This journal is the official publication of Bangladesh Society of Physiologists (BSP)
Web URL: www.banglajol.info/index.php/JBSP

Abstracted /indexed in Index Copernicus, Director of Open Access Journal, HINARI Index Medicus for South East Asia Region, Google Scholar, 12OR, infobse index, Open J gate, Cite factor, Scientific indexing services

pISSN-1983-1213; e-ISSN-2219-7508

Article

Article information:
Received: Aug 2024
Accepted: Nov 2024
DOI:https://doi.org/10.3329/jbsp.v19i2.79574

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Cite this article:
Sultana S, Begum S, Ferdousi S. Power spectral analysis of heart rate variability in drug naive essential hypertension: Comparison between two antihypertensive drugs. J Bangladesh Soc Physiol 2024;19(2): 82-88

Power spectral analysis of heart rate variability in drug naive essential hypertension: Comparison between two antihypertensive drugs

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Abstract

Background: Autonomic imbalance is associated with drug naïve essential hypertension and antihypertensive drugs may improve autonomic balance. Losartan and amlodipine are two different drug of choice to treat essential hypertension. Power spectral analysis of heart rate variability (HRV) is an important marker for detecting autonomic balance. **Objective:** To compare the effect of losartan and amlodipine on autonomic balance in essential hypertensive patients. **Method:** This longitudinal study enrolled 120 drug naive male hypertensive patients (age 30-55 years) from the Out Patients Department of Cardiology, BSMMU, Dhaka. Sixty apparently healthy normotensive male subjects with similar age were control. Patients were divided into two equal groups. One group received daily oral dose of 50 mg losartan and other group 5 mg amlodipine. Autonomic balance was assessed by power spectral analysis of Heart Rate Variability (HRV) and HRV data were recorded by a polyrite D. HRV of the patients were measured at baseline, after 3 months, and 6 months of medication. For statistical analysis ANOVA, independent sample 't' test and paired sample 't' were performed. **Result:** High frequency normalized units (HFn.u), total power (TP) were significantly lower ($P<0.001$) and low frequency normalized unit (LF n.u), LF/HF ratio were significantly higher ($P<0.001$) in all patients compared to control at baseline. In both drug groups HF n.u and total power significantly increased($P<0.001$) whereas LF n.u and LF/HF ratio were found significantly decreased($P<0.001$) after 3 months of treatment compared to their baseline values. After 6 month treatment data demonstrated further significantly increased ($p<0.05$) HF n.u and total power compared to their values of 3 months treatment. But these values were found significantly higher in losartan treated patients compared to amlodipine group. **Conclusion:** The result concluded that autonomic balance was improved by both drugs but losartan was more potent.

Key words: Untreated essential hypertensive patients, heart rate variability.

Introduction

Essential hypertension is characterized by altered cardiac autonomic modulation indicated by reduced heart rate variability which may predispose to increased cardiovascular morbidity[1,2]. Essential hypertension is associated with sympathetic over activity and attenuation of parasympathetic modulation of the heart and overall reduced heart rate variability[1,3,4].

HRV is a noninvasive, quantitative and reliable technique for assessment of sympathetic and parasympathetic activity of the cardiac autonomic nerve function. Among different methods used for HRV analysis, in frequency domain method, Power Spectral Analyzes the information of total power (Variance). Low frequency (LF) and high frequency (HF) are the components of total power in a spectrum of continuous ECG recording for 5-10 minutes[5].

Previous studies demonstrated reduced HRV in essential hypertension[1,2,6]. Reduced HRV has been associated with a higher risk for all mortality in survivors of an acute myocardial infarction[7] and sudden cardiac death[8]. It was suggested that antihypertensive drug therapy that not only control blood pressure but also improve HRV. Effect of some antihypertensive drugs individually or in combinations on HRV has been studied in hypertensive patients [9- 15].

It has been reported that various antihypertensive drugs modify the sympathoparasympathetic balance[1,4,16]. All antihypertensive drugs lower blood pressure but their mechanism of action are different in relation to autonomic nervous system activity[1,4]. There are conflicting reports on the effect of losartan and amlodipine on cardiac autonomic activity. Some study showed that autonomic balance shifted toward the increased vagal activity treated with losartan in hypertensive patients[1,9,17]. On the other hand, few study reported that amlpdipine had no significant effect on HRV[13]. Similar reports were also found about the effect of amlodipine.[9,12-14].

In addition to the conflicting result of this two drugs, information about the effect of treatment duration on HRV is still uncertain. Therefore, this study has been designed to compare the effect of losartan and amlodipine after 3 months and 6 months interval on HRV in hypertension.

Methods

Design &Setting

This prospective observational study was conducted in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka.

Study participants

Total 120 drug naïve male hypertensive patients aged 30-55 years were enrolled from Cardiology OPD, (BSMMU). Age, BMI matched 60 apparently healthy normotensive male subjects were control.

Grouping

According to follow up period of treatment, patients were divided into losartan and amlodipine groups with 3 months and 6 months of treatment. Losartan group included 60 patients received losartan 50 mg daily and amlodipine group included 60 patients received amlodipine 5 mg daily. Data were collected before the treatment, after3 months medication and after 6 months medication.

Exclusion criteria

Hypertensive patients with history of taking antihypertensive drugs, previously diagnosed as hypertension, diabetes mellitus, ischaemic heart diseases, renal disease, psychic disorder and smoking were excluded from the study.

Data collection procedure

After selection, the objectives of the study were explained to all the subjects and a informed written consent was taken. Then the subject was prepared for Autonomic Nerve Function Test. They were advised to finished their meal by 9.00 pm on the previous night of test day, avoid any type of stress and not to take any sedative hypnotic medication. They were requested to

take a light breakfast without tea or coffee and to attend autonomic nerve function laboratory in the Department of Physiology, BSMMU between 8.00-9.00 am on the test day. Immediately after enrollment, data were recorded before initiating treatment with any antihypertensive drugs. HRV measures were recorded by polyrite D (RMS, India). The subject was kept in supine position in a bed for 15-20 minutes in a controlled laboratory environment. Then all preparations for recording of the Heart rate variability parameters were made by connecting the channels of ECG and a 5 minutes recording was taken in resting position.

Then all the patients were requested to attend the Department of Physiology of BSMMU, after 3 months and after 6 months of antihypertensive medication for recording of follow up HRV data.

Statistical analysis

Data were expressed as Mean ± SE. For statistical analysis ANOVA, independent sample 't' test and paired sample 't' were performed.

Results

General characteristics of all subjects are given in table I.

Mean resting pulse, SBP, DBP, LFn.u., LF/HF ratio were significantly higher and HF n.u., total power were significantly lower in untreated hypertensive patients in both treatment group compared to healthy normotensive subjects (table II&III). In both losartan and amlodipine groups HF n.u. and total power significantly increased and LF norm and LF/HF significantly decreased after 3 months and 6 months of treatment compared to their corresponding baseline and 3 months values. (table IV&V). Again LF n.u., LF/HF ratio were significantly lower and H.F n.u. was found significantly higher in losartan group compared to amlodipine group after 6 months treatment (table VI).

Table I: General characteristics in different group (n=180)

Variable	Control	Losartan group	Amlodipine group
Age (years)	42.04±1.134	41.64±1.165	42.74±1.312
BMI (kg/m^2)	23.24±0.243	23.27±0.216	23.36±0.198

Data were expressed as mean±SE. Values in parenthesis indicate ranges.
Data analysis were performed by one way ANOVA;BMI-Body Mass Index; n= Total number of subjects

Table II: Baseline measures of pulse, BP, TP, HF, LF and LF/HF ratio in losartan group(n=60)

	Control (n=60)	Hypertensive (n=60)
Pulse (beats/min)	78.15±0.862	83.55±0.919***
SBP(mmHg)	126.4±0.603	141.6±0.462***
DBP(mmHg)	73.2±0.515	91.5±0.295***
TP(ms^2)	3349.2±140.47	2384.1±96.87***
LF(n.u)	54.89±.973	75.28±.745***
HF(n.u)	32.22±.70	20.97±.70***
LF/HF ratio	1.54±.051	3.58±.131***

Data were expressed as mean±SE. Values in parenthesis indicate ranges. Statistical analysis were done by independent sample 't' test;BP-Blood Pressure; SBP-Systolic blood pressure; DBP-Diastolic blood pressure; TP-Total power; LF (n.u)-Low power in normalized unit; HF (n.u)-High power in normalized unit; LF/HF-ratio of spectral power of low and high frequency; n-Number of subject. *** $p<0.001$.

Table III: Baseline measures of pulse, BP, TP, HF, LF and LF/HF ratio in amlodipine group(n=60)

Parameters	Control (n=(60)	Hypertensive (n=60)
Pulse (beats/min)	78.15±0.862	82.33±0.994***
SBP (mmHg)	126.4±0.603	142.8±0.520***
DBP (mmHg)	73.2±0.515	91.2±0.265***
TP (ms^2)	3349.2±140.47	2025.9±127.27***
LF(n.u)	54.89±.973	71.88±.527***
HF(n.u)	32.22±.70	24.41±.304***
LF/HF ratio	1.54±.051	2.94±.068***

Data were expressed as mean ±SE. Values in parenthesis indicate ranges; Statistical analysis were done by independent sample 't' test; BP-Blood Pressure; SBP-Systolic blood pressure; DBP-Diastolic blood pressure; TP-Total power; LF(n.u)-Low power in normalized unit ;HF (n.u)-High power in normalized unit; LF/HF-ratio of spectral power of low and high frequency; n-Number of subjects; *** p<0.001.

Table IV: Pulse, BP, TP, HF, LF and LF/HF ratio in losartan group before & after treatment (n=60)

parameters	Before treatment	After 3 month	After 6 month
Pulse (beats/min)	83.55±0.919	76.37±0.767***	75.33±0.664***
SBP (mmHg)	141.6±0.462	127.7±0.45***	127.7±0.45***
DBP (mmHg)	91.5±0.295	77.4±0.510***	76.2±0.476***
TP (ms^2)	2384.1±96.87	2776.9±119.18***	3182.0±144.57***###
LF(n.u)	75.28±.745	67.29±.624***	58.62±.383***###
HF(n.u)	20.97±.70	27.14±.80***	31.86±.80***###
LF/HF ratio	3.58±1.3	2.47±.073***	1.83±0.56*** ###

*p<0.05, **p<0.01, ***p<0.001; # The depicts comparison within treatment groups 3 months to 6 months; # p<0.05, ## p<0.01, ### p<0.001;Statistical analysis were done by paired 't' tests ;BP-Blood Pressure SBP-Systolic blood pressure; DBP-Diastolic blood pressure; TP-Total power; LF(n.u)-Low power in normalized unit; HF(n.u)-High power in normalized unit; LF/HF-ratio of spectral power of low and high frequency; n-Number of subjects.

Table V: Pulse, BP, TP, HF, LF and LF/HF ratio before & after treatment in amlodipine group (n=60)

Parameters	Before treatment	After 3 month	After 6 month
Pulse(beats/min)	82.33±0.994	76.95±0.978***	75.10±0.950*** ###
SBP (mmHg)	142.8±0.520	128.2±0.474***	127.4±0.381***
DBP(mmHg)	91.2±0.265	77.4±0.545***	76.4±0.429*** ##
TP (ms^2)	2025.9±127.27	2555.9±155.33***	3189.0±199.18***###
LF(n.u)	71.88.53±.527	68.87±.635***	62.27±.497***###
HF(n.u)	24.41±.304	27.09±.481***	29.85±.511***###
LF/HF ratio	2.94±.068	2.52±.067***	2.08±0.036***###

*p<0.05, **p<0.01, ***p<0.001, # The depicts comparison within treatment groups 3 months to 6 months, # The depicts comparison with control group, # p<0.05, ## p<0.01, ###p<0.001.Statistical analysis were done by paired 't' ;BP-Blood Pressure SBP-Systolic blood pressure; DBP-Diastolic blood pressure; TP-Total power; LF(n.u)-Low power in normalized unit; HF (n.u)-High power in normalized unit ;LF/HF-ratio of spectral power of low and high frequency; n-Number of subjects;

Table VI: Pulse, BP, TP, HF, LF and LF/HF ratio in both groups after 6 months (n=60)

Parameters	Losartan group (n=60)	Amlodipine group (n=60)
Pulse (beats/min)	75.33±0.66	75.10±0.950
SBP (mmHg)	127.7±0.45	127.4±0.381
DBP (mmHg)	76.2±0.48	76.4±0.50
TP (ms^2)	3182.0± 144.57	3189.0±199.18
LF(n.u)	58.62±0.38	62.27± 0.497***
HF(n.u)	31.86±0.80	29.85± 0.511***
LF/HF ratio	1.83±0.56	2.08±0.036***

*p<0.05, **p<0.01, ***p<0.001,.Statistical analysis were done by independent sample 't' test., BP-Blood Pressure SBP-Systolic blood pressure; DBP-Diastolic blood pressure; TP-Total power; LF (n.u)-Low power in normalized unit; HF (n.u)-High power in normalized unit ; LF/HF-ratio of spectral power of low and high frequency; n-Number of subjects;

Discussion

In the present study, values of the HRV parameters in healthy normotensive group were almost similar to other investigators[11,18,19].

In this study, hypertensive patients before treatment were found associated with compared higher sympathetic & lower parasympathetic activity demonstrated by the results of frequency domain parameters of HRV compared to normotensive subjects. This findings were similar to other researcher[1,2,3,11,18].

These results demonstrated the derangement of cardiovascular homeostasis in drug naive hypertensive patients.It is suggested that derangement mostly neurogenic and involved either sympathetic overdrive or parasympathetic inhibition or both contributed to essential hypertension.[20] Therefore present study found autonomic dysfunction and derangement of autonomic regulation in current series of hypertensive patients before treatment[21].

Hypertensive patients were treated by two anti-hpertensive drugs, losartin and amlodipine. The results of HRV parameters showed significant improvement in both group after 3 months of treatment with both anti-hypertensive drugs by reducing sypathetic and increasing para-sympathetic activity[1,6,9,10,12-14,17]. Results of these parameters after 6 months treatment also showed further improvements of parasympathetic and decreased sympathetic activity in both groups but more significant in losartan grpup. In addition further improvement in HF n.u and LF/HF ratio was observed in losartan treated patients. This suggest losartan is more effective for improvement of autonomic function in hypertensive patients.

It has been suggested that blocking the type-I receptor (AT_1) of Angiotensin II and increase production of nitric oxide from vascular endothelium and neuron by losartan facilitate the regulation of BRS (Baroreflex sensitivity) and HRV. Furthermore, NO has been demonstrated to augment cardiac vagal control in human suggesting beneficial effect of losartan on BRS and HRV[22,23].

Amlodipine prevent calcium influx in sympathetic nerve ending and inhibit depolarization induced norepinephrine release.[24,25]

However, it is clear that all the above mentioned mechanisms may influence the degree of deterioration of these variables in hypertension

patients and improvement after treatment with losatan and amlodipine. From the result though the improvement of cardiac autonomic nerve function was marked after 3 months of treatment but data after 6 months of treatment showed further improvement.

Conclusion

The results concluded that impaired autonomic balance in drug naïve essential hypertensive patients was restored by both losartan and amlodipine and losartan was found more potent. The improvement of impaired autonomic balance is better with longer duration of treatment.

Ethical aspects

The ethical aspects of this study was approved by Institutional Review Board, BSMMU.

Conflict of interest

There was no conflict of interst

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