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VARIABILITY IN PERIPHERAL BLOOD FLOW AND MORPHOLOGY INDEX IN CONTROLS AND HYPERTENSIVE SUBJECTS

Physiology

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ABSTRACT

Peripheral pulse has been recorded in controls and hypertensive subjects with the help of peripheral pulse analyzer for analyzing peripheral blood flow and morphological index variability as an alternative to blood pressure variability. Data in controls and patients has been age (less than and above 30 years of age) and gender (male and female) stratified. One way analysis of variance has shown significant difference among all the 8 subgroups in 13 out of 16 variability parameters at 5% level of significance. Tukey's HSD test at the same significance level has shown gender wise difference in 2 out of 64 comparisons, age wise difference in 7 out of 64 comparisons. Hypertension has shown significant change in 2 and 3 parameters in young male and female subjects respectively; with no significant change in higher age group. Significant changes observed in very low frequency and high frequency parameters are similar to those observed in blood pressure variability.

KEYWORDS

heart rate variability, peripheral blood flow variability, morphological index variability, hypertension

I. INTRODUCTION

The average heart rate (HR) of a healthy person is around 72 beats per minute, which may vary from person to person. It also varies with mental and physical state of the person. Minor fluctuation in HR is observed even when a person is at rest. This is termed as physiological variability. The most extensively studied variability is that of HR commonly known as heart rate variability (HRV), resulting in its use for the objective assessment of autonomic nervous system (ANS). Other variabilities, which have been studied, are systolic and diastolic blood pressure variability (SBPV and DBPV), peripheral blood flow variability (PBFV) and morphology index variability (MIV). Study of blood pressure variability is considerably difficult as compared to HRV, since data collection is either invasive orexpensive due to prohibitively high-cost of noninvasive beat-to-beat BP monitors. Peripheral blood flow measured for long intervals in controls and hypertensive subjects in the past has shown suppressed rhythmic variations in patients[1] as shown in Figure 1.

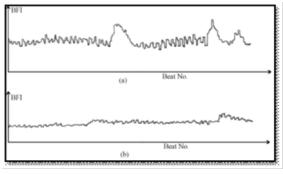

Fig.1 *Blood flow index plotted against beat number in (a) a control subject and (b) a hypertensive subject. Prominent and damped fluctuations are seen in (a) and (b) respectively.*

A typical HRV spectrum is divided into three frequency ranges, commonly known as very low frequency (VLF), low frequency (LF) and high frequency (HF) regions; ranging 0.004-0.039 Hz, 0.04-0.15 Hz and 0.151-0.40 Hz respectively. Based on studies conducted on HRV during the past 4 decades LF component represents sympathetic drive, HF represents vagal modulation and LF/HF ratio represents sympatho-vagal balance[2,3]. Some of the studies showing correlation of VLF, LF, HF peaks in HRV, SBPV or DBPV with various physiological activities are briefed in Table-1.

Table-1: Summary of physiological correlation of VLF, LF, HF peaks in HRV, SBPV or DBPV

Sr. No.	Authors	Investigations	Findings
1.	Hyndman et al[4], 1971	Study of spontaneous repetitive fluctuations of a typical period of 10 seconds in mean arterial pressure.	Spontaneous fluctuation in peripheral blood flow occurs due to adjustment in cutaneous circulation by thermoregulatory system.
2.	Akselrod et al [3] 1981	Blockade of renin-angiotensin in trained unanesthesized conscious dogs.	2 to 3 fold increase in area of VLF in 3 out of 4 dogs.
3.	Mancia et al[5] (1985)	Intravenous phenylephrine or nitroglycerine responses in 82 subjects.	Baro-reflex sensitivity shows an inverse relation with HF component in SBPV and direct relation with HRV.
4.	Sleight et al[6] (1995)	Study with controlled respiration (0.25Hz) and sinusoidal neck suction	Increase in HF component in HRV as an evidence of good baroreflex response.
5.	Lucini et al[7](2002)	Impairment in cardiac autonomic regulation preceding arterial hypertension in humans.	The LF component of SBP and variance of SBP increase significantly with rising baseline arterial pressure.
6.	Virtanen et a[8] (2003)	Association with plasma renin activity in 105 controls and 191 newly diagnosed untreated hypertensives (35-54 yrs).	Reduction in HRV and its HF component is independently associated with high heart rate, higher age and higher mean arterial pressure.
7.	Nishikino et al[9] (2006)	Genetic variation in the renin-angiotensin system and autonomic nervous system function.	Renin-angiotensin system alters HRV and BPV in lower frequencies.
8.	Hesse et al[10] (2007)	Correlation of baroreceptor sensitivity with blood pressure and heart rate variability (19 males and 31 females).	Baroreceptor sensitivity correlates inversely with day time blood pressure variability and positively with day time heart rate variability.
9.	Lutfi et al [11] (2011)	Effect of Blood Pressure on HRV (28 Males & 28 Females).	Systolic, diastolic and mean blood pressure correlates positively with LF and LF/HF. SBP correlates negatively with HF. DBP correlates negatively with HF and total power.
10.	Patil et al[12] (2015)	Study of HR, BP and HRV at rest in 30 normotensive and 30 hypertensive male subjects.	Alteration in sympatho-vagal balance by sympathetic predominance in essential hypertension is supported by significant decrease in parasympathetic activity

In our previous HRV study in controls and hypertensive subjects, HRV_LF_PA (peak amplitude of LF in HRV spectrum) and HRV_LF_A (area under LF peak in HRV spectrum) showed significant increase in young hypertensives (18 to 30 years) and no significant change in elder hypertensives (30 to 45 years)[13]. To explore the usefulness of PBFV and MIV and also to explore relation between PBFV and SBPV in hypertensive subjects, these variabilities have been derived from the peripheral pulse analyzer (PPA) data already acquired in the above study. The results and analysis are briefly reported in this paper

II. MATERIALAND METHODS

The study on HRV was conducted at Bio-Medical Engineering Department of MGM College of Engineering and Technology, Kamothe, Navi Mumbai. It was approved by the ethics committee of MGM Institute of Health Sciences (Deemed University) in its meeting held on 25th March 2015 as 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 with history of 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. Data has been stratified gender wise in two age groups of 18-30 and 31-45 years as shown in Table-2.

Table-2: Number of subjects included in each group

Subjects	18-30		31-45	
	Males	Females	Males	Females
Controls	34 (A)	34 (B)	34 (C)	34 (D)
Hypertensives	22 (E)	28 (F)	30 (G)	20 (H)

Acquired PPA data has been used to derive PBFV and MIV in a graphic user interface (GUI) shown in Figure 2 as follows.

Pre-acquired data can be viewed in the top graph. 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 inter-systolic-peak interval (closely corresponding RR-interval of electrocardiogram) as a function of time. Third and fourth graphs below the second graph represent blood flow index and morphological index as a function of time. Faulty peak detection can be edited with the help of arrow and insert/delete buttons provided in the bottom towards right. Edited saved data is then opened in DISPLAY panel (Figure 3) for viewing PBFV and MIV spectra. Variability in time domain and frequency domain and computed variability parameters are seen side by side in this panel. By clicking on SAVE EXCEL, data is transferred to designated excel sheet.

Data saved in Excel sheet is then processed for statistical analysis. To begin, five values of an individual PBFV and MIV parameter (obtained from 5 recordings on the subject) in a subject are averaged. The mean of such average values in all the subjects in a particular group is then obtained. Mean thus obtained has a lowered value of standard deviation (SD) in comparison to un-averaged values, as reported by Jindal et al [14]. The average parameter gives the advantage of using parametric statistics in conformity to central limit theorem.

One way ANOVA (analysis of variance) has been performed on all the PBFV and MIV parameters using SPSS software. Subsequently Tukey's HSD test has been performed to identify significant difference between any two stratified groups.

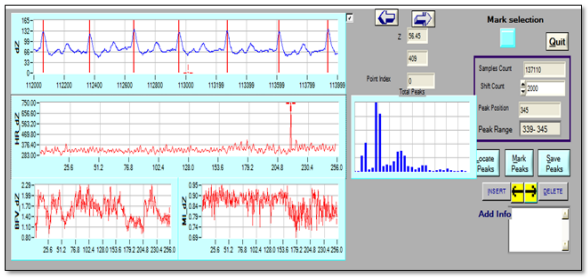

Figure 2: Processing panel for derivation of PBFV and MIV.

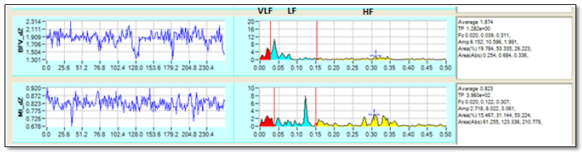

Figure 3: *Shows DISPLAY panel: Graphs on the left display time domain and that on the right give frequency domain variations. Computed parameters are displayed in the box on the extreme right. VLF, LF and HF are highlighted with red, blue and yellow color respectively.*

III RESULTS

Table-3 gives mean and standard deviation (SD) values computed from average values of a PBFV and MIV parameter in each subject. The parameters are abbreviated as follows. For PBFV, eight parameters are: total power (PBFV_TP), mean (PBFV_Mean), amplitude of VLF peak (PBFV_VLF_PA), Area of VLF peak (PBFV_VLF_A), amplitude of LF peak (PBFV_LF_PA), area of LF peak (PBFV_LF_A), amplitude of HF peak (PBFV_HF_PA), area of HF peak (PBFV_HF_A). Similarly for MIV, respective parameters are: total power (MI_TP), mean (MI_Mean), amplitude of VLF peak (MI_VLF_PA), area of VLF peak (MI_VLF_A), amplitude of LF peak (MI_LF_PA), area of LF peak (MI_LF_A), amplitude of HF peak (MI_HF_PA) and area of HF peak (MI_HF_A).

Table-3: Mean and Standard Deviation Values of Parameters in Control and Hypertensive Subjects

Stratified Group Parameters	A	B	C	D	E	F	G	H
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
PBFV_TP	8.358 ± 4.269	4.661 ± 2.513	4.599 ± 3.600	3.380 ± 2.502	5.651 ± 3.990	3.460 ± 3.351	12.022 ± 7.445	47.289 ± 18.460
PBFV_ Mean	2.771 ± 0.877	2.674 ± 0.859	1.609 ± 0.701	1.607 ± 0.726	1.683 ± 0.530	1.594 ± 0.686	2.505 ± 1.600	2.928 ± 1.509
PBFV_VLF_PA	17.793 ± 3.154	16.632 ± 2.772	17.004 ± 5.271	15.525 ± 5.676	13.846 ± 6.804	12.328 ± 4.949	17.761 ± 8.017	12.519 ± 6.288
PBFV_VLF_A	50.176 ± 11.180	47.974 ± 10.791	45.843 ± 14.257	44.180 ± 13.510	37.478 ± 17.014	29.099 ± 12.605	49.539 ± 18.441	38.703 ± 17.570
PBFV_LF_PA	7.157 ± 2.434	6.210 ± 1.764	5.627 ± 2.838	5.033 ± 1.611	5.721 ± 2.832	6.302 ± 3.224	4.302 ± 1.500	4.098 ± 1.439
PBFV_LF_A	38.547 ± 11.314	35.625 ± 9.317	30.208 ± 10.358	29.946 ± 8.720	34.311 ± 11.201	35.702 ± 9.950	25.966 ± 8.406	28.911 ± 8.789
PBFV_HF_PA	0.733 ± 0.322	1.122 ± 0.695	1.177 ± 0.663	1.353 ± 0.652	1.465 ± 0.898	2.234 ± 1.783	1.412 ± 0.940	2.474 ± 1.786
PBFV_HF_A	9.098 ± 3.376	13.970 ± 6.597	19.741 ± 11.179	22.095 ± 12.313	26.409 ± 16.406	31.962 ± 14.425	22.433 ± 14.576	30.528 ± 15.397
MI_TP	1980.4 ± 1639.5	2230.3 ± 1596.7	2502.6 ± 1711.3	2250.2 ± 1946.3	4026.6 ± 3237.8	3384.2 ± 2601.7	2968.1 ± 2901.4	2818.8 ± 2646.6
MI_Mean	0.730 ± 0.057	0.748 ± 0.064	0.718 ± 0.110	0.735 ± 0.096	0.682 ± 0.152	0.662 ± 0.155	0.681 ± 0.146	0.663 ± 0.155
MI_VLF_PA	18.131 ± 3.558	18.826 ± 4.779	16.281 ± 7.344	16.606 ± 6.335	17.389 ± 10.584	14.123 ± 6.254	18.146 ± 7.238	14.490 ± 8.922
MI_VLF_A	49.219 ± 11.016	50.021 ± 13.192	44.140 ± 13.907	44.209 ± 12.512	40.333 ± 19.369	33.084 ± 12.551	48.204 ± 15.828	39.540 ± 20.501
MI_LF_PA	5.798 ± 2.074	4.819 ± 1.587	5.196 ± 2.767	4.406 ± 1.343	5.030 ± 2.469	5.128 ± 2.465	3.761 ± 1.375	3.852 ± 2.838
MI_LF_A	31.817 ± 9.072	27.766 ± 8.089	29.039 ± 10.059	26.380 ± 7.904	31.090 ± 11.637	32.823 ± 11.207	23.570 ± 7.268	25.047 ± 10.780
MI_HF_PA	1.415 ± 0.771	1.684 ± 0.917	1.846 ± 1.291	1.711 ± 0.707	1.699 ± 1.002	2.308 ± 1.689	2.054 ± 1.920	2.462 ± 1.893
MI_HF_A	16.441 ± 7.470	19.145 ± 8.776	23.422 ± 14.217	25.491 ± 10.583	26.355 ± 14.961	30.622 ± 12.178	26.556 ± 13.742	32.236 ± 19.579

Table-4 gives combined analysis of variance (ANOVA) of all the subgroups and comparison of mean values between two of subgroups stratified gender, age and disease wise. Groups A-B, C-D, E-F and G-H represent gender stratification, groups A-C, B-D, E-G and F-H represent age stratification and Groups A-E, B-F, C-G and D-H represent disease stratification. As can be seen from the table, out of 16 variability parameters ANOVA shows significant difference in 13 parameters at 5% significance level. Three parameters showing no significant difference among different groups are PBFV_TP, MI_VLF_PA and MI_HF_PA. Therefore sensitivity of these three parameters for assessment of hypertension can be said to be very low. Tukey's HSD test ($\alpha = 0.05$) on mean values performed on gender stratified groups has shown significant difference in only two comparisons out of 64 (3.12%) suggesting minimal relevance of gender-wise stratification. Similar comparison for age stratification reveals 7 comparisons out of 64 (10.94%) to be significantly different indicating its higher relevance. Comparison of age and gender stratified data in controls and hypertensive males (age < 30 years) show significant difference in mean of PBFV_VLF_A, and MI_TP parameters and that in controls and hypertensive females (age < 30 years) show significant difference in mean of PBFV_VLF_A, MI_VLF_A and MI_HF_A parameters. Similar comparison in higher age group failed to show any significant difference. This suggests that variability changes due to aging mask those due to increased blood pressure.

Table-4: Summary of ANOVA and Tukey's HSD test in age, gender and disease stratified subjects

Parameters	ANOVA F-Crit (2.049)	Probability as per Tukey's HSD test (Level of significance 5%)											
		Gender Stratification				Age Stratification				Disease stratification			
Groups	A to H	A-B	C-D	E-F	G-H	A-C	B-D	E-G	F-H	A-E	B-F	C-G	D-H
PBFV_TP	1.670	1.000	1.000	1.000	0.298	1.000	1.000	1.000	0.101	1.000	1.000	0.999	0.071
PBFV_Mean	10.649	1.000	1.000	1.000	0.810	0.005-	0.003-	0.055	0.001+	0.001-	0.001-	0.008+	0.008+
PBFV_VLF_PA	4.544	0.988	0.953	0.977	0.023-	0.999	0.991	0.169	1.000	0.137	0.051	0.999	0.519
PBFV_VLF_A	7.204	0.998	1.000	0.445	0.155	0.917	0.958	0.054	0.315	0.026-	0.001-	0.970	0.876
PBFV_LF_PA	5.834	0.686	0.963	0.986	1.000	0.114	0.408	0.338	0.028-	0.288	1.000	0.295	0.835
PBFV_LF_A	5.726	0.923	1.000	1.000	0.968	0.013-	0.254	0.049-	0.275	0.751	1.000	0.671	1.000
PBFV_HF_PA	8.524	0.762	0.996	0.137	0.008+	0.618	0.982	1.000	0.993	0.137	0.001+	0.983	0.003+
PBFV_HF_A	12.248	0.706	0.993	0.733	0.280	0.008+	0.103	0.933	1.000	0.006+	0.005+	0.986	0.205
MI_TP	2.460	1.000	1.000	0.970	1.000	0.980	1.000	0.700	0.999	0.002+	0.510	0.999	0.999
MI_Mean	2.431	0.999	0.999	0.998	0.999	1.000	1.000	1.000	1.000	0.804	0.089	0.912	0.366
MI_VLF_PA	1.721	1.000	1.000	0.704	0.593	0.954	0.886	1.000	1.000	1.000	0.143	0.960	0.958
MI_VLF_A	4.399	1.000	1.000	0.658	0.451	0.842	0.728	0.525	0.810	0.328	0.003-	0.955	0.949
MI_LF_PA	3.108	0.557	0.792	1.000	1.000	0.941	0.993	0.388	0.466	0.885	0.999	0.132	0.984
MI_LF_A	3.507	0.640	0.941	0.998	0.999	0.927	0.999	0.082	0.101	1.000	0.430	0.289	1.000
MI_HF_PA	1.914	0.990	1.000	0.726	0.961	0.875	1.000	0.977	1.000	0.993	0.586	0.998	0.460
MI_HF_A	5.086	0.987	0.998	0.934	0.774	0.308	0.435	1.000	1.000	0.075	0.012+	0.975	0.554

Symbols "+ or –" to the numerical figures in columns 3 to 14 indicate increase or decrease in the mean value of the later group in comparison to that of former.

IV. DISCUSSION

Hypertension related studies on HRV and BPV have shown a) two to 3 fold increase in area of VLF in 3 out of 4 dogs during selective renin-angiotensin blockade[3], b) baro-reflex sensitivity having an inverse relation with BPV and direct relation with HRV (increase in HF component suggests good baroreflex response)[4,8], c) LF component of SBP and variance of SBP increase significantly with rising baseline arterial pressure in hypertensive subjects[7] and d) LF component of HRV in younger age group is seen to increase in amplitude as well as area due to hypertension[13].

In the present study stratified data has been maintained for gender and age. Variability has been compared in health and disease with respect to specific age and gender group. Though gender has been found to influence 2 (PBFV_VLF_PA, PBFV_HF_PA), age has influenced 4 parameters (PBFV_Mean, PBFV_LF_PA, PBFV_LF_A and PBFV_HF_A. PBFV_HF_A). Due to their sensitivity to gender and age, these six parameters are not considered for disease analysis even though they have shown significant change.

Hypertensive males (age < 30 years) show significant difference in mean of PBFV_VLF_A, and MI_TP and hypertensive females (age < 30 years) show significant difference in mean of PBFV_VLF_A, MI_VLF_A and MI_HF_A with respect to their age and gender stratified control group. PBFV_VLF_A has consistently decreased in both the groups. Increase in MI_TP in young male hypertensives and that in MI_HF_A in young female hypertensives is similar to increase in HF component of blood pressure variability in hypertension. Higher age group subjects have not shown any specific change in variability parameters; probably due to age related changes mask those of hypertension. This has also been observed by some researchers in the past[8].

Peripheral blood flow variability and morphology index variability has probably been studied for the first time in gender and age stratified data. Results of the study indicate that their behavior is more like that of blood pressure variability in contrast to heart rate variability. Thus PBFV and MIV offer a noninvasive, simple and inexpensive alternative to blood pressure variability.

V. CONCLUSION

The study demonstrates that variability parameters PBFV_VLF_A, and MI_TP are significantly different in male subjects in the lower age group and variability parameters PBFV_VLF_A, MI_VLF_A and MI_HF_A are significantly different in female subjects in the lower age group. These parameters can be considered specific of early hypertension. Age related changes in the blood vessels appear to mask those of hypertension in the higher age group (> 30 years) subjects.

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