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Case report

Treatment of patients with hypertension and high cardiovascular risk

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Abstract Hypertension with high cardiovascular (CV) risk is characterized by significant increase of one of the risk factors, especially cholesterol above 8 mmol/l in, for instance, familial hypercholesterolemia, or blood pressure (BP) ≥180/110 mmHg (stage III hypertension), diabetes mellitus, hypertensive left ventricular hypertrophy (LVH), moderate chronic renal failure with eGFR of 30-59 mL/min/1.73 m^2 and/or calculated 10-year SCORE of 5-10%.

Case report: We presented in this paper a patient with hypertension and high risk in whom diastolic hypertension, left ventricular hypertrophy, metabolic syndrome and obesity were predominant in the beginning, while diabetes mellitus prevailed in the further disease course. We presented the diagnostic protocol, as well as the risk assessment according to the European and American guidelines, and a proper selection of non-medicamentous and medicamentous therapy. The patient was treated and observed for 20 years, and the therapy based on the official hypertension guidelines was able to prevent major cardiovascular events and to suspend the progression of target organ damage in hypertension.

Conclusion: Proper risk assessment in hypertensive patients, presence of risk factors and target organ damage have a decisive role in the selection of adequate therapy in hypertension. Achievement of target BP values, control of risk factors and regression of target organ damage constitute the basis of good quality of life of hypertensive patients and prevention of major cardiovascular events.

Key words hypertension, left ventricular hypertrophy, metabolic syndrome, diabetes mellitus

Introduction

According to the categorization of 10-year cardiovascular (CV) risk (the SCORE system), the patients with hypertension who have a high CV risk are the individuals with one of the following characteristics: a significant increase of one of the risk factors, especially cholesterol above 8 mmol/l in, for instance, familial hypercholesterolemia, or blood pressure (BP) ≥180/110 mmHg (stage III hypertension), diabetes mellitus, hypertensive left ventricular hypertrophy (LVH), moderate chronic renal failure with eGFR of 30-59 mL/min/1.73 m^2 and/or calculated 10-year SCORE of 5-10%[1,2]. These high risk patients require special diagnostic and therapeutic approach for the purpose of prevention of major cardiovascular events and further target organ damage in hypertension, with an adequate level of quality of life. This can be accomplished by achieving and maintaining the recommended target BP values and by controlling other present risk factors.

Case report

A 49 years old man with hypertension was referred for examination and complete diagnostic management to the Out-patient Department for Hypertension in October 1999. At the first examination, his BP values were 140/110 mmHg, which were classified as stage III hypertension according to the European Guidelines for Hypertension at that time (1999) (and all the later European guidelines for that matter)[3]. Of all the risk factors, obesity should be mentioned (BMI of 31 kg/m^2, with waist circumference of 119 cm – abdominal obesity), as well as the level of sugar of 6.2 mmol/l, and the patient fulfilled three out of five metabolic syndrome criteria[4]. During the first month, complete diagnostic management was done, involving the assessment of target organ damage: heart (electrocardiography, echocardiography, exercise stress test, 24-hour blood pressure monitoring, Holter ECG), blood vessels (Doppler ultrasound of the carotid arteries and abdominal aorta), kidneys (estimated glomerular filtration rate and microalbuminuria). On 24-hour monitoring, hypertensive values above the normal were found (135/93 mmHg) (systolic-diastolic hypertension), with a physiological nocturnal BP drop (dipper). Echocardiographically, concentric LVH was confirmed (with septum thickness of 13 mm, and posterior wall thickness of 12.5 mm, and with left ventricular mass index (LVMI) of 150 g/m^2)[5]. Exercise stress test was

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Table 1. Clinical variables of treated patients during the examined period

	1998	2000	2014	2019
SCORE ESH risk	3 High to very high	3 High	5-10 High	3 Moderate to high-risk
BP	140/110; 82	140/95; 58	146/91; 72	137/88; 72
Glucose Glycosylated HbA1C	6 mmol/l -	5.3 -	26.4 8.6%	10.08 5.9%
Cholesterol	5.3	5.34	5.29	5.1
LDL cholesterol	3.3	3.4	2.28	3.01
HDL cholesterol	1.1	1.3	1.1	1.22
Triglicerides	1.18	1.76	4.25	1.87
Creatinine	99	84	108.4	97
BMI	30.7	29.2	35	31
MS	yes	no	yes	no
Smoker	no	no	no	no

SCORE, Systematic Coronary Risk Estimation; BP, blood pressure; BMI, body mass index; MS, metabolic syndrome

Table 2. Selected diagnostic parameters of treated patients during the examined period

	1998	2000	2014	2019
ECG LVH ECHO LVH LVM index (g/m^2) IVSd (mm) Type LVH E/A LA	no yes 150 13 C 0.78 44	no yes 137,6; 12.5 END 1 40	no yes 157.5 14 END 0,72 52	no yes 150.9 14.4 END 0,88 50
24 ambulatory monitoring BP	135/93; 74; dipper;	129/86; 60	137/86; 68	128/84; 72
Holter ECG SDNN	17 SVES 115	20 SVES 120	4 VES, 5 SVES 164	5 VES, 24 SVES 122
Exercise testing	negative	negative	Negative	negative
Dopler carotid artery IMC	Without plaqe	Without plaqe	Without plaqe 0.85	Without plaqe 0.8
Therapy	Amlodipin 5	Enalapril 20 Amloidpin 5	Ramipril 10 Felodipin 10 Spirinolactone 25	Ramipril/ Felodipin 10/10 fixed comb Spirinolactone 25
Phisical activity	Walking 5 km day	Irregular walking	Weight gain 11 kg	Walking 10 km day

ECG, electrocardiogram; LVH, left ventricular hypertrophy; ECHO, ehocardiography; LVM, left ventricular mass; IVSd, septum in diastole; LA, left atrium; BP, blood pressure; SDNN, standard deviation NN interval; SVES, extrasistole suoaventricularis; VES extrasistole ventrisularis; IMC, itima media thickness

negative for ischemia, and Holter ECG demonstrated a low frequency of arrhythimias, with normal heart rate variability (HRV) expressed over time domain SDDN. Examination of the carotid arteries with intima-media complex measurement and renal examination yielded normal findings.

The treatment for this patient was initiated with recommendations of moderate physical activity, dietary salt restriction, weight-reduction advice, and 5 mg Amlodipin was introduced as well. A month afterwards, 5mg Ramipril was added (BP, 135/100 mmHg), so that two months after that BP values were below 140/90 mmHg. The patient was regularly monitored (in three-month intervals in the first year, and after that every 6 months). Once a year, echocardiography and exercise stress test were performed. In 5-year intervals, Doppler ultrasound of the carotid arteries, 24-hour BP monitoring and Holter ECG were done.

Until 2014, both BP and metabolic status were adequately maintained. In 2014 the patient gained 11 kg BW, and high blood sugar values of 26.4 mmol/l were detected. A diabetologist was involved in the treatment, and he recommended more intense physical activity, a strict dietary regimen, weight reduction and metformin administration. Due to poorer BP regulation, the patient was on full-dose therapy with three drugs: 10 mg Ramipril, 10 mg felodipine, and 25 mg spironolactone.

At his last control visit to the Department in March 2019, a complete examination was done again, showing that after 20 years of follow-up and treatment in accordance with the official recommendations, the patient had well regulated diastolic hypertension (137/86 mmHg on 24-hour monitoring), a satisfactory lipid status, well controlled diabetes mellitus (glycosylated hemoglobin a1C, 5.9%), and the mass of the left ventricle was not significantly higher (septum 14.4 and LVMI 150.9 g/m^2). The exercise stress test was negative for ischemia, Holter ECG recorded a low frequency of extrasystoles and SDNN was 122. Carotid artery Doppler ultrasound did not detect any plaques, and renal function was preserved. In addition to his regular triple-drug therapy and metformine, the patient walks for about 10 km every day.

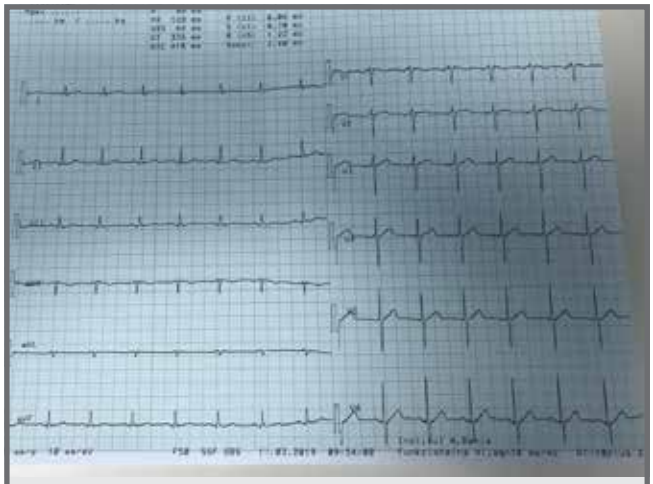

Figure 1. ECG in patient with ECHO LVH

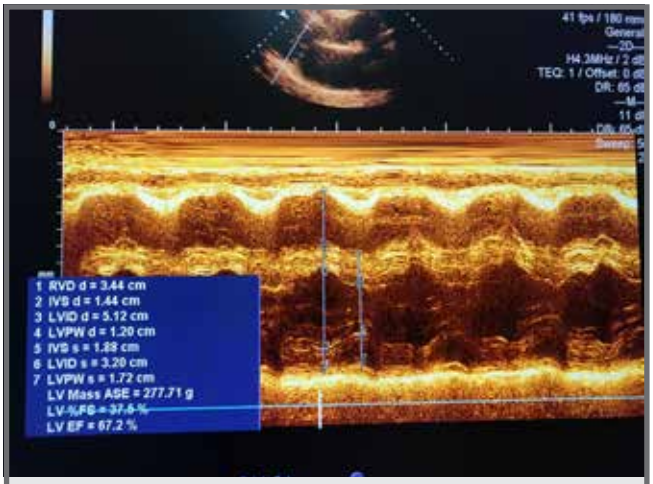

Figure 2. Reconstruction of anatomical M-mode images from 2D images and measuring and calculation LVM – patients with echo LVH

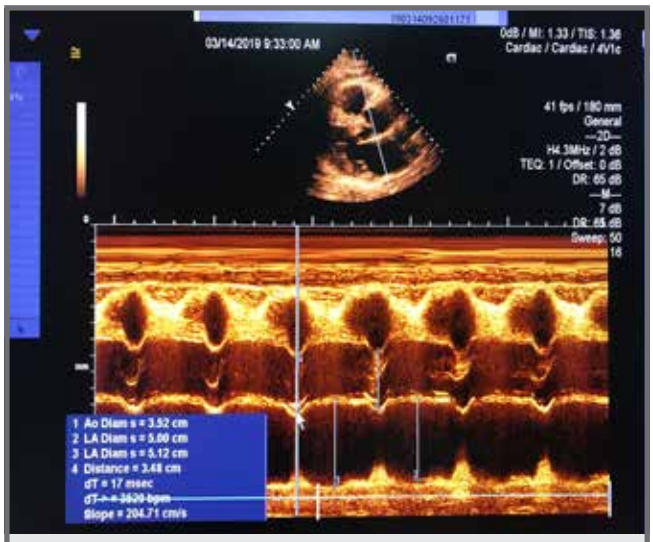

Figure 3. Reconstruction of anatomical M-mode images from 2D images and measuring aortae and left atrium – patients with echo LVH

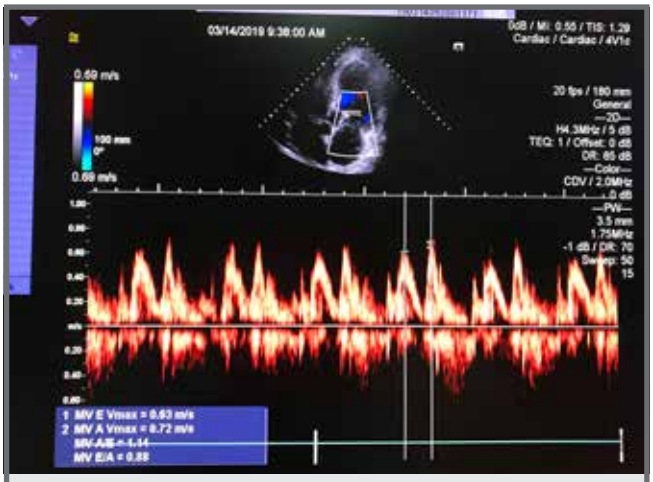

Figure 4. Doppler values for diastolic measurements

Discussion

The aim of this case report was to emphasize the importance of complete diagnostic management of hypertensive patients, importance of regular and adequate follow-up, and the potential to bring about benefits for the patient, preventing major adverse cardiovascular events, stopping further target organ damage with the maintenance of adequate quality of life of the patient.

BP measurement is the simplest screening method in medicine, invaluable in patient risk estimations. The measured BP values (diastolic BP values: 110 mmHg, according to the latest guidelines of 2018 were stage III hypertension according to the European guidelines, and stage 2 according to the American guidelines)[2,6] at patient presentation classified our patient among the hypertensive high risk patients. Our preliminary results have shown that 10-year mortality of these patients is about 10%, suggesting the need for an adequate diagnostic and therapeutic approach. This also agrees with the SCORE system risk estimation of 5-10% for these patients (the European Prevention Guidelines)[1].

Both European and American guidelines[2,6] have stressed the importance of precise BP measurements. Ambulatory BP measurements are still of principal value as to the institution of therapy, but the great importance of 24-hour ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) is nevertheless stressed as well. In our patient, the average 24-hour BP value was 135/93 mmHg, which exceeded normal values in both the European and American guidelines (≥130/80 mmHg). After one year of therapy, the average BP value was 129/86 mmHg in our patient.

The main modifiable risk factor in our patient was obesity, especially the abdominal obesity type. According to the ATP III, our patient had metabolic syndrome (3 out of 5 components were present)[4].

Both these and earlier guidelines have paid special attention to the estimation of target organ damage in hypertension and treatments which should be adjusted to the level of damage of these organs in individual patients. The European Guidelines of 2013[7] presented the assessment of diagnostic methods in relation to their predictive significance, but also related to their availability and examination costs. ECG, echocardiography, estimated glomerular filtration rate, microalbuminemia, and measurement of the thickness of intima-media complex are the methods with the best ratio of predic-

tive significance, availability and costs. In the latest ESH guidelines of 2018[2], the significance of these methods in the monitoring of hypertensive patients was presented based on their sensitivity to changes, reproducibility of findings, and prognostic value of changes. Cardiac MRI-assessed left ventricular hypertrophy, urinary protein excretion and pulse wave velocity have the greatest sensitivity. ECG-assessed left ventricular hypertrophy, cardiac MRI-assessed left ventricular hypertrophy, and estimated glomerular filtration rate have the best reproducibility, while the greatest prognostic value has been reported for ECG-assessed left ventricular hypertrophy, echocardiography-assessed left ventricular hypertrophy, and estimated glomerular filtration rate. In the American guidelines, in addition to the above examinations, pulse wave velocity measurement, measurement of the thickness of intima-media complex, coronary artery calcium score and echocardiography- and MRI-assessed left ventricular mass.

Based on our diagnostic methods, we came to the conclusion that our patient was a high risk hypertensive individual with metabolic syndrome and left ventricular hypertrophy. The aim of the therapy was to achieve and maintain target BP values with both non-pharmacological and pharmacological treatments. The target BP value, according to the earlier ESH guidelines, was <140/90 mmHg for individuals with LVH, and according to the 2018 guidelines 120-130 mmHg, similar to the American 2017 guidelines[6].

Any treatment of hypertension, similar to that in our patient, involves non-pharmacological approaches, primarily weight reduction, dietary salt restriction and increased physical activity. It would be excellent if the ideal weight could be achieved; however, our patient lost mostly 1-2 kg until 2014, when he suddenly gained weight and got diabetes. After that, in the period from 2014 to 2019, he lost 13 kg BW, which had a beneficial effect on BP control. He also icreased the level of his physical activity and in the period from the onset of diabetes mellitus, he walked about 10 km a day. According to the data from the American guidelines, any BW reduction of 1 kg reduces systolic BP by 1 mmHg, the level of dietary salt restriction to below 1500 mg daily reduces BP by 5-6 mmHg, and regular physical activity further reduces BP by 5-8 mmHg.

The choice of antihypertensive drugs in our patient depended on the presence of metabolic syndrome and LVH. Since ECG was normal and cardiac ultrasound was done in the month after the first examination, the treatment could be initiated immediately with 5 mg Amlodipine. After echocardiography and diagnosis of concentric LVH[5] with left atrial enlargement and impaired diastolic relaxation, in addition to the presence of metabolic syndrome, the treatment of our patient was continued with two drugs: an ACE inhibitor, Enalapril, and a calcium antagonist, Amplodipine. In order to achieve better drug tolerance, amlodipine was replaced with felodipine. According to the 2007 ESH recommendations[8], the treatment can be started with monotherapy in hypertensive patients with low or intermediate risk, while the combinations of two drugs from different groups are reserved for high risk individuals. For patients with LVH, the drugs of choice belong to the groups of ACE inhibitors, calcium antagonists or angiotensin II receptor blockers (ARBs). According to the 2018 ESH guidelines, RAS blockers combined with calcium antagonists or diuretics are recommended for patients with LVH (class I recommendation; A level of evidence). Systolic BP should be reduced to the range 120-130 mmHg. These groups of drugs are also first line treatments for patients with metabolic syndrome, combined with thiazides/thiazide-like diuretics. The target systolic BP is 130 mmHg and below, if tolerated, but not below 120 mmHg. The target diastolic BP is <80 mmHg, but not below 70 mmHg.

Until 2013 the patient was on combined therapy with 10 mg ramipril and 10 mg felodipin, and with such an approach his BP was below 140/80 mmHg, and then 25 mg spironolactone was introduced due to poorer BP control. At that time, high blood sugar values were reported and the diagnosis of diabetes mellitus was established. The therapy with metformin was introduced by his endocrinologist, and ramipril plus felodipine fixed drug combination was supplemented with a highly selective beta-blocker, Nebivolol at 2.5 mg. An increased level of physical activity accompanied this medicamentous therapy, and the patient walked about 10 km a day, reducing his BW by 13 kg in the following five years. Such a therapy with four antihypertensive drugs in combination was continued until the last control visit, which demonstrated adequate BP control, with 130/80 mmHg. Comparing the new ultrasound findings to those 20 years ago, a mild thickening of the septum was observed, as well as mild left atrial enlargement, improvement of diastolic relaxation, with preserved global contractile function. Physical exercise stress tests were always negative for ischemia, Doppler ultrasound examination of the carotids showed normal intima-media thickness, and Holter ECG revealed a low frequency of extrasystoles with normal cardiac heartbeat variability.

The whole years-long therapy of the patient reported here was designed in accordance with the recommendations from the guidelines, and later adjusted in accordance with the American and European guidelines. The fundamental goal of antihypertensive treatment has been achieved: the patient has not experienced any major cardiovascular event and further progression of target organ damage (especially left ventricular hypertrophy) has been suspended. The main obstacle to adequate treatment was the patient's obesity at the beginning of therapy, which further on was the main culprit in the development of diabetes. However, a significant weight reduction was achieved later on. Adequate glycoregulation was achieved and the onset of diabetes-induced micro- and macrovascular complications was prevented[1].

Conclusion

The therapy of hypertension takes long, involves the combination of non-pharmacological with pharmacological approaches, including the use and modification of antihypertensive drugs depending on

the associated risk factors, target organ damage and accompanying comorbid conditions. Abiding by the healthy lifestyles and regular medicamentous therapy are able to prevent major cardiovascular events in hypertensive patients.

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Sažetak

Tretman pacijenata sa hiprtenzijom i visokim kardiovaskularnim rizikom rizikom

Hipertenziju sa visokim kardiovaskularnim (KV) rizikom karakteriše: značajno povećanje jednog faktora rizika, pogotovu holesterola >8 mmol/l npr. Familijarna hiperholesterolemija, ili krvnog pritiska (KP) ≥180/110 mmHg (hipertenzija trećeg stepena), diabetes melitus, hipertenzivna hipetrofija leve komore (HLK), umerena hronična bubrežna insuficijencija sa eGFR 30-59 mL/min/1.73 m^2 i/ili izračunat 10-godišnji SCORE 5-10%.

Prikaz slučaja: *pikazali smo slučaj pacienta sa hipertenzijom i visokim rizikom kod koga je dominantna bila dijastolna hipertenzija, hipertrofija leve komore, metabolički sindrom i gojaznost na početku a diabetes mellitus u daljem toku. Prakazali smo dijagnostički protokol kao i procena rizika prema evropskim i američkim vodičima, kao i pravi izbor nemedikamentne i medikamentne terpije. Pacijent je lečen i praćen 20 godina a terapija zasnovana na vodičima za hipertenziju uspela je da prevenira velike kardiovaskularne događaje i zaustavi porgresiju oštećenja ciljnih organa u hipertenziji.*

Zaključak: *Pravilna procena rizika kod hipertenzivnih pacijenata, prisustva faktora rizika i oštećenja ciljnih organa odlučujući su u izboru prave terapije hipertenzije. Dostizanje ciljnih vrednosti, kontrola faktora rizika i regresija oštećenja ciljnih organa osnova su dobrog kvaliteta života pacijenata i prevencije velikih kardiovaskularnih događaja.*

Ključne reči: *hipertenzija, hipetrofija leve komore, metabolički sindrom, diabetes mellitus*