients are listed in table 1 [12]. Many authors believe that HTN developing in young and elderly age presents two different diseases, and suggest new classification of HTN based on the level of vascular lesion [13] (tab. 2).

According to Framingham study, only 40 % of subjects with isolated systolic HTN developed systole-diastolic HTN in younger age. The remaining 60 % patients develop isolated systolic HTN starting with "high normal" BP [13].

Table 1

THE MAIN AGE DIFFERENCES IN HEMODYNAMICS IN HYPERTENSION (MODIFIED FROM [12])

Young patients	Older patients
Normal elastin	Elastin degeneration
High or normal cardiac output	Normal or low cardiac output
Normal and then elevated peripheral resistance	Normal or slightly elevated peripheral resistance
Functional increase of arterial stiffness	Structural increase of arterial stiffness
Systolic or isolated diastolic hypertension	Isolated systolic hypertension
Normal pulse pressure	High pulse pressure

Table 2

HYPERTENSION CLASSIFICATION ACCORDING TO LEVEL AND MECHANISM OF ARTERIAL DAMAGE (IZZO J., 2008 [13])

Type	Mechanisms	Clinical manifestation
Arteriolar hypertension	Arterial stiffness elevation	Diastolic and average BP elevation
Hypertension of large arteries	Aorta impedance elevation	Isolated systolic HTN and pulse pressure elevation
Neurovascular hypertension	Changes in central regulatory conrol, reflexes and vascular reactivity	"White coat" HTN, postural hypotension, BP variability elevation

Increasing vascular stiffness leads to higher amplitude of reflected pulse wave, which cause pulse pressure growth and as a result, further increasing of vascular stiffness [11, 12]. In young patients, reflected wave returns to the ascending aorta during diastole and lead to the increase in DBP and mean arterial pressure and coronary perfusion. In this case, there is a physiological phenomenon of SBP and DBP amplification. Therefore, the pressure on the brachial artery is 15–25 mm Hg higher than in aorta. From 20 to 70 years, vascular stiffness cause doubling of pulse wave velocity (PWV). As a result, the reflected wave returns to aorta much earlier — during late systole, increasing SBP, which leads to DBP decrease and increase of pulse BP.

It should be noted that patients with isolated systolic HTN have higher risk compared to subjects with non-isolated systolic HTN and comparable SBP values: European guidelines for hypertension 2007 included pulse pressure in the elderly as a risk factor and suggested to refer all patients with SBP ≥ 160 mm Hg and DBP < 70 mm Hg to the high-risk group. Thus, the cardiovascular risk evaluated by SBP in an elderly patient should be reassessed based on the pulse BP value [13].

Target BP values

Target BP for young people according to novel recommendations is not higher than 140/90 mm Hg. However, experts disagree about target BP levels in elderly patients. In general, the benefits of HTN treatment in older age is indisputable and proven by great number of studies and meta-analyses. Before 2008, active treatment of elderly patients was valid only for people under 80 years old. However, the experts recognized that in case of effective and well-tolerated treatment it should be continued when the patient reaches 80 years old, and there is no reason for its withdrawal or modification. HYVET study [14] showed indisputable benefits of treatment of HTN in this subgroup — 21% mortality reduction, 30% decrease in stroke rate (fatal — 39%) and 64% reduction in the risk of heart failure development.

According to the European Guidelines 2013, the recommended target BP level is below 140–150 mm Hg for patients younger than 80 years with SBP ≥ 160 mm Hg. In patients with satisfactory performance status, SBP reduction below 140 mm Hg might be appropriate. In persons older than 80 years with an initial SBP ≥ 160 mm Hg reduction of SBP below 140–150 mm Hg is recommended in case of satisfactory physical and mental health. When hypertensive patient reaches 80 years old, the treatment should be continued if it is well tolerated. American guidelines JNC 8 take target blood pressure for people over 60 years as 150 mm Hg, which has been criticized by other experts [15].

In younger patients, despite the absence of clear data from randomized clinical trials, treatment of persistent HTN is recommended, especially when associated with other risk factors. In case of isolated SBP elevation and "white-coat" HTN without organ damage the patients should be followed-up. Beta-blockers are not the first-line drugs in young [1].

It is important to note, that the treatment is expected to be long-term in young patients, so there is a high risk of side effects and poor compliance. Thus, the drugs with good tolerability and favorable metabolic profile (slowing cardiovascular remodeling, kidney and other organ damage) should be preferred. Angiotensin II receptor blockers have optimal tolerability profile and a large number of proven organoprotective properties (but they are forbidden in pregnancy and young women planning pregnancy). In particular, candesartan favorably affects left ventricular and vascular wall remodeling, as well as carbohydrate and lipid exchange. Low BP variability during the day, good tolerance with a single daily dosing contribute to higher compliance. Long-lasting effect enables high BP control even in case of single dose missing.

HTN treatment approaches in elderly patients are based on clinical trial data. Almost all classes of antihypertensive drugs (including beta-blockers) have proven high efficiency in elderly patients regarding morbidity and mortality reduction. Thus, all classes of antihypertensive

About the League

The "Antihypertensive League" is a nation-wide non-governmental organization created to combine efforts in combating such socially significant cardiovascular diseases as hypertension and its complications.

Membership in the organization is voluntary. It unites the leading experts in cardiology from more than 40 regions of Russia.

The activities of the League are carried out under the guidance of the President, Professor N.V.Nedogoda, M.D., Ph.D. Regional offices are headed by the leading Russian cardiologists — members of the League's Council.

The "Antihypertensive League" plays a major role in the organization of cardiological congresses, seminars and conferences nation-wide. Members of the League also take part in international cardiological events in order to join forces with the leading specialists from all over the world.

We work closely together with such organizations as:
- The Russian Scientific Society of Cardiology (BHOK);
- International Hypertension League;
- European Society of Hypertension;
- The North-Western Division of the Russian Academy of Medical Sciences.

Members of the League actively participate in the development of clinical guidelines for practicing physicians.

One of the League's major activities is organization of instructional courses for patients with cardiac risk factors — "The School for Cardiological patients".

drugs can be used in elderly patients, although diuretics and calcium channel blockers should be preferred in isolated systolic HTN. BP reduction is highly significant in elderly patients considering cardiovascular prevention due to the high rate of cardiovascular complications. The stroke incidence was reduced by 37–47 % in treated elderly patients with HTN.

There are two main obstacles in reaching target BP in elder patients — high SBP and low DBP. There are certain difficulties in reaching target SBP in isolated systolic HTN. Moreover, low DBP might be associated with the higher risk. Neurologists are arguing for setting low BP threshold, as BP decrease leads to the impairment in autoregulation of cerebral blood flow and higher risk of cerebrovascular events. However, clinical trial data are controversial. Some researchers show higher risk in patients with DBP below 70 mm Hg (SHEP study [16]), others demonstrated that DBP decrease even till 55 mm Hg was not associated with worse prognosis [17]. A meta-analysis of several studies have shown that BP reduction below 120/60 mm Hg was accompanied by an increased risk, but causal relationship between treatment and risk was not proven. In general, a safe low BP level in the elderly should still be clarified. Perhaps, the most rational solution of this issue is an indication that target BP achievement should be accorded with good tolerance. The latter is stated in all available guidelines. However, this can lead to higher "medical inertia" as gives legal grounds to limit target BP achievement.

Like other patient groups, hypertension treatment in elderly should be started with lifestyle changes — weight and salt consumption reduction, physical activity, but these measures have well-known limitations in old patients [18].

Current guidelines recommend combined therapy in most elderly patients. Thus, the drug choice appears to be not so important. ACE inhibitors and their combination with low doses diuretics are highly effective in this subgroup. According to some authors, angiotensin II receptor blockers (ARB) have better tolerability and lower risk of hypotension, compared to angiotensin converting enzyme (ACE) inhibitors, in this group [19].

Most of the patients require combination treatment (two drugs and more). The ideal medication is a well-tolerated and with low risk of adverse effects. Antihypertensive treatment of elderly patients is associated with the decreased mortality and risk of myocardial infarction, stroke, kidney disease and dementia.

Recent epidemiology data demonstrated that dementia is present in 24 millions of living people, with 60 % rate in developed countries [20]. Different types of cognitive impairment occur in elderly (Alzheimer disease, vascular dementia, dementia of mixed origin), However, HTN is the common risk factor for all of them, and antihypertensive treatment reduces cognitive decline progression. Calcium channel blockers and ARB are preferred drugs in cognitive decline prevention. MOSES [22] and OSCAR studies [23] demonstrated possible cognitive function improvement in hypertensive patients, receiving ARB. The tolerability of antihypertensive treatment in patients with cognitive decline is a disputable topic. The treatment should be reduced or withdrawn when it is associated with cognitive function worsening. Later therapy might be restarted in order to goal BP achievement. One of the biggest prospective, randomized, double-blind, parallel study — the SCOPE study (Study on COgnition and Prognosis in the Elderly) [24] included 4937 elderly patients with HTN with 3–5 years of follow-up (18445 patient-year follow-up). The primary endpoints were cardiovascular mortality, nonfatal stroke and nonfatal myocard ial infarction incidence. Patients received either candesartan (Atacand, AstraZeneca, Sweden) at a dosage of 8–16 mg per day or standard therapy. Primary endpoint was registered in 242 patients receiving candesartan and in 268 subjects in the control group, constituting 10,9 % risk reduction (95 % confidence interval from –6,0 to 25,1, p = 0,19). Overall, the study demonstrated the effects of candesartan for cardiovascular prevention. It showed a non-significant reduction in the risk of any stroke (by 24 %) in the candesartan group

(p = 0.056), significant nonfatal stroke risk reduction (by 28%) in candesartan group (p = 0.04), as well as significant reduction in the risk of fatal and non-fatal stroke (by 42%) in patients with isolated systolic HTN in candesartan group (p = 0.049). The substudy did not show any difference in cognitive function, although in candesartan group there was an increase in attention level and episodic memory.

It should be noted that an elderly patient has high risk of adverse events incidence due to the drug-food interactions and features of pharmacodynamics and pharmacokinetics [25]. Concomitant diseases, polypragmasia, different nutrition disorders and metabolism impairment increase the risk. Anorexia, intestinal diseases, dementia, depressive disorders, social and economic factors affect pharmacodynamics in elderly patients. Visual, mechanical and swallowing impairment should be also considered. Personal characteristics and medical condition, life style and concomitant diseases should be taken into account when individual treatment approach is developed.

The certain reasons for low BP control in elderly are well understood, while the approaches are unclear. SBP is difficult to be controlled, and age is an independent risk factor preventing SBP reduction. SBP decrease is less efficient in elderly compared to young patients, and more profound reduction is required.

Several studies suggest that persons older than 75 years may have difficulties with the correct intake of some medicines, as well as just with the removing drugs from the blisters. Sometimes they also cannot follow the treatment regimen everyday. Visual disorders causes difficulties in reading drug instructions and prescriptions. Thus, planning the treatment of an elderly patient these issues should be addressed, and long-lasting drugs and fixed drug combinations are preferred. Otherwise, we risk to recommend very effective treatment, that patients will not be able to take [26–30].

In summary, ARB have certain advantages in elderly patients: good tolerability, long-lasting effects (intake once per day), decrease of BP variability and the risk of orthostatic reactions, decreased risk of dose missing, organoprotection, in particular, reductions of the risk of stroke and cognitive decline, and possibility of combination treatment with thiazide diuretics and calcium channel antagonists.

Conclusions

In general, our understanding of the pathophysiology and optimal treatment of HTN in patients of different age has recently advanced due to the reevaluation of pulse BP role, data regarding necessity of HTN treatment at any age, effects of treatment with various drugs and combinations. However, a number of issues, especially concerning optimal treatment strategy, remains unanswered. What is the prognostic role and optimal treatment in young patients? Is there an ideal treatment, providing improvement to elastic properties of the arteries? How aggressive should be the treatment in elderly patients, especially in presence of dementia? All of these issues will be clarified in future. However, it is clear now, that HTN pathogenesis in young and elderly people are different requiring distinct diagnostic and treatment approaches.

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