HEART RATE VARIABILITY TIME-DOMAIN ANALYSIS IN PULMONARY METASTASIS TO ASSESS PERFORMANCE STATUS

REEMA SHYAMSUNDER SHUKLA[a1] AND YOGENDER AGGARWAL[b]

[ab]Birla Institute of Technology, Mesra. Ranchi, Jharkhand, India

ABSTRACT

The time domain measures of Heart Rate Variability (HRV) were calculated from Electrocardiograph (ECG) recording of 5 minutes duration obtained from twenty four pulmonary metastasis subjects and thirty controls. The different sites of primary cancer were thymus, synovial sarcoma of thigh, oesophagus, testicle, cervix, gastro-oesophageal junction, sigmoid colon, gall bladder, peritoneum, Non Hodgkin lymphoma, breast, thymus, mandible and thyroid. The present study deals with the function of autonomic nervous system in pulmonary metastases. The obtained HRV indices were subjected to statistical analysis and classifier to test the statistical significance and classification which can serve as an aid for diagnosis of performance status. Based on treatment and gender, HRV indices were obtained. More sympathetic dominance and decrease in parasympathetic activity exists in ECOG 4 as compared to other performance status (PS) but parasympathetic activity increases after the treatment due to vagal nerve activity pre-dominance and males had higher values of measures than females.

KEYWORDS: Heart Rate Variability, Lung, Cancer, Metastasis, Autonomic

Autonomic nervous system (ANS) is considered very vital in cancer, which is related to fatigue [1]. Several studies have used heart rate variability (HRV) variable to evaluate ANS [2]. HRV is analyzed by extracting beat-to-beat intervals of electrocardiogram (ECG) that changes in time [3]. It has been suggested that longer duration stress stimulates growth of cancer and its progression thereby decreasing survival rate [4]. It was observed that subjects having Standard Deviation of Normal to Normal RR Intervals (SDNN)<70ms had lowered values of percentage of adjacent RR intervals separated by more than 50 ms (pNN50) and square root of mean squares of differences in adjacent RR Intervals (RMSSD). [5].The aggregation of relatively undeveloped and pathologically activated myeloid-derived suppressor cells (MDSCs) with effective immunosuppressive action is frequent in tumors; MDSCs aids in spreading the cancerous cells by penetrating the healthy tissue thereby promoting angiogenesis and metastases [6]. Sympathetic neurotransmitters like epinephrine, norepinephrine regulates the development and progression of cancer cells leading to metastasis, whereas vagal nerves stops the migration of cancerous cells [7]. SDNN, Integration of RR Interval histogram divided by height of the histogram (TI), RMSSD was lower in hypertensive subjects compared to controls [8]. The Karnofsky's index of performance status (KPS) and the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) are extensively applied ways of evaluating the functional status of cancer patients [9]. It has six levels starting from 0 (zero) (patients with no symptoms) to 5 (Dead) [10].

It was hypothesized that HRV indices shows lower values in pulmonary metastatic subjects and have lower survival rate. There exists elevation in sympathetic activity and depression in parasympathetic activity but after the treatment parasympathetic activity increases. Males have higher time domain measures than females. The classifier can serve as an aid in diagnosis of performance status in subjects.

MATERIALS AND METHODS

Lead II ECG for 5 minutes in supine position was recorded from 24 lung metastatic cancer patients and 30 controls with cut-off values (0.5 Hz to 35 Hz) sampled at 200 samples/sec. The recording was made using SS2LA leads and disposable electrodes with the help of MP45 unit of BIOPAC Inc, USA [11]. The tachogram plot was obtained from recorded ECG signal using Acknowledge 4.0 of BIOPAC Inc, USA [12]. HRV analysis was conducted using Kubios 2.0 HRV analysis tool [13]. The theory and details of HRV analysis was discussed earlier, which is also used for this study [14- 15]. Statistical Analysis was done with Statistical R, 64 bit, v.3.3.2 [16]. One-way analysis of variance (ANOVA) and two-tailed student t-test was conducted when the null hypothesis was not applicable. All the differences were considered significant at $P < 0.05$. In Figure 2, we have mentioned classifier accuracy, which has classified subjects into its performance status of five classes including ECOG 1, ECOG 2, ECOG 3, ECOG 4 and controls. The architecture of Artificial Neural Network (ANN) is

---

[1]**Corresponding author**

given in Figure 1. ANN based on feedforward network with backpropagation algorithm with hidden layer of 100 neurons, 5 inputs and 5 outputs; and varied learning rate to obtain maximum accuracy in MATLAB, 2014 [17]. Windows 7, Intel Core i3-2330M Processor 2.20GHz, 64-bit, HDD 320gb, RAM 2GB System was used for Support Vector Machine (SVM) classifier wherein, Radial Basis Function (RBF) kernel was utilized and multi-classifier was used to give classification accuracy for 5 outputs [18].
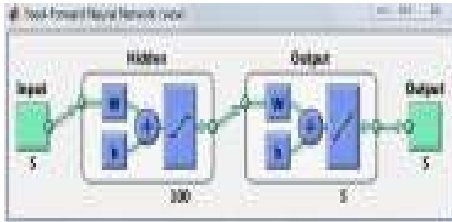

Figure 1: Architecture of Neural Network

RESULTS

Patient demographics is given in Table 1.

Table 1: Patient Demographics

Characteristics	No.	%
Gender		
Male	11	45.83
Female	13	54.17
Age		
Median (range)	51.5	(22 to 86)
<=65	6	25
>=65	18	75
Primary		
Breast	4	16.67
Gall Bladder	3	12.5
Thyroid	1	4.16
Non-Hodgkin Lymphoma	2	8.33
Peritoneum	1	4.16
Synovial Sarcoma	1	4.16
Mandible	1	4.16
Thymic	1	4.16
Cervix	3	12.5
Sygmoid Colon	1	4.16
Gastric	1	4.16
Oesophagus	2	8.33
Testicular	3	12.5
ECOG Scale (Performance Status)		
ECOG 1	4	16.67
ECOG 2	1	4.16
ECOG 3	7	29.16
ECOG 4	12	50
Metabolic disorder		
Oedema	4	16.67

Loss of appetite	1	4.16
Vomiting	2	8.33
Smoking	1	4.16
Diarrhoea	1	4.16
Fever	2	8.33
Ascitis	1	4.16

In HRV analysis mentioned in Table 2 including ECOG 1, ECOG 2, ECOG 3 and ECOG 4, it was found that ECOG 4 has least values of SDNN, Standard Deviation of Heart Rate (STD HR), RMSSD, PNN50, and Baseline width of RR Interval histogram (TINN). It has also been observed that controls had higher values than all performance states of measures in Mean RR and HRV TI. All the values are in the form of mean ± standard error. RMSSD, pNN50 and SDNN had a very high classification output in both the classifiers, SVM and ANN mentioned in Figure 2.
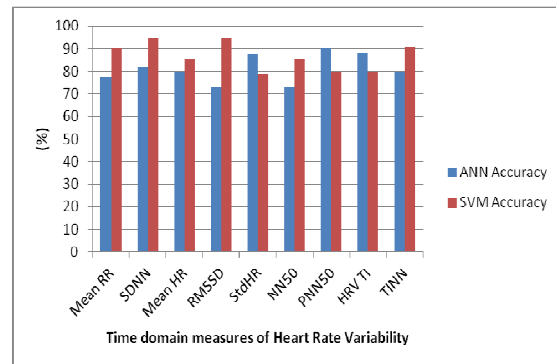

Figure 2: Classifier Output

Table 2: HRV Analysis based on time domain including all performance status (PS) from ECOG 1 to ECOG 4.

Time domain Measure	ECOG 1	ECOG 2	ECOG 3	ECOG 4	Control
Mean RR	646.51 ±4319.77	792.3	672.75 ±33.93	602.78 ±22	826.39 ±29.9
SDNN	131.3 ±19.24	78.53 ±0	40.93 ±4.85	14.3 ±2.28	104.50 ±24.99
Mean HR	99.12 ±13.14	76.53	91.01 ±4.68	100.94 ±3.38	76.35 ±24.99
Std HR	10.63 ±1.22	9.71 ±0	6.49 ±0.98	2.58 ±0.4	7.47 ±1.04
RMSSD	172.62 ±11.91	116.3 ±0	49 ±10.1	13.5 ±2.38	115.779 ±28.86
NN50	80.5 ±40.84	17 ±0	32.86 ±15.46	2 ±0.7	52.53 ±7.8
PNN50	18.57 ±9.69	4.5 ±0	7.59 ±3.55	0.41 ±0.14	16.13 ±2.62
HRV TI	6.29 ±1.99	8.79 ±0	4.67 ±1	3.33 ±0.54	9.56 ±0.78
TINN	571.25 ±30.23	545 ±0	360 ±64.06	130.83 ±31.7	309.33 ±28.26

On the basis of treatment given and no treatment applied, all the values are mentioned in Table 3. Further, obtained results also suggested that after the given treatment in the form of chemotherapy or radiotherapy, the values of HRV indices increased in Mean RR, SDNN, NN50, PNN50 and HRV TI, with performance status ECOG 3 and 4.

Table 3: Time-domain HRV Analysis based on treatment

Time domain Measure	ECOG 3 Treatment	ECOG 3 No Treatment	ECOG 4 Treatment	ECOG 4 No Treatment	Control
Mean RR	710.01 ±56.33	635.72 ±38.2	615.41 ±24.99	604.81 ±9.22	826.39 ±29.9
SDNN	47.25 ±5.39	41.38 ±7.93	37.7 ±20.83	9.27 ±3.86	104.50 ±24.99
Mean HR	86.74 ±7.47	98.49 ±6.06	100.48 ±3.83	99.29 ±1.57	76.35 ±24.99
Std HR	6.52 ±1.71	6.74 ±0.29	5.03 ±2.32	1.88 ±1.01	7.47 ±1.04
RMSSD	48.91 ±16.22	58.8 ±14.92	48.45 ±33.86	12.44 ±7.9	115.78 ±28.86
NN50	48.5 ±22.82	12.67 ±4.98	24.69 ±11.12	1.33 ±1.33	52.53 ±7.8
PNN50	11.59 ±5.1	2.57 ±0.86	5.02 ±4.48	0.26 ±0.26	16.13 ±2.62
HRV TI	6.51 ±1.29	2.92 ±0.71	3.94 ±0.61	1.95 ±0.36	9.56 ±0.78
TINN	262.5 ±62.73	486.67 ±54.57	128.33 ±108.33	128.33 ±108.33	309.33 ±28.26

Moreover, the values HRV indices increased after treatment in RMSSD, STD HR and TINN in ECOG 4. Based on gender, all the significant graphs are mentioned in Table 4. We found that males had higher values of Mean RR, SDNN, RMSSD, PNN50 and NN50 than females in ECOG 3 and 4. Control males had lower measures of HRV than control females.

Statistically, it was found that SDNN (p=0.000392), STD HR (p=0.006054), RMSSD (p=0.006262) and TINN (p=0.007199) were significant by two-tailed t-test. ANOVA analysis stated that Mean RR (F-statistic=6.6387, p=0.000237), mHR (F-statistic=7.7524, p=0.00006365), STD HR (F statistic= 3.474, p=0.01414), NN50 (F-statistic=4.42, p= 0.003931), PNN50 (F-statistic=4.0027, p=0.0069), HRV TI (F-statistic=7.4962, p=0.00008568) and TINN (F-statistic=9.0106, p=0.00001549) were statistically significant.

Table 4: Time-domain HRV Analysis based on gender
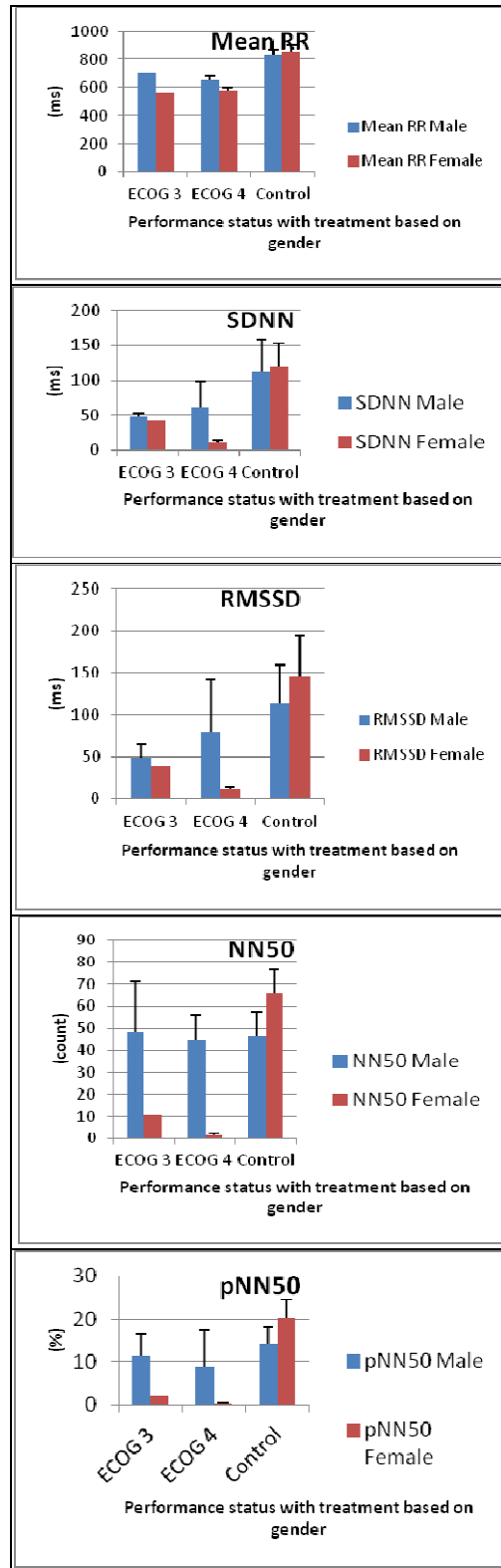
DISCUSSION

It was found that heart rate (HR) was prominently higher and SDNN and RMSSD were prominently lower in the breast cancer survivors than in the matched counterparts [19]. Decreased SDNN, HR and increased RR interval indicates parasympathetic activity dominance [21]. TI and TINN is increased when stressed [20]. The association between HRV and parasympathetic effect is explained as there is an rising limb where HRV rises as parasympathetic effect enhances until it reaches a flat level; HRV then is lowered as parasympathetic effect is increased [21]. HRV may be affected by gender and age [22]. It is observed that later stages patients have more decreased HRV values than in their initial stages [23]. TINN is not efficient index for the current study, because a 5-minute ECG recording is too short to assess the parameter [3]. Salminen gave 8 cycles of treatment to cancer patients with combination chemotherapy but found neither any cardotoxicity nor any HRV change [24]. Brouwer analyzed HRV variations after 22 years of treatment in malignant bone tumor patients treated with doxorubicin and found decreased HRV as compared to the healthy subjects [25]. NN50 and PNN50 describe parasympathetic activity [26]. There exists correlation between performance status ECOG scale and the critical condition of cancer patients [27]. ANN and SVM has played a vital role in giving a high classification accuracy of all HRV measures and establishing its significance [28].

CONCLUSION

In pulmonary metastases, HRV time domain measures decreased but after the application of required treatment of chemotherapy or radiotherapy or its combination gave us increased HRV time domain measures. Therefore, it can be stated that increased sympathetic and decreased parasympathetic functioning occurs before treatment which is vice-versa after the treatment, wherein parasympathetic functioning takes over.

ACKNOWLEDGEMENT

REFERENCES

Thayer J.F. and Sternberg E., 2006. "Beyond heart rate variability", Annals of the New York Academy of Sciences, **1088**:361-372.

Chiang J.K., Koo M., Kuo T.B. and Fu C.H., 2010. "Association between cardiovascular autonomic functions and time to death in patients with terminal hepatocellular carcinoma", Journal of pain and symptom management, **39**:673-679.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability: standards of measurement, physiological interpretation and clinical use", Circulation, **93**:1043–1065, 1996.

Riley V., 1975. "Mouse mammary tumors: alteration of incidence as apparent function of stress", Science, **189**:465-467.

Guo Y., Koshy S., Hui D., Palmer J.L., Shin K., Bozkurt M. and Yusuf S.W., 2015. "Prognostic value of heart rate variability in patients with cancer", Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society, **32**:516.

Kumar V., Patel S., Tcyganov E. and Gabrilovich D.I., 2016. "The nature of myeloid-derived suppressor cells in the tumor microenvironment", Trends in immunology, **37**:208-220.

Entschladen F., Drell T.Lt., Lang K., Joseph J. and Zaenker K.S., 2004. "Tumour-cell migration, invasion, and metastasis: navigation by neurotransmitters", Lancet Oncol, **5**:254-258.

Pavithran P., Nandeesha H., Sathiyapriya V., Bobby Z. and Madanmohan T., 2008. "Shortterm heart variability and oxidative stress in newly diagnosed essential hypertension", Clin Exp Hypertens, **30**:486–496.

Buccheri G., Ferrigno D. and Tamburini M., 1996. "Karnofsky and ECOG performance status scoring in lung cancer: a prospective,

longitudinal study of 536 patients from a single institution", European Journal of Cancer, **32**:1135-1141.

Lilenbaum R.C., Cashy J., Hensing T.A., Young S. and Cella D., 2008. "Prevalence of poor performance status in lung cancer patients: implications for research", J. Thorac Oncol., **2**:125-129.

Sarkar S., Bhattacherjee S. and Pal S., 2015. "Extraction of respiration signal from ECG for respiratory rate estimation", Michael Faraday IET International Summit 2015, IET, pp. 336-340.

Aggarwal Y., Singh N. and Sinha R.K., 2012. "Electrooculogram based study to assess the effects of prolonged eye fixation on autonomic responses and its possible implication in man-machine interface", Health Technol., **2**:89-94.

Hong S., Yang Y., Lee J., Yang H., Park K., Lee S. and Jang Y., 2010. "Ambulatory stress monitoring with a wearable luetooth electrocar-diographic device", Global Telehealth: Selected Papers from Global Telehealth 2010 (GT2010): 15th International Conference of the International Society for Telemedicine and Ehealth and 1st National Conference of the Australasian Telehealth Society, IOS Press, **161**:66.

Aggarwal Y., Singh N., Ghosh S. and Sinha R.K., 2014. "Eye gaze-induced mental stress alters the heart rate variability analysis", J. Clin Eng., **39**:79-89.

Acharya U.R., Joseph K.P., Kannathal N., Lim C.M. and Suri J.S., 2006. "Heart rate variability: a review", Medical and biological engineering and computing, **44**:1031-1051.

Neter J., Kutner M.H., Nachtsheim C.J. and Wasserman W., 1996. "Applied linear statistical models", Chicago: Irwin, **4**:318.

Hagan M.T. and Menhaj M.B., 1994. "Training feedforward networks with the Marquardt algorithm", IEEE transactions on Neural Networks, **5**:989-993.

Scholkopf B., Sung K.K., Burges C.J., Girosi F., Niyogi P., Poggio T. and Vapnik V., 1997. "Comparing support vector machines with Gaussian kernels to radial basis function classifiers", IEEE transactions on Signal Processing, **45**:2758-2765.

Caro-Morán E., Fernández-Lao C., Galiano-Castillo N., Cantarero-Villanueva I., Arroyo-Morales M. and Díaz-Rodríguez L., 2015. "Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments A Case-Controlled Study", Biological research for nursing, 1099800414568100.

Thalange A.V. and Mergu R.R., 2010. "HRV analysis of arrhythmias using linear-nonlinear parameters", Int. J. Comput. Appl., **1**:71-77.

Goldberger J.J., Challapalli S., Tung R., Parker M.A. and Kadish A.H., 2004. "Relationship of heart rate variability to parasympathetic effect", Circulation, **103**:1977-1983.

Pagani M., Lombardi F., Guzzetti S., Rimoldi O., Furlan R., Pizzinelli P. and Piccaluga E., 1986. "Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog", Circ. Res., **59**:178–193.

De Couck M. and Yori G., 2013. "Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients", Cancer Epidemiology, **37**(5):737-741.

Salminen E., Syvänen K., Korpela J., Varpula M., Antila K., Varjo P. and Ekholm E., 2003. "Docetaxel with epirubicin—investigations on cardiac safety", Anti-cancer drugs, **14**:73-77.

Brouwer C.A.J., Gietema J.A., Van Den Berg M.P., Bink-Boelkens M.T.E., Elzenga N.J., Haaksma J. and Postma A., 2006. "Long-term cardiac follow-up in survivors of a malignant bone tumour", Annals of oncology, **17**:1586-1591.

Ewing D.J., Neilson J.M. and Travis P., 1984. "New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms.", British Heart Journal, **52**:396-402.

Glare P., Sinclair C., Downing M., Stone P., Maltoni M. and Vigano A., 2008. "Predicting survival in patients with advanced disease", European Journal of Cancer, **44**:1146-1156.

Bogdan M. and Michael B., 2006. "Artificial neural networks and machine learning for

man-machine-interfaces-processing of nervous signals." ESANN.