The Significance of Amlodipine on Autonomic Nervous System Adjustment (ANSA Method): A New Approach in the Treatment of Hypertension

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SUMMARY

Introduction Cardiovascular autonomic modulation is altered in patients with essential hypertension.

Objective To evaluate acute and long-term effects of amlodipine on cardiovascular autonomic function and haemodynamic status in patients with mild essential hypertension.

Methods Ninety patients (43 male, mean age 52.12 ±10.7) years with mild hypertension were tested before, 30 minutes after the first 5 mg oral dose of amlodipine and three weeks after monotherapy with amlodipine. A comprehensive study protocol was done including finger blood pressure variability (BPV) and heart rate variability (HRV) beat-to-beat analysis with impedance cardiography, ECG with software short-term HRV and nonlinear analysis, 24-hour Holter ECG monitoring with QT and HRV analysis, 24-hour blood pressure (BP) monitoring with systolic and diastolic BPV analysis, cardiovascular autonomic reflex tests, cold pressure test, mental stress test. The patients were also divided into sympathetic and parasympathetic groups, depending on predominance in short time spectral analysis of sympathovagal balance according to low frequency and high frequency values.

Results We confirmed a significant systolic and diastolic BP reduction, and a reduction of pulse pressure during day, night and early morning hours. The reduction of supraventricular and ventricular ectopic beats during the night was also achieved with therapy, but without statistical significance. The increment of sympathetic activity in early phase of amlodipine therapy was without statistical significance and persistence of sympathetic predominance after a few weeks of therapy detected based on the results of short-term spectral HRV analysis. All time domain parameters of long-term HRV analysis were decreased and low frequency amongst spectral parameters. Amlodipne reduced baroreflex sensitivity after three weeks of therapy, but increased it immediately after the administration of the first dose.

Conclusion The results of the study showed that amlodipine affected autonomic modulation as a shift to sympathetic hyperactivity, but without statistical significance. In the selected group of patients with vagal predominance in sympathovagal balance, amlodipine increased sympathetic and decreases vagal activity. Therefore we conclude that amlodipine mostly exerts impact on autonomic function modulation in patients with vagal predominance in resting state.

Keywords: amlodipine; hypertension; autonomic function; heart rate variability; haemodynamic; baroreflex sensitivity

INTRODUCTION

Cardiovascular autonomic modulation is altered in patients with essential hypertension [1, 2]. Sympathetic overdrive, parasympathetic withdrawal and diminished baroreflex function are well documented in patients with hypertension [3, 4, 5]. Although their precise role in the etiopathogenesis of essential hypertension is not accurately defined, they have at least contributed to the increased risk for cardiovascular morbidity and mortality in this cohort of patients. Enhanced sympathetic activity in the early morning hours in patients with hypertension is connected with increased cardiovascular morbidity and mortality in this period of the day [6-10]. Baroreflex sensitivity predicts all-cause mortality and a sudden death in hypertensive patients with chronic renal failure [11, 12].

Pharmacological effects of any drug given to the patient with essential hypertension should be evaluated completely; not only its primary antyhypertensive effect, but also its effects on autonomic cardiovascular function, haemodynamic status and myocardial vulnerability. This approach is complex, demanding not only one or few tests, but a battery of tests.

Amlodipine is a long-acting dihydropiridine calcium channel blocker widely used in antihypertensive treatment. Data concerning the influence of amlodipine on autonomic function and haemodynamic parameters in patients with essential hypertension are conflicting, some stating that amlodipine has little if any effects on the autonomic nervous system (ANS), and others that it increases sympathetic activity [13, 14, 15]. According to the latter, amlodipine even stimulates vagal activity [16]. In these studies, the effect of amlodipine on the autonomic function was assessed frequently in small numbers of patients using incomplete autonomic evaluation, with the results often projecting the limitation of the employed tests.

OBJECTIVE

The aim of this study was to thoroughly evaluate early and long-term effects of amlodipine, on cardiovascular autonomic function, haemodynamic status and myocardial vulnerability in patients with mild uncomplicated essential hypertension.

METHODS

Study population

In this study 90 patients were enrolled (43 male), mean age 52.12±10.7 years. The patients were recruited from previously treated hypertensive patients in whom antihypertensive treatment did not meet therapeutic goals: systolic blood pressure (BP) lower than 140 mm Hg and diastolic BP lower than 90 mm Hg. In all patients antihypertensive drugs were withdrawn and one week placebo pretreatment started. The inclusion criteria were prehypertension or hypertension stage one (JNC VII), normal physical examination, normal electrocardiography and normal laboratory tests (fasting plasma glucose, blood urine nitrogen, serum creatinine, liver function tests and serum electrolytes). Exclusion criteria were secondary arterial hypertension, renal failure, coronary artery disease, diabetes mellitus, autoimmune disease or the use of drugs such as neuroleptics, antidepressants, lithium, antiarrhythmics, or cimetidine. All patients completed the trial and demonstrated good drug compliance. There were no adverse events observed in this trial.

Study protocol

After one week of pretreatment with placebo, baseline evaluation was done and included the evaluation of autonomic function and haemodynamic status (according to the three steps protocol performed in our Neurocardiology Laboratory), 24-hour ambulatory electrocardiography monitoring with heart rate variability (HRV) analysis and 24-hour ambulatory blood pressure monitoring (ABPM).

After baseline evaluation, we investigated the effects of the first 5 mg dose of amlodipine on the autonomic function and haemodynamic status in all patients, using real time beat-to-beat heart rate and BP monitoring and calculating HRV and blood pressure variability (BPV), as well as baroreflex sensitivity (Task Force monitor) [17]. In 10 patients changes in haemodynamic parameters 30 minutes after the first 5 mg dose of amlodipine were determined using impedance cardiography (Task Force monitor).

After baseline evaluation and analysis of the effects of the first dose, all patients were assigned to receive 5 mg amlodipine once daily for three weeks. Next, amlodipine monotherapy, evaluation of autonomic function and haemodynamic status, as well as 24-hour ambulatory ECG monitoring with HRV analysis and 24-hour ABPM were repeated. Results were compared with baseline values before amlodipine treatment. The study was approved by the Scientific Ethical Committee of Clinical Hospital Center "Bežanijska kosa". All participants gave written informed consent in accordance with the declaration of Helsinki.

Evaluation of autonomic function and haemodynamic status

All patients were tested in the Neurocardiology Laboratory of the Clinical Hospital Centre "Bežanijska kosa" using comprehensive three steps protocol for the assessment of ANS and haemodynamic status. The three steps protocol included: 1) five standard Ewing's clinical autonomic function tests, cold pressure and mental stress test, 2) short-term ECG and short-term HRV analysis, 3) non-invasive beat-to-beat monitoring and analysis of haemodynamic parameters and autonomic function (Task Force monitor) [18, 19]. The patients were tested under conditions of ideal room temperature (23°C), without any previous consumption of alcohol, nicotine, or food.

Clinical autonomic function tests

Cardiovascular reflex tests according to Ewing's battery were the first step in our assessment of autonomic function [20]. The participants rested in supine position for 10 minutes before starting the tests and also rested for 2 minutes between each test.

Parasympathetic tests: heart rate response to Valsalva manoeuvre, heart rate response to deep breathing, heart rate response to standing (ratio 30:15).

Sympathetic tests: BP response to standing, BP response to sustained handgrip test, cold pressure test, mental stress test.

The results of cardiovascular reflex tests were expressed as a scoring system: normal (0), borderline (1) and abnormal (2), related to the normal values from tables according to Ewing.

Short-term ECG and short-term heart rate variability analysis

The analysis of standard 12 leads ECG recording using a commercially available software (Schiller AT-10, Austria) included ECG wave and interval analysis: duration of P wave, PQ interval, QRS complex, QT and QTc interval.

Short-term HRV analysis was done from 512 consecutive RR intervals using the commercial software (Schiller AT-10, Austria) according to previously published guideline [21]. Using nonlinear HRV analysis, we compared the shape of Poincare plot before and after amlodipine therapy.

Task Force Monitor: beat-to-beat analysis of HRV and BPV, baroreflex sensitivity and haemodynamic parameters.

Holter ECG: rhythm analysis, long-term HRV analysis, ST segment, QT and QTc analysis, T wave morphology analysis.

From time domain HRV analysis, the following time domain variables were computed: mean RR interval for 24 hours (mean NN), standard deviation of normal RR intervals (SDNN), standard deviation of all 5-minute mean normal RR intervals (SDANN), square root of the mean of the sum of the squares of differences between adjacent RR intervals (r-MSSD), and percentage of adjacent RR intervals differing >50 ms (pNN50). From frequency domain HRV analysis, the following 24-hour frequency domain indices were determined: total power (TP; 0-0.4 Hz), high frequency power (HF; 0.15-0.4 Hz), low frequency power (LF; 0.04-0.15 Hz), and the LF/HF ratio. Heart rate was measured in milliseconds (ms); variance, referred to as

the power in a portion of the total spectrum of frequencies, was measured in milliseconds squared (ms^2). From ambulatory ECG recording, beat-to-beat analysis of QT and QTc interval was performed [22].

24-hour ambulatory blood pressure monitoring

The evaluation of a 24-hour profile of BP was done using a recorder and a commercial software for analysis (Mobil-O-graph). The monitoring began at approximately 11 a.m. and BP measurements were performed by oscillometric method every 15 minutes all day long.

Autonomic nervous system adjustment (ANSA) method

In order to precisely define the effect of amlodipine on sympathovagal balance we hypothesized that the effects of the drug depended greatly on the basal state of sympathovagal balance which changed with sympathetic or vagal predominance. Having in mind that basal sympathovagal balance differs among patients, in the first phase of our study we determined the type of disturbance, that is, dominance. According to the recommendations by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, a short-term spectral analysis, which enables LF and HF values in normalized units to be obtained, is the most adequate method of determining sympathovagal balance [21]. According to tables with normal values, we divided our patients into sympathicus and parasympathicus groups depending on predominance. Each group was further divided into two subgroups depending on whether marked or moderate dominance existed. Marked sympathetic dominance existed with high LF and low HF values, while sympathetic dominance was moderate if only LF values were high. Marked vagal dominance was diagnosed if high HF and low LF values were registered, while moderate dominance was associated with the elevation of HF values only. LF and HF analysis in normalized units enabled definite grouping of patients into sympathetic (47 patients: 29 male and 18 female) and parasympathetic groups (39 patients: 12 male and 27 female). The main groups were further subdived into two subgroups with marked or moderate sympathetic or vagal predominance (Table 1).

Table 1. Study population

Group	Number of patients		
	Male	Female	Total
Sympathetic I	16 (64.0%)	9 (36.0%)	25
Sympathetic II	13 (59.1%)	9 (40.9%)	22
Total	29 (61.7%)	18 (38.3%)	47
Parasympathetic I	6 (30.0%)	14 (70.0%)	20
Parasympathetic II	6 (31.6%)	13 (68.4%)	19
Total	12 (30.8%)	27 (69.2%)	39

Statistics

All data were analyzed using computer software package SPSS 11.05 system for Windows. Results were compared using paired samples by means of Student t-test or χ^2-test and General Linear Model with repeated measures. Significance level was defined as $p<0.05$.

RESULTS

Clinical autonomic testing

Among the basic tests of parasympathetic function, Valsalva ratio decreased after three weeks of amlodipine therapy (before vs. after therapy: 1.1±0.7 vs. 0.9±0.7, p=0.034), heart rate response to deep breathing and heart rate response to standing (30:15) did not change significantly. Results of sympathetic tests did not differ significantly before vs. three weeks after amlodipine therapy (orthostatic hypotension test: 0.6±0.6 vs.0.5±0.5 mm Hg, p=0.463; hand grip test: 1.6±0.6 vs. 1.7±0.5 mm Hg, p=0.471; mental stress test: 0.4±0.5 vs. 0.4±0.5, p was non-significant; cold pressure test: 0.7±0.4 vs.0.5±0.5, p was non-significant).

Short-term ECG: P wave, PQ, QRS and QT analysis

Analysis of the QT, QTc interval, P wave and PQ interval duration in classic short time ECG recordings revealed that all parameters after amlodipine therapy became shorter (P wave: 108.66±20.2 vs. 107.97±17.3 ms; PQ interval 158.32±23.6 vs. 156.92±20.0 ms; QT interval: 391.49±31.4 vs. 388.31±35.0 ms and QTc interval: 426.94±25.3 vs. 424.08±33.7 ms). QRS duration before and after amlodipine therapy was stable (QRS: 92±21.0 vs. 92.7±3.6 ms). All results were without statistical significance.

Short-time HRV analysis

Short-time RR variability analysis did not establish statistically significant changes for virtually all parameters, compared for periods before and after therapy. The parameters corresponding to the general status of the ANS, mean dRR, SD, MD, became significantly lower. Time domain parameters pNN50% and RMS, corresponding to vagal activity were also lower after three weeks of therapy with amlodipine. HF spectral component, as a reflection of vagal activity became also considerably lower with amlodipine therapy, whereas LF, which reflected sympathetic function, reached higher values. Sympathovagal LF/HF ratio increased, indicating the dominance of the sympathetic system after therapy.

Using nonlinear HRV analysis, we did not find significant changes after amlodipine therapy. There were no statistical significances related to the shape of Poincare plot before and after amlodipine therapy.

Holter ECG: heart rate and rhythm analysis

Amlodipine therapy reduced average and maximal heart rate during 24-hour period, however, this reduction was not of statistical significance. Ventricular ectopic activity became less prominent after therapy where the number of VPB/h during the night was reduced, but not statistically significant. Also, the average number of SVPB was reduced.

Holter ECG: long-term heart rate variability analysis

Time domain parameters corresponding to the general status of the ANS (SDNN, SDNN index) and total power became significantly lower after amlodipine therapy. Time domain parameters corresponding to vagal activity, RMSSD and pNN50% also became lower. After amlodipine treatment all spectral parameters, including total power (TP), ultra low frequency (ULF), very low frequency (VLF), LH, and HF significantly decreased as well as LF/HF ratio. LF corresponding to sympathetic activity decreased with statistical significance (553.4±370.0 vs. 497.5±305.6, p=0.007).

Baroreflex sensitivity three weeks after amlodipine therapy

Parameters, Minimal Slope was lower and Maximal Slope higher after administration of the first dose of amlodipine (Table 2).

Parameter Baroreflex Efficacy Index (BEI) measured by sequence method and reflecting baroreflex sensitivity, was significantly lower after three weeks of amlodipine therapy (Table 3).

Table 2. Beat-to-beat baroreflex sensitivity before vs. 30 minutes after the first dose of amlodipine

Baroreflex sensitivity	Before	After 30 minutes	p
Minimal slope (ms/mm Hg)	2.1±1.2	1.4±0.9	0.000
Maximal slope (ms/mm Hg)	33.7±22.5	45.8±30.8	0.000
Mean slope (ms/mm Hg)	11.6±7.4	10.4±5.6	NS
Baroreflex efficacy index (%)	93.6±37.9	94.2±35.6	NS

NS – non-significant

Table 3. Beat-to-beat baroreflex sensitivity before vs. three weeks after amlodipine therapy

Baroreflex sensitivity	Before	After 3 weeks	p
Minimal slope (ms/mm Hg)	7.6±4.9	6.1±4.6	NS
Maximal slope (ms/mm Hg)	33.0±26.9	29.6±23.8	NS
Mean slope (ms/mm Hg)	11.7±7.4	10.3±7.1	NS
Baroreflex efficacy index (%)	90.3±36.4	75.9±40.8	0.007

NS – non-significant

24-hour ambulatory blood pressure monitoring

The average systolic, diastolic and pulse pressure during the whole 24 hours, during daytime and night time were significantly lower after three weeks of amlodipine therapy. Early morning systolic and diastolic BP also became lower after amlodipine therapy. Amlodipine reduced the frequency of non-dipper episodes (night time systolic BP not at least 10% lower of the average daytime systolic BP (Table 4).

Autonomic nervous system adjustment (ANSA) methodology

In the selected patient group with vagal dominance during resting state, LF, which is an index of sympathetic activity, showed a statistically significant increase in value after three weeks of amlodipine therapy (p=0.007, Table 5, Graph 1).

In the same patient group, HF, as an index of parasympathetic activity, showed a statistically significant reduction in value after three weeks of amlodipine therapy (p=0.007, Table 6, Graph 2).

In the sympathicus group, there was a tendency towards a fall in sympathetic and a rise in vagal activity; however these observations were not of statistical significance.

Table 4. 24-hour ambulatory blood pressure monitoring

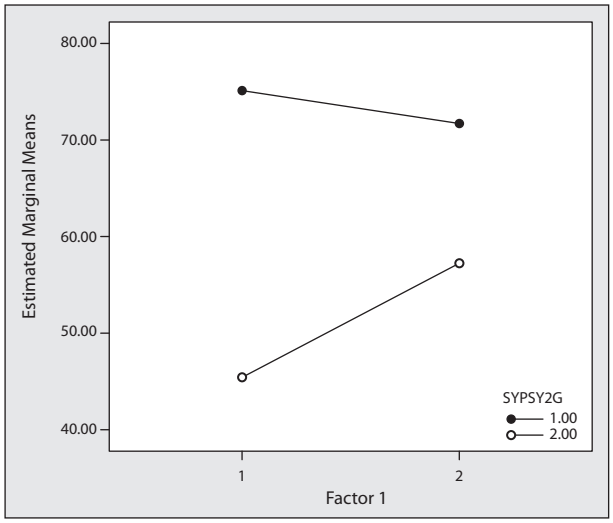
Parameter		Before amlodipine therapy	After amlodipine therapy	p
24-hour average values (mm Hg)	SBP	134.98±14.9	127.52±11.9	0.001
	DBP	84.33±9.8	80.23±7.9	0.001
	PP	50.72±8.7	47.44±7.7	0.001
Average values during day (mm Hg)	SBP	136.77±19.8	131.31±11.9	0.003
	DBP	86.40±10.2	82.49±8.2	0.008
	PP	52.21± 9.5	48.52±8.6	0.016
Average values during night (mm Hg)	SBP	123.09±17.7	116.96±14.3	0.005
	DBP	76.96±10.7	73.89±9.4	0.016
	PP	45.88±10.0	42.93±8.5	0.024
	Non-dipper* (%)	0.70±0.4	0.60±0.4	0.015
Early morning values (mm Hg)	SBP	135.41±30.9	129.17±18.2	0.048
	DBP	88.95±15.6	84.09±11.0	0.041
SD of BP during day (BPV during day)	SBP	16.01±4.1	16.59±5.7	0.163
	DBP	11.27±3.3	11.67±4.4	0.827
SD of BP during night (BPV during night)	SBP	11.6±6.5	11.2±5.1	0.703
	DBP	9.36±3.9	9.20±3.3	0.956

* frequency of SBP during night time that are not lower than 10% of the average daytime SBP
SBP – systolic blood pressure; DBP – diastolic blood pressure; PP – puls pressure; SD – standard deviation; BP – blood pressure; BPV – blood pressure variability

Table 5. Low frequency before vs. three weeks after amlodipine therapy

Group	Before	After 3 weeks	p
Sympathetic	74.1±8.7	71.0±13.9	NS
Parasympathetic	49.3±16.2	59.3±17.1	0.007

NS – non-significant

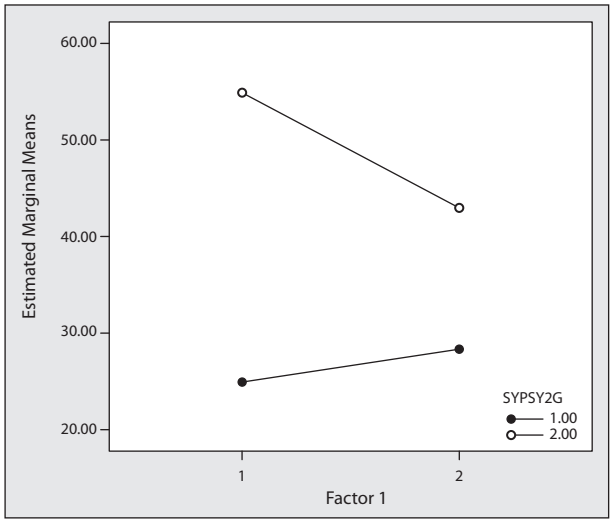


Graph 1. Low frequency before vs. three weeks after amlodipine therapy: increase of sympathetic activity (lower line) in vagal group

Table 6. High frequency before vs. three weeks after amlodipine therapy

Group	Before	After 3 weeks	p
Sympathetic	25.8±8.7	28.9±13.9	NS
Parasympathetic	50.8±16.3	40.8±16.9	0.007

NS – non-significant



Graph 2. High frequency before vs. three weeks after amlodipine therapy: decrease of vagal activity (upper line) in parasympathetic group

DISCUSSION

The influence of calcium antagonists on the ANS differs between classes and depends on the pharmacodynamic profile of the specific drug [23-27]. Short-acting dihydropyridine (DHP) calcium antagonists have been associated with increased morbidity and mortality in patients with hypertension and coronary artery disease due to reflex sympathetic activation in response to vasodilatation [27, 28]. In contrast, long acting DHP and non-DHP act as vasodilators, but with less significant increase in sympathetic activity. Data regarding the effects of amlodipine on sympathovagal balance are controversial and largely depend on the methodology used for the assessment of autonomic function. This study was aimed to fully evaluate the effects of amlodipine on autonomic function and related risk predictors, using a comprehensive protocol.

Cardiovascular Ewing's reflex tests are simple and useful screening tests for the assessment of ANS, but with relatively limited sensitivity compared to new methods based on the spectral analysis of biological signals, i.e. heart rate and blood pressure. In our study, Valsalva ratio, a marker of vagal activity became less positive. The results of other cardiovascular tests before vs. after three weeks of amlodipine therapy did not change significantly. These data presumably reflect insufficiency of a standard cardiovascular reflex test to detect discrete changes in autonomic function. Even Ewing in patients with diabetic neuropathy and normal results of cardiovascular tests found significant changes in spectral analysis of heart rate, implying relatively limited sensitivity of standard tests [20].

HRV is widely used for the assessment of sympathovagal balance. In this study we performed time and frequency domain methods of short-term, long-term and beat-to-beat analysis of HRV before and after amlodipine therapy. Short-term HRV analysis, three weeks after amlodipine therapy, revealed significantly lower values of all time domain parameters, as well as HF component, whereas LF component and LF/HF ratio were increased. At the same time, long-term HRV analysis revealed a reduction of all time domain parameters, reduction of all spectral components with statistical significance for LF in concordance with decreased sympathetic activity. In long-term HRV analysis, LF/HF ratio was decreased, as well as mean and maximum heart rate during 24 hours were reduced, and the results were more suggestive of a shift towards vagal activity.

Rosinnen et al. [29] investigated the anti-ischemic affect of amlodipine in patients with coronary artery disease treated with beta blocker and also revealed unfavourable changes in the autonomic modulation of the heart induced by amlodipine (significant reduction of total variability and VLF component). Lefrandt et al. [24] also found in hypertensive patients that amlodipine induced a shift in sympathovagal balance, as measured by spectral analysis of HRV and plasma NE, toward sympathetic predominance compared with vagal predominance induced with verapamil. Lindqist et al. [30] and Leenen et al. [31] confirmed that long-term calcium antagonists including amlodipine increased sympathetic nerve activity.

However, other authors demonstrated that amlodipine did not cause increment in sympathetic activity and that it did not cause significant changes either in time domain or spectral analysis of HRV [16]. Other studies also demonstrated that amlodipine was quite neutral regarding autonomic function [14, 32], whereas, nifedipine increased adrenergic, and verapamil vagal activity [24, 33]. Zaliunas et al. [16] found decreased LF without changes in HF of HRV spectrum in 30 patients with angina pectoris and hypertension. According to our data we also found decreased LF as an index of sympathetic activity during 24-hour ECG ambulatory monitoring and could therefore conclude that amlodipine resulted in neutral or higher vagal activity following therapy.

In long-term analysis we found slight, but not statistically significant, prolongation of QT interval after three weeks of amlodipine, however, in short-term analysis, QT interval was shorter without statistical significance. Amlodipine non-significantly reduced the number of SVPB and VPB during the night, which could have been a potentially vagal effect.

We found that baroreflex sensitivity was temporarily increased after the first dose of amlodipine. With chronic amlodipine therapy baroreflex sensitivity became significantly decreased compared to basal values. Siché et al. [15] in a smaller study, comprising 36 patients, did not find a statistical significance relation between amlodipine therapy and baroreflex sensitivity, whereas Lefrandt et al. [24], in a much larger study, found that chronic amlodipine therapy improved baroreflex sensitivity, although less effectively compared to verapamil.

By impendence cardiography we monitored the early effect of the first dose of amlodipine in 10 patients. The data obtained from haemodynamic assessment 30 minutes following the first dose of amlodipine, suggested a favourable influence of amlodipine on haemodynamic profile that could suggest safety of amlodipine in patients with heart failure, but these results were not statistically significant. Lindqvist et al. [30] also demonstrated increased cardiac output after amlodipine with increased adrenergic activity.

The effectiveness of amlodipine in BP reduction was confirmed in our study, concerning both systolic and diastolic BP. These data are in concordance with other studies [30, 34]. However, we found that the first dose of amlodipine slightly and transitorily increased BP, predominantly diastolic BP. After three weeks of therapy, systolic BP, diastolic BP and pulse pressure decreased, though BPV during daily activities became more pronounced, but without statistical significance. According to previously published data, obtained in a lower number of patients, amlodipine decreased or did not affect BPV [34, 35].

By combining a number of methods we were able to confirm with great certainty the existence of a tendency towards sympathetic predominance following amlodipine therapy; the obtained results were not statistically significant, thereby developing a totally new approach in diagnosing autonomic dysfunction. We confirmed the hypothesis that in patients with hypertension two types of autonomic dysfunction existed concerning dominance. Following up the effects of amlodipine in the sympathetic and vagal groups, a statistically significant increase in sympathetic and reduction in vagal activity in the vagal group was evidenced. That is, in this patient group we confirmed that amlodipine proved efficacious in restoring the autonomic balance. In the sympathetic group a similar tendency was evidenced, but it was not of statistical significance.

By developing a totally new approach in diagnostics and treatment of autonomic disturbances, we also confirmed our initial hypothesis which stated that there were no general rules regarding the effects of the drug; its effects primary depended on basal sympathovagal balance in each individual patient. The analysis of patients with hypertension enabled grouping into 2 groups and 2 subgroups, depending on the existence of strong or weak sympathetic or vagal dominance. This new diagnostic approach and treatment focused attention on the importance of restoring distorted autonomic balance in various diseases. Acceptance of this new approach brings into question the adequacy of prescribing individual drugs in individual patient groups. That is, the patient group in which a drug is most efficient will be determined.

CONCLUSION

Amlodipine has the most potent effect in correcting autonomic disbalance in patients with increased vagal acitivity in resting state.

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Значај амлодипина у подешавању функције аутономног нервног система (метода ПАНС): нов начин лечења хипертензије

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КРАТАК САДРЖАЈ

Увод Аутономна модулација функција кардиоваскуларног система измењена је код особа с есенцијалном хипертензијом.

Циљ рада Циљ рада је био да се испитају непосредни и дугорочни ефекти амлодипина на кардиоваскуларну аутономну функцију и хемодинамски статус болесника са благом есенцијалном хипертензијом.

Методе рада Истраживање је обухватило 90 болесника (43 мушкараца) са благом есенцијалном хипертензијом, просечне старости од 52,12±10,7 година, који су испитивани непосредно пре, 30 минута после прве дозе од 5 *mg* оралног амлодипина и након три недеље лечења амлодипином. Протокол истраживања је обухватао: анализу променљивости крвног притиска и срчане фреквенције (енгл. *heart rate variability – HRV*), анализу промена „удар-до-удар" помоћу импеданције кардиографије, ЕКГ са софтвером за краткорочну *HRV* и нелинеарну анализу, 24-часовни холтер ЕКГ мониторинг са анализом *QT* интервала и *HRV*, 24-часовни холтер притиска са пратећом анализом промена систолног и дијастолног крвног притиска, тестове за испитивање кардиоваскуларног аутономног рефлекса, тест хладном водом и тест менталне стимулације. Испитаници су сврстани у две групе, назване „симпатикус" и „парасимпатикус", у зависности од предоминације у краткорочној спектралној анализи симпатовагалне равнотеже, у складу с вредностима ниске и високе фреквенције.

Резултати Забележено је значајно смањење вредности систолног и дијастолног крвног притиска и пулсног притиска током дана, ноћи и раних јутарњих сати. Смањење броја суправентрикуларних и вентрикуларних ектопичних удара током ноћи је такође постигнуто примењеном терапијом, али оно није било статистички значајно. Повећање симпатичке активности у раној фази лечења амлодипином је такође било без статистичке значајности, док је одржавање симпатичке предоминације после неколико недеља лечења забележено на основу резултата краткорочне спектралне анализе *HRV*. Забележено је и смањење вредности свих временски зависних параметара дугорочне *HRV* анализе, као и спектралног параметра ниске фреквенције. Амлодипин је смањио барорефлексну сензитивност након три недеље лечења и довео до њеног повећања непосредно након примене прве терапијске дозе.

Закључак Резултати ове студије показују да амлодипин доводи до помака симпатовагалне равнотеже у смислу предоминације симпатикуса, али без статистичке значајности. У изабраној групи болесника са предоминацијом вагуса амлодипин повећава симпатичку, а смањује активност вагуса. Закључује се да амлодипин има највећи утицај на модулацију функције аутономног нервног система код особа са предоминацијом вагуса у стању мировања.

Кључне речи: амлодипин; хипертензија; аутономна функција; променљивост срчане фреквенције; хемодинамика; сензитивност барорецептора

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