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Original Article

Study of Heart Rate Variability in Control and Hypertensive Subjects

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Abstract

Autonomic nervous system comprising sympathetic and parasympathetic divisions has important role in regulating the cardiovascular system. Heart rate variability has been shown to give objective assessment of autonomic function. Peripheral Pulse Analyzer has been used to study heart rate variability in controls and hypertensive subjects for understanding manifestations of hypertension on autonomic activity. Subjects have been divided in two age groups; 18-30 years and 31-44 years and variability parameters have been compared with respect to gender stratification, age stratification and disease stratification. Statistical analysis has shown marked reduction in the coefficient of variation for variability parameter expressed as logarithm (to the base 10) in comparison to raw or average value of the parameter and has yielded higher discriminatory strength in various stratified groups. Excluding age and gender sensitive parameters, significant difference is observed in amplitude of low frequency component for lower age group male/female hypertensives and amplitude as well as area of low frequency component for higher age group female hypertensives. These observations are in agreement with similarly targeted previous studies. Higher age group male controls and hypertensives, however, could not be discriminated by variability study probably due to similar changes manifested by senility and hypertension. Thus amplitude and area of low frequency component in heart rate variability spectrum is identified as hypertension specific parameter.

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Introduction

Autonomic nervous system is a control system that acts unconsciously and regulates bodily function such as heart rate, blood pressure, respiratory rate, digestion, contraction of involuntary muscles, size

of the pupil, secretion of glands etc. It comprises of sympathetic and parasympathetic divisions having opposite responses. Stimulation of sympathetic nervous system increases heart rate, constricts the blood vessels, decreases gastro-intestinal motility and so on, whereas that of parasympathetic induces opposite effect. The variation in sympathetic and parasympathetic activity can be studied through variability in physiological parameters (1). The most explored physiological variability is that of heart rate (HRV); other variabilities investigated are those of peripheral blood flow variability (PBFV), systolic and diastolic blood pressures (SBP, DBP) and peripheral pulse morphology index (MIV). Long term variability (usually 24 hours) is dominant with ultra low frequency (ULF) representing circadian, thermoregulatory rhythms etc. Short term variability gives 3 spectral components namely Very Low Frequency (VLF), Low Frequency (LF) and High Frequency (HF) peaks in frequency ranges 0.004-0.039, 0.04-0.15 and 0.15-0.4 Hz respectively. Common consensus about the genesis of these frequency components is that HF is marker of vagal modulation and LF is marker of sympathetic modulation (2). Little is known about VLF; some researchers have associated this component with activity of renin-angiotensin (3).

Manifestations of clinical conditions like myocardial infarction, hypertension, diabetes, renal failure, cardiac arrhythmia etc., have been reviewed by Acharya et al (4). They have also reviewed effect of smoking, alcohol, beta blockers, calcium channel blockers and sleep on HRV. In general, there is decrease in total power (TP) and HF power in HRV in majority of diseases. For instance HF power is seen to be reduced in myocardial infarction, hypertension and diabetes. In addition to these general manifestations, large numbers of studies have been conducted involving particular disease in search of specific manifestation.

Akselrod et al (3) used nona-peptide converting enzyme inhibitor to block renin-angiotensin system in 4 un-anesthetized dogs and observed 2 to 4 fold increase in area under VLF in 3 out of 4 dogs. Baroreflex sensitivity assessment by bradycardia and tachycardia has shown inverse relation to blood pressure variability and direct relation with heart rate variability (5, 6). Baroreflex response sensitivity is evidenced by increase in HF power (7, 4). Power spectral density (PSD) analysis of heart rate and arterial pressure has shown increase in LF component in the presence of hypertension (8, 9, 10). HRV spectrum analysis at workplace study has revealed an increase in LF/(VLF+HF) during freeze frame and decrease during internal coherence (11). New onset hypertension in 931 male subjects has been observed to change HRV spectrum (LF) in contrast to that in 1111 female subjects (12). In normotensive, low HRV has been associated with higher risk of hypertension (13). Mean variability and HF component is observed to decrease significantly in hypertensives (14). Da Silva et al have observed that LF power decreases and LF/HF increases before treatment, which regress to normal after treatment. HF decreases after treatment (15). LF/HF ratio has significantly increased during mental stress in hypertensives in contrast to that in normal subjects (16). Lufti et al have shown that systolic, diastolic and mean blood pressure correlate positively with LF and LF/HF ratio; SBP correlates negatively with HF and DBP correlates negatively with HF and total power (17). Coexistence of hypertension with type-2 diabetes has shown significant change in heart rate recovery (18); it has synergistic effect causing worsening of autonomic recovery. Similar work by Solanki et al on Gujarati population has shown decrease in HRV parameters, which is not affected by optimum pressure or glycemic control (19, 20).

Half of the studies cited above have followed the Task Force Recommendations for the study of heart rate variability described by Camm et al (21). As described above, LF power and LF/HF ratio in general increase with increase in BP; VLF and HF power are associated with renin-angiotensin system and baro-reflex sensitivity respectively. Some of the above studies have given conflicting views due to use of absolute power of HRV components in place of normalized power. Large values of standard deviation of HRV parameters and non-segregation with respect to age and sex in the above studies make it necessary to have a fresh look on the manifestation of hypertension on HRV spectrum. In present study we aim to evaluate changes in spectrum of HRV in controls and early untreated hypertensive subjects

in segregated groups. Results of the study are briefly described in this paper.

Material and Methods

The study has been carried out at Bio-Medical Engineering Department of MGM College of Engineering and Technology, Kamothe, Navi Mumbai and has been approved by the human ethics committee of MGM Institute of Health Sciences (Deemed University) in its meeting held on 25th March 2015 item no. 2. The controls and hypertensive subjects, in the age group of 18 to 45 years, were derived from students and staff population of the institute conforming to inclusion and exclusion criteria. Smokers, tobacco chewers, those on regular medication and those suffered major sickness in the past were excluded from the study. Also subjects with history of cardiovascular (except hypertension) or autonomic sickness were excluded from the study. Initially subject's information, past history and consent were taken. The subjects were then rested comfortably for 15 minutes in supine position. Continuing in supine position blood pressure is measured twice with digital BP monitor (Omron HEM-7121) of which second reading has been considered for including the subject in the study. Blood pressure less than 130/80 were included in the control group. Those having >140/85, consistently on two different days, were taken in the hypertension group. These subjects have thus been freshly detected hypertensives, who have not been subjected to any treatment. Data has been stratified with respect to age, gender and hypertension in 8 groups (CML, CFL, CMH, CFH, HML, HFL, HMH and HFH). Demographic characteristics of these subjects are given in Table-I. Minimum sample size of 16 has been arrived at considering precision level to be 50% of the sample standard deviation.

For assessment of heart rate variability, peripheral blood flow (PBF) has been recorded in all the subjects with the help of Peripheral Pulse Analyzer (an R&D product of Bhabha Atomic Research Centre (BARC), Mumbai), shown in Fig. 1. PBF recordings have been made following the protocol and guidelines recommended for HRV studies (22). Five consecutive

Fig. 1: Peripheral Pulse Analyzer instrument with electrodes attached to a control subject. Carrier electrodes C1 and C2 have red clips and sensing electrodes S1 and S2 have black clips seen on subject's hand.

TABLE I: Demographic characteristics of Controls and Hypertensive subjects (*Alphabets represent Control/Hypertension, Male/Female and Lower-age/Higher-age sequentially).

Parameters	*Controls*				*Hypertension*			
	*CML**	*CFL**	*CMH**	*CFH**	*HML**	*HFL**	*HMH**	*HFH**
Number of subjects (n)	34	34	34	34	23	27	30	20
Weight (kg)	70.24±8.10	63.50±11.43	73.94±9.69	64.21±10.82	80.04±13.56	67.26±10.36	69.4±11.2	65.80±10.77
SBP (mmHg)	112.21±8.67	108.76±9.96	117.41±7.59	107.52±9.46	148.70±8.16	147.22±6.19	150.90±13.0	148.90±12.2
DBP (mmHg)	75.35±6.09	70.91±7.21	76.03±7.64	70.76±6.09	93.13±7.00	93.04±2.95	97.3±8.5	93.15±7.34
Pulse Rate (bpm)	80.03±8.21	74.71±11.21	75.62±7.37	75.36±10.96	82.65±10.36	77.67±8.41	78.80±10.50	73.40±11.46
Age (yrs)	21.47±3.31	19.91±2.67	36.65±4.80	37.42±3.95	26.52±3.20	27.78±2.69	39.10±3.70	41.30±4.41

recording of 275 seconds duration each (with an inter-recording gap of 2 minutes) have been done after 10 minutes of rest to the subject for the first reading. Two hours gap was provided for recording specifically after breakfast or lunch. With the subject in supine, carrier electrodes C1 and C2 were applied on the right upper extremity just below the elbow and palm respectively, in form of loop around the limb. Sensing electrodes S1 and S2 were placed 5 cm apart around the wrist as shown in the figure. Subject's information was filled before acquisition. A Click on ACQUIRE button (Fig. 2) in the application software starts data acquisition, which stops after 275 seconds by default. In case of motion artifact, it can be stopped in between and restarted. Data gets saved with subject's information in a file. The acquired data is then processed in another graphical user interface (GUI) shown in Fig. 3.

After loading pre-acquired data in the application, one can go to PROCESSING Panel (Fig. 3). Entire signal can be viewed in the top graph by panning with the help of arrows provided on right side. The systolic peak is marked by placing the cursor on the second peak and then clicking on LOCATE PEAKS. Vertical red lines appear on the peak positions as seen in the graph. The second graph, below the raw signal, displays time elapsed between

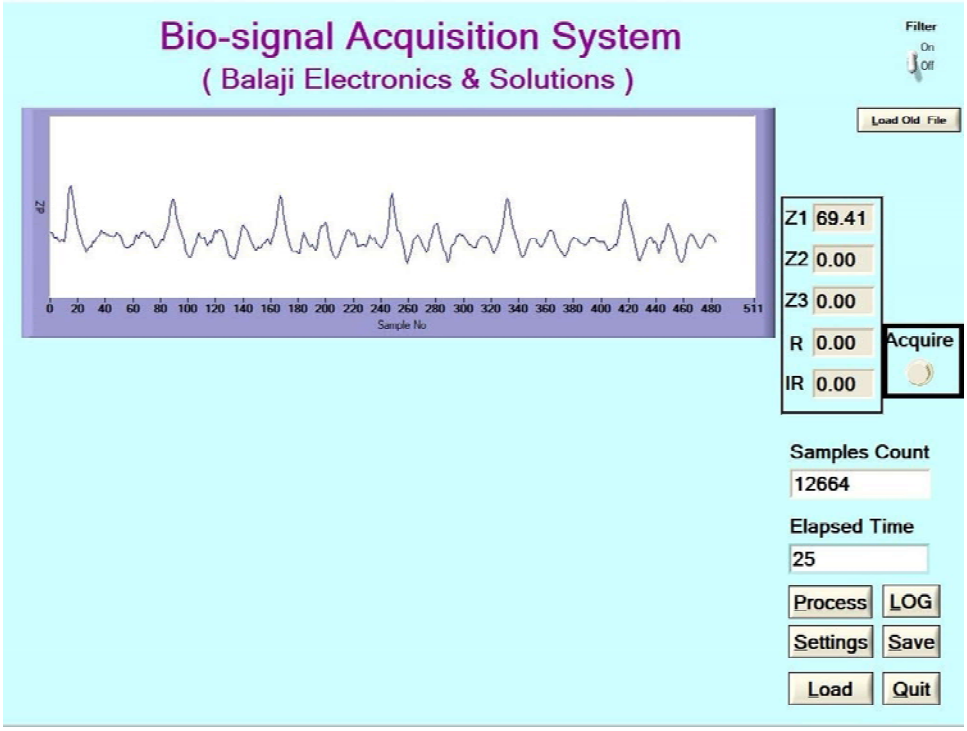

Fig. 2: Bio-signal Acquisition Software panel in which by clicking on ACQUIRE button we acquired signal for 275 seconds.

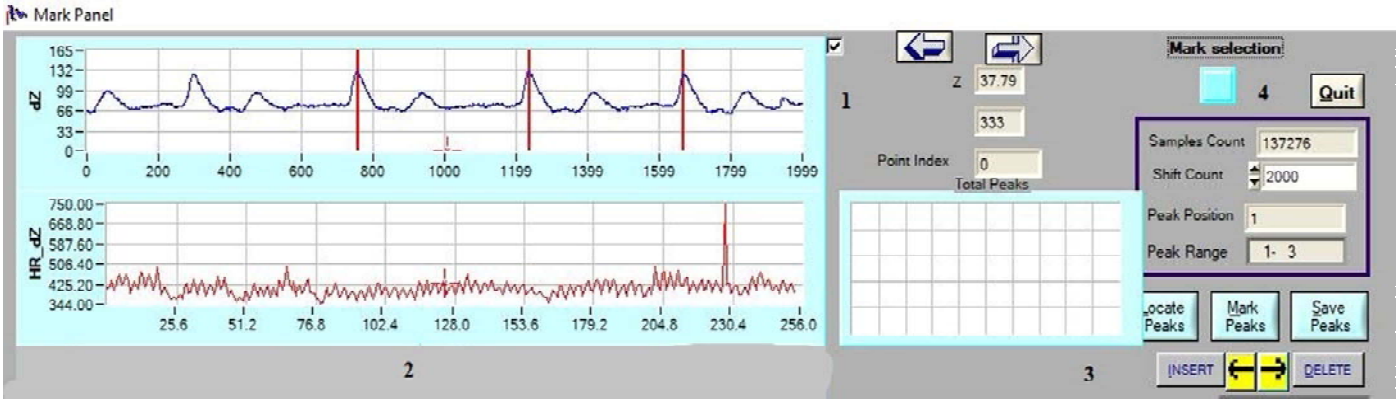

Fig. 3 : Processing Panel: First graph displays raw signal and the second graph below raw signal display beat to beat RR-interval (equivalent to RR interval of ECG). Entire signal can be panned by clicking on arrows provided on top. Editing of the peaks can be done with the help of buttons provided on the right side of the panel.

two peaks (equivalent to approximate RR interval of ECG) as a function of time. By clicking on any irregularity in lower graph, one can see corresponding signal in the upper graph. Editing of peak can be done with the help of arrow buttons and insert/delete buttons provided in the bottom towards right. Edited data is then saved. From the application, one can move on to DISPLAY panel, which displays Heart Rate Variability (HRV) spectrum as shown in Fig. 4. Variability in time domain and frequency domain can be seen on left and right graph respectively. The computed variability parameters are displayed on right side of the panel. By clicking on SAVE EXCEL, data is transferred to designated excel sheet. A click on quit button exits the application.

Data saved in Excel sheet is then processed for statistical analysis. To begin, five values of a particular HRV parameter (obtained from 5 recordings in a subject) are averaged. The average values, hereafter referred to as Average (Avg), for all the parameters in a particular subject are thus obtained. Mean and standard deviation (SD) values of these parameters are then obtained from this data in all the subjects in a particular group. The process is repeated for all the groups. Mean thus obtained has lowered value of SD in comparison to individual values as reported by Jindal et al (23). ANOVA and Tukey's HSD (honestly significant difference) test were performed to find out the significant difference in the data stratified with respect to age, gender and disease. In view of the large scatter even in the averaged data, logarithm of every individual value to the base 10 was taken, hereafter referred to as Log. The whole statistical analysis performed on Avg data has been repeated on Log data.

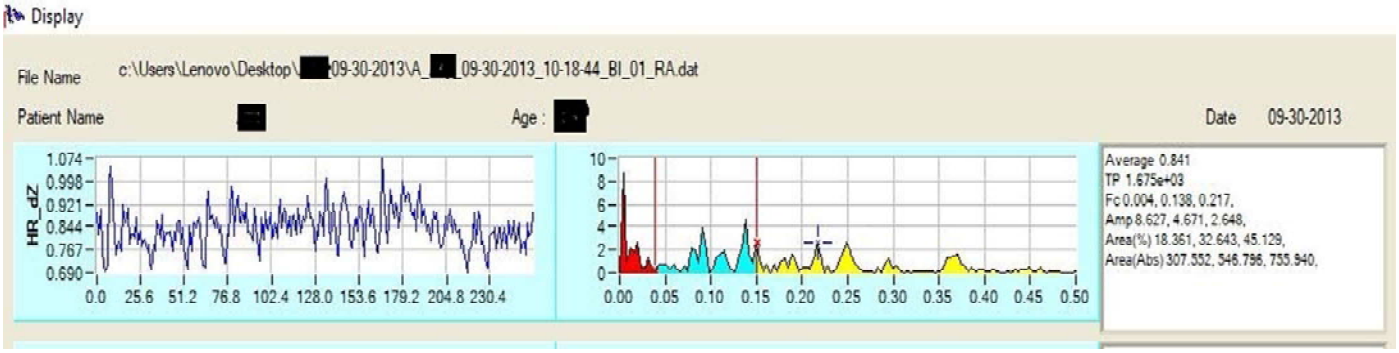

Fig. 4 : DISPLAY panel: Graph on the left displays time domain and that on the right gives frequency domain variations. Computed parameters are displayed in the box on the extreme right. VLF, LF and HF are highlighted with red, blue and yellow color respectively, the data is then saved to excel.

Results

Table II gives group mean and standard deviation (SD) values computed from Avg and Log data. As can be seen coefficient of variation has come down drastically for Log data. Histogram plot for a particular parameter in a particular group has been observed to be more symmetric for Log data than that of the Avg data. Similarly Table III gives ANOVA and Tukey's HSD statistic values for Avg as well as Log data. Probability values are given for eight comparisons between various groups stratified with respect to gender, age and disease. For instance male and female controls are compared in the lower age groups (CML_CFL) and in the higher age group (CMH_CFH) for gender stratification. Similarly CML_CMH and CFL_CFH represent age stratification and CML_HML, CFL_HFL, CMH_HMH and CFH_HFH represent disease stratification.

As can be seen from the table, ANOVA shows an overall significant difference in HRV parameters in the Avg as well as Log data derived from 8 different groups. Fine difference is revealed from Tukey's HSD analysis, which shows honestly significant difference between any two groups. Significantly different values are highlighted as "bold". Gender stratification shows no significant difference in Avg data from control subjects in respective age group, in contrast to that in Log data showing significant difference in 3 out of 16 comparisons. Similarly Age stratification shows significant difference in 3 and 8 comparisons (each out of 16) for Avg and Log data respectively. Thus it is seen that Log data is more sensitive in identifying significant difference in comparison to Avg data.

For disease stratification, comparison is made between control and hypertensive groups for respective gender and age. For instance control-male-lower (CML) has been compared with hypertensive-male-lower (HML) and so on. Significant difference is noted in 8 and 16 comparisons (each out of 32) in Avg and Log data respectively, suggesting higher sensitivity of Log data. Excluding age and gender sensitive parameters, significant difference (highlighted by italics and bold) is observed in A_VLF for CFH_HFH; Amp_LF for CFL_HFL; A_HF for CFL_HFL in Avg data. Similarly significant difference (highlighted by italics and bold) is observed in Amp_LF for 3 comparisons (out of 4); and A_LF for CFH_HFH in Log data.

TABLE II: Group Mean and SD in controls and hypertensives.
(TP: Total power; RR-mean: Mean of RR interval values; Amp_VLF: Amplitude of VLF peak; A_VLF: Area of VLF peak; Amp_LF: Amplitude of LF peak; A_LF: Area of LF peak; Amp_HF: Amplitude of HF peak; A_HF: Area of HF peak; ms^2 = milli-second square, n.u. = Normalized unit)

Groups Parameters	*Data Type*	*CML* Avg±SD	*CFL* Avg±SD	*CMH* Avg±SD	*CFH* Avg±SD	*HML* Avg±SD	*HFL* Avg±SD	*HMH* Avg±SD	*HFH* Avg±SD
TP (ms^2)	Avg	1357.05± 1120.56	1253.01± 1147.22	730.04± 558.97	1006.10±1 360.05	676.93± 830.93	697.64± 898.16	683.70± 756.50	503.11± 609.01
	Log	2.99±0.36	2.97±0.31	2.75±0.32	2.81±0.37	2.65±0.36	2.61±0.41	2.64±0.42	2.50±0.41
RR_Mean	Avg	852.11± 100.79	794.98± 115.51	811.22± 118.59	815.17± 122.01	737.23± 110.82	760.02± 103.90	770.33± 80.92	813.73± 144.18
(ms)	Log	2.92±0.05	2.89±0.06	2.90±0.05	2.91±0.06	2.86±0.06	2.87±0.06	2.88±0.04	2.90±0.08
Amp_VLF	Avg	13.47±8.46	9.48±6.12	13.43±8.09	11.77±8.13	11.32±7.84	14.05±7.22	12.63±7.62	17.21±7.80
(n.u.)	Log	1.03±0.31	0.89±0.26	1.05±0.24	0.96±0.35	0.95±0.30	1.08±0.24	1.02±0.27	1.19±0.19
A_VLF	Avg	32.98±18.47	26.21±13.73	36.09±15.33	32.41±15.69	30.06±18.46	35.13±18.14	36.25±17.32	45.75±14.17
(n.u.)	Log	1.42±0.31	0.89±0.26	1.51±0.20	1.44±0.28	1.39±0.27	1.47±0.26	1.50±0.24	1.63±0.15
Amp_LF	Avg	4.75±2.30	4.36±2.23	5.24±2.77	4.54±2.19	6.07±3.16	5.46±2.54	5.22±2.87	3.27±1.99
(n.u.)	Log	0.62±0.21	0.59±0.20	0.66±0.22	0.60±0.22	0.72±0.22	0.68±0.21	0.65±0.23	0.50±0.25
A_LF	Avg	34.81±14.33	32.98±13.25	34.71±12.41	32.21±13.71	40.00±15.20	36.45±14.91	34.25±14.02	25.49±11.21
(n.u.)	Log	1.50±0.19	1.48±0.18	1.51±0.16	1.46±0.20	1.56±0.19	1.51±0.20	1.49±0.19	1.36±0.21
Amp_HF	Avg	3.67±3.09	4.28±2.78	2.40±1.74	3.45±3.23	2.11±1.28	2.70±2.26	2.74±3.33	2.86±2.49
(n.u.)	Log	0.45±0.30	0.54±0.27	0.32±0.20	0.42±0.29	0.23±0.29	0.28±0.37	0.24±0.40	0.33±0.32
A_HF	Avg	30.12±15.98	39.25±14.70	26.04±13.97	32.34±15.42	28.14±14.63	26.69±13.38	26.99±17.18	26.23±14.15
(n.u.)	Log	1.41±0.25	1.55±0.18	1.35±0.23	1.45±0.22	1.38±0.25	1.35±0.26	1.34±0.29	1.35±0.25

TABLE III: Analysis of Variance and Tukey's HSD test.
(*Comparison between two groups designated by abbreviations given in Table-I)

Groups Parameters	*Data Type*	*ANOVA* ($F_{crit.}$=2.017)	*Tukey's HSD test (p-value)*							
			*CML_ CFL**	*CMH_ CFH**	*CML_ CMH**	*CFL_ CFH**	*CML_ HML**	*CFL_ HFL**	*CMH_ HMH**	*CFH_ HFH**
TP	Avg	7.58	0.994	0.992	**0.003**	0.088	**0.001**	**0.003**	1.000	0.871
	Log	31.17	1.000	0.771	**0.001**	**0.002**	**0.001**	**0.001**	0.157	**0.001**
RR_Mean	Avg	6.78	0.258	1.000	**0.015**	0.872	**0.002**	0.071	0.736	1.000
	Log	15.89	**0.001**	1.000	**0.013**	0.764	**0.001**	0.087	**0.046**	1.000
Amp_VLF	Avg	2.74	0.518	0.991	1.000	0.923	0.968	0.203	1.000	0.073
	Log	13.47	**0.001**	**0.029**	0.981	0.373	0.354	**0.001**	0.942	**0.001**
A_VLF	Avg	3.31	0.736	0.941	0.987	0.879	0.996	0.568	1.000	**0.033**
	Log	14.28	0.103	0.178	**0.045**	**0.022**	0.978	**0.001**	1.000	**0.001**
Amp_LF	Avg	3.51	0.897	0.667	0.985	1.000	0.492	**0.045**	1.000	0.967
	Log	10.77	0.833	0.186	0.735	0.999	**0.005**	**0.005**	1.000	**0.010**
A_LF	Avg	2.733	0.872	0.977	1.000	1.000	0.823	0.210	1.000	0.850
	Log	9.93	0.983	0.365	1.000	0.993	0.115	0.741	0.997	**0.001**
Amp_HF	Avg	5.26	0.754	0.874	0.080	**0.041**	**0.042**	**0.002**	1.000	0.997
	Log	19.03	0.072	0.061	**0.004**	**0.004**	**0.001**	**0.001**	0.402	0.275
A_HF	Avg	3.95	0.078	0.452	0.917	0.420	1.000	**0.003**	1.000	0.622
	Log	14.61	**0.001**	**0.005**	0.405	**0.003**	0.986	**0.001**	0.999	**0.018**

Discussion

Gender stratification shows no significant difference in Avg data from control subjects in respective age group, in contrast, Log data shows significant difference in 3 out of 16 comparisons. Similarly Age stratification shows significant difference in 3 and 8 comparisons (each out of 16) for Avg and Log data respectively. Thus Log data appears more sensitive than Avg data. This is probably due to much lower coefficient of variation of the Log data (12.04% in contrast to 82.6% for TP). Over all 3 comparisons are significantly different in gender stratification, suggesting that gender stratification can be dispensed with little risk of error (9.4%). However age stratification need be maintained as the risk of error becomes (34.4%).

Maintaining age and gender stratification, comparison of data in hypertensive subjects with that of respective control subjects shows significant difference in 8 and 16 comparisons (each out of 32) in Avg and Log data respectively, again suggesting higher sensitivity of Log data for the reason specified for control data. Therefore further discussion is limited to only Log data. Out of these comparisons, age and gender sensitive parameters need be eliminated, as these parameters (TP, RR_mean, Amp_VLF, A_VLF, Amp_HF and A_HF) are not changing due to hypertension per se. Thus significant difference observed in Amp_LF for lower age group male/female hypertensives and Amp_LF as well as A_LF for higher age group female hypertensives appears to be specific for hypertension. However, no parameter is specific for higher age group male hypertensives. It may probably be due to reason that senile changes are similar to that of hypertension in higher age group males. Since higher age group female hypertensives have two specific parameters, namely Amp_LF and A_LF, and male hypertensives in higher age group do not yield a specific parameter, it appears that gender stratification cannot be dispensed.

In previous studies (8, 9, 10) increase in LF component and decrease in HF are associated in hypertension. In present study LF component is observed to be affected either in amplitude or in area. Thus this study is in agreement with previous observations. Thus this study indicates that increase in LF amplitude or/and area can be considered specific of hypertension and it can be used for early detection of hypertension.

Conclusion

The study demonstrates that Log data gives higher discrimination in variability parameters in comparison to raw or average data. Amplitude or power of LF

component in HRV spectrum is observed to be specifically related to untreated hypertension in young males and young as well as old females and therefore can be used to detect hypertension in these categories.

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