Effect of Gender and Diabetes on Major Depressive Disorder using Heart Rate Asymmetry

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***Abstract*— In this study, we have investigated how heart rate asymmetry (HRA) changes in major depressive disorder (MDD) subjects with comorbid diabetes as well as in male and female. Depression score was determined based on PHQ-9 questionnaire and from 135 subjects 70 subjects were selected with 1000 or more RR intervals. Heart rate asymmetry is a Poincaré plot based nonlinear technique to analyze the asymmetry using RR interval time-series signal. Three commonly used HRA indices Guzik's index (GI), Porta's index (PI) and Ehlers' index (EI) were used to understand the changes in HRA in MDD. Results indicate significantly ($p<0.05$) different GI and EI values between 'Dep' and 'NonDep' subgroups in 'Combined' group. All three HRA indices are found significantly different in presence of depression in female subjects. These results provide better understanding about changes in HRA in MDD and HRA indices could be a plausible nonlinear HRV feature for differentiating Depression 'Dep' from NonDepression 'NonDep' group – i) without comorbid diabetes; ii) in Female subjects.**

I. Introduction

Depression is associated with an increased risk of developing cardiovascular disease (CVD) in otherwise healthy individuals. A plausible link between depression and CVD is dysregulation of the neural cortical-brainstem axis, which regulates cardiac rhythm via the efferent and afferent cardiac autonomic nervous system fibers. The left and right prefrontal cortex is differently associated with normal emotional function and affective disorders such as depression being preferentially localized to one hemisphere [1]. An asymmetric interaction between ascending information from the autonomic nervous system centers in the brainstem to the left and right forebrain areas and a reciprocal descending modulation by the forebrain associated with autonomic nervous system output can be the neuroanatomical link between depression and risk of adverse cardiac outcomes such as arrhythmia[2]. Prolonged sympathetic activation and decreased parasympathetic modulation have been found in patients with depression [3, 4].

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Several physiological as well as pathophysiological factors influence the function of the autonomic nervous system, which may be correlated with a higher incidence of depression or cardiovascular disease. As such females have a higher incidence of depression than males [5] and differ in incidence of cardiovascular disease as well as autonomic nervous system dysfunction assessed by heart rate variability (HRV) [6]. Similarly, diabetes is associated with an increased incidence of depression and cardiovascular disease [2, 7].Worldwide, the prevalence of mood and anxiety disorders is higher among persons living with diabetes compared to those without diabetes [8-10]. In a meta-analysis of 42 published studies comprised of 21,351 adults, the prevalence of major depression in people with diabetes was 11% and the prevalence of clinically relevant depression was 31% [8, 11]. The first data on gender differences in the prevalence of depression episodes comes from the National Comorbidity Survey (NCS) in the United States, where it was reported that women are approximately 1.7 times more likely as men to report a lifetime history of depression episodes. This higher prevalence in women commences in early adolescence and is found up to middle age [12]. A complex relationship between gender, diabetes and depression exists as a study by Ali et al. has shown [13]. These authors reported a higher prevalence of depression in females with diabetes (23.8%) compared with males (12.8%). However, the odds ratio for depression in patients with Type 2 diabetes compared with those without was higher in males (OR = 1.9, 95% CI 1.7–2.1) than females (OR = 1.3, 95% CI 1.2–1.4) [14]. To elucidate the association of gender and diabetes with depression further, the current study investigated data from a rural cohort attending a diabetes-screening clinic, who answered the PHQ9 depression questionnaire and had a long-term ECG recorded.

Analysis of heart rate variability (HRV) is a simple and noninvasive way of quantifying autonomic activity or sympathetic–parasympathetic balance from an ECG recording [14, 15]. Nonlinear methods of HRV analysis have become prominent, since they have improved predictive power for determination of sudden cardiac death risk and characterization of disease states associated with autonomic nervous system function [16]. Time irreversibility or asymmetry analysis can detect a more specific type of nonlinear dynamics [17] capable of producing temporal asymmetries of the heart rate and resulting in statistical properties that are different when the heart rate series are observed after time reversal. In this study, we investigated how HRA changed with presence of depressive symptoms

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determined by the PHQ-9 questionnaire, which is a validated instrument used in clinical settings to determine the symptoms of depression in individuals with or without a diagnosis of depression, in a diabetic and non-diabetic population as well as comparing male and female HRA with respect to depression.

II. Data and Methods

A. Data

Data were collected during February to November 2012 from people attending the Diabetes Screening Initiative at Charles Sturt University with either type 2 diabetes or healthy. Ethical approval for this research was granted by The Charles Sturt Ethics Committee Protocol Number 2010/093. Level of depression was assessed by PHQ-9, which is a validated instrument used in clinical settings but is also used to determine the symptoms of depression in individuals with or without a diagnosis of depression. A total of 182 individuals attended the screening. Of these 135 returned the PHQ-9 questionnaire and had an electrocardiogram (ECG) result as well as complete demographic data. Known hypertension was reported in 39 individuals of the cohort and 14 participants reported depression or antidepressive treatment. Participants in the type 1 diabetes group were taking oral antidiabetic medication. One person in the cohort reported smoking.

High frequency noise was removed with a 45 Hz low pass filter and a 0.5 Hz high pass filter adjusted for wandering baseline. RR intervals, and the difference of successive R waves of the QRS complex, were calculated using the algorithm developed by Pan and Tomkin [18]. Ectopic beats were selected visually and deleted manually. Finally, 70 subjects were selected with more than 1000 RR intervals for HRA analysis.

Subjects were divided into five groups (Table I), which were further divided into two subgroups namely "NonDep" – subjects with minimal or no symptom ($PhQ-9\ score<5$) and "Dep" – subjects with moderate or severe depressive symptoms ($PhQ-9\ score\geq 5$). The number of subjects in each subgroup and their age is shown in Table I. There were no significant differences in age between the subgroups.

B. HRA Indices

The following HRA indices were used to measure the asymmetry of the RR interval time-series:

1) Guzik's Index (GI): Guzik et al. have defined the index for measuring the asymmetry of the time series using a Poincaré plot [19]. GI, is defined as the distance of the plotted points from the line of identity. Any point on the plot is given as $P_i(RR_i, RR_{i+1})$. The distance from line of identity is calculated as:

$$D_i = \frac{|RR_i - RR_{i+1}|}{\sqrt[2]{2}} \tag{1}$$

and GI is defined as:

$$GI = \frac{\sum_{i=1}^{C(P_i^+)}(D_i^+)^2}{\sum_{i=1}^{N-1}(D_i)^2} \times 100 \tag{2}$$

where, P_i^+ represents the point above the line of identity ($RR_i < RR_{i+1}$), D_i^+ represents the corresponding distance of P_i^+ from the line of identity, $C(P_i^+)$ represents the total number of points above the line of identity and N is the total number of RR intervals.

2) Porta's Index (PI): In contrast to the distance from the line of identity, PI is defined based on the distribution of points below and above the line of identity. PI is calculated as the percentage of the number of points below the line of identity with respect to the total number of points [20].

$$PI = \frac{C(P_i^-)}{N-1} \times 100 \tag{2}$$

where, P_i^- represents the point below the line of identity ($RR_i > RR_{i+1}$), $C(P_i^-)$ represents the total number of points below the line of identity and N is the total number of RR intervals.

3) Ehlers' Index (EI): Ehlers et al. [21] have used the first derivative of the RR interval series for assessing asymmetry of the given distribution. Skewness is measured over the first derivative signal to estimate the asymmetry of the distribution. Hence, for a RR interval time series it can be defined as follows:

$$EI = \frac{\sum_{i=1}^{N-1}(RR_i - RR_{i+1})^3}{(\sum_{i=1}^{N-1}(RR_i - RR_{i+1})^2)^{\frac{3}{2}}} \tag{3}$$

where, N is the total number of RR intervals. Unlike GI and PI, EI is not defined as a percentage but a non-zero value of EI indicates asymmetry.

TABLE I. Subject Groups and Demographies (Mean ± SD).

Group	Subgroup	n	Age
Combined	NonDep	47	69 ± 10
	Dep	23	69 ± 9
	p value		0.975
Diabetic	NonDep	12	69 ± 9
	Dep	10	68 ± 8
	p value		0.644
NonDiabetic	NonDep	35	68 ± 10
	Dep	13	69 ± 9
	p value		0.834
Female	NonDep	26	70 ± 8
	Dep	18	67 ± 9
	p value		0.11
Male	NonDep	21	67 ± 11
	Dep	5	74 ± 3
	p value		0.236

n is the number of subjects in each subgroup
"Dep" subject with depressive symptoms
"NonDep" subject with minimal or no depressive symptoms

C. Statistics

The non-parametric Mann-Whitney U-test was performed to allow pair-wise testing for significant differences of HRA parameters between the two subgroups (NonDep and Dep) within each group (Combined, Diabetic, NonDiabetic,

Female and Male). Since, the number of subjects are small and their distribution is not normal a non-parametric test is more appropriate than parametric test.

III. Results & Discussion

The mean ± SD (standard deviation) values of HRA indices for each subgroup are shown in Table II and the corresponding error bar plot shown in Figure 1. Guzik's index (GI) was found to be more asymmetric, i.e., mean GI values are far from 50%, in the NonDep subgroup than that of the Dep subgroup for all groups of the study. This shows that the RR time series of subjects with no or minimal depressive symptoms are more asymmetric than subjects with depression. This is in line with previous findings where HRA is reported to be highest for healthy physiological systems under resting conditions [22] and decrease with pathology, thus providing a marker for any loss of normal functionality.

The decreased asymmetry of subjects within the Dep subgroup may be attributed to the loss of autonomic nervous system functionality. Although GI (%) was higher in NonDep subgroup than Dep subgroup for each group, a statistically significant ($p<0.01$ or $p<0.05$) difference was only found between the "Combined" "NonDiabetic" and "Female" groups.

In contrast to GI, PI was symmetric in both NonDep and Dep subgroups i.e. values are close to 50%, for each group and no significant difference in PI values between no or minimal depressive symptoms and subjects with depressive symptoms was found.

TABLE II. Mean ± SD values of HRA indices (GI, PI and EI) and p-value between two subgroups of each group using Mann-Whittney U-test.

Group	HRA Index	NonDep	Dep	p
Combined	GI (%)#	52.36 ± 3.88	49.54 ± 3.48	***0.004***
	PI (%)	49.55 ± 2.16	51.28 ± 2.93	0.056
	EI#	-0.01 ± 0.01	-0.00 ± 0.01	***0.006***
Diabetic	GI (%)	51.73 ± 3.63	49.03 ± 3.90	0.06
	PI (%)	49.95 ± 1.68	51.58 ± 3.28	0.277
	EI	-0.01 ± 0.01	0.00 ± 0.01	0.07
NonDiabetic	GI (%)*	52.58 ± 3.99	49.92 ± 3.23	***0.033***
	PI (%)	49.41 ± 2.31	51.04 ± 2.75	0.144
	EI	-0.01 ± 0.01	-0.00 ± 0.01	0.06
Female	GI (%)#	51.97 ± 3.34	49.00 ± 3.34	***0.005***
	PI (%)*	49.67 ± 2.28	51.69 ± 2.96	***0.044***
	EI#	-0.01 ± 0.01	0.00 ± 0.01	***0.006***
Male	GI (%)	52.85 ± 4.50	51.46 ± 3.64	0.603
	PI (%)	49.40 ± 2.06	49.78 ± 2.55	1
	EI	-0.01 ± 0.02	-0.00 ± 0.01	0.558

* p<0.05; # p<0.01

All values are given in Mean ± SD.

EI was found negatively asymmetric in the NonDep subgroup within each of the groups of the study. This indicates that the distributions of increment/decrement of RR interval time-series for the NonDep and Dep groups were different in direction i.e., negatively skewed for NonDep and positively skewed for Dep (Diabetic and Female) (Figure 1). The EI values between NonDep and Dep subgroups were significantly different only for the Combined and Female groups.

There are various measures available to quantify asymmetry in cardiovascular signals. Recent studies suggest that simple HRA indices such as Guzik's, Porta's, and Ehlers' index are sensitive to shifts in sympatho-vagal balance. PI compares the number of increments and decrements in the RR time-series signal (i.e. deceleration and acceleration of the heart rate), whereas GI compares the magnitude of such acceleration and deceleration. On the other hand, EI measures the skewness of the magnitude of acceleration/deceleration distribution. These different methods may provide partially independent information and their simultaneous quantification might be useful in order to detect their reversibility and thus asymmetry more comprehensively.

Although the results of this study indicates that GI and EI performed better than PI in detecting subjects with depressive symptoms, the importance of PI should not be dismissed since, it has been reported to perform better in measuring the change in HRA due to postural change [23].

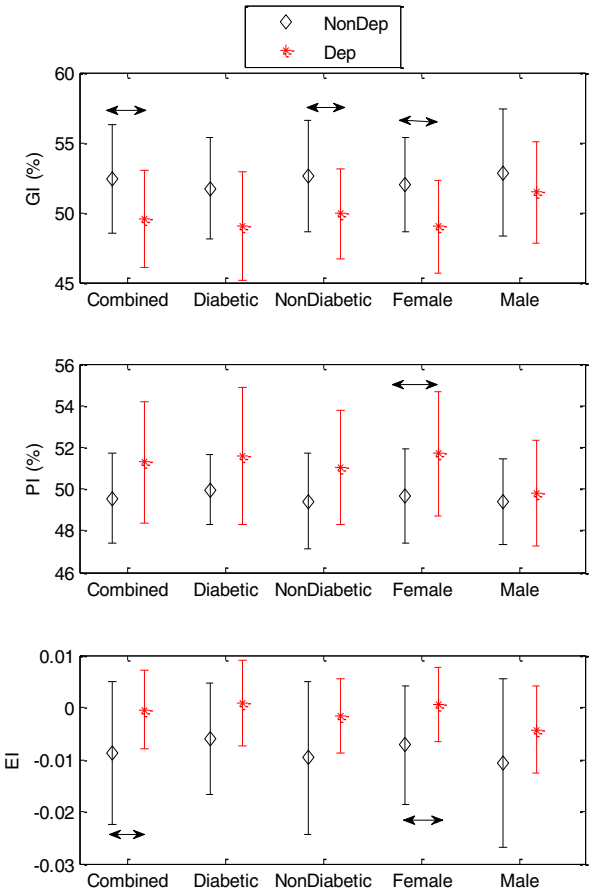

Figure 1. Errorbar (mean ± SD) of GI, PI and EI for each group of subject. Double ended arrow shows the values are significantly different between sbujects with no or minimal depressive symptoms and subject with moderate to severe depressive symptoms.

Within the context of depression the current result highlights that the number of accelerations and decelerations, that is, sympathetic and parasympathetic influence did not change significantly. Rather it is the magnitude of these intervals that decreases in the depression group (measured by GI) combined with a shift towards sympathetic predominance (measured by EI).

The mean values of GI were not significantly ($p=0.06$) different between NonDep and Dep subgroups in the Diabetic group. But this may be due to the small number of subjects in the Diabetic group. An alternate reason could be an effect attributable to diabetes affecting autonomic nervous system function, which counteracts the effect of depression in terms of the magnitude of changes in RR intervals. The mean GI value in Diabetic NonDep subjects is more symmetric (close to 50) than that for the NonDiabetic NonDep subjects, with no substantial change between the nondiabetic and diabetic groups with depression. This indicates that diabetes has a greater effect on asymmetry measured by GI index only in the NonDep group and that if depression is present this difference is lost with both groups having a lower GI and a lesser RR interval asymmetry. EI was insignificantly different between NonDep and Dep neither for the Diabetic nor for the NonDiabetic group.

Some interesting gender differences were observed, with PI, GI and EI values of the Female group significantly different between the NonDep and Dep subgroups, compared to the Male group. The mean PI value for the female depression group was larger and thus indicates more acceleration compared to the male depression group. This greater acceleration activity or more sympathetic activity indicates greater risk of an adverse cardiac. The mean EI value has also significantly changed in the Dep subgroup, and is positively skewed in the Female in contrast to negatively skewed value in Male, indicating a sympathetic predominance.

IV. Conclusion

In summary, this study presents the analysis of HRA analysis to look at how depression with or without presence of comorbid Diabetes and gender affect the HRA from RR intervals. The results show that in the presence of diabetes, HRA indices cannot differentiate depressive subjects from non-depressive. However, only GI can differentiate depressed subjects from non-depressed ones without the presence of diabetes. Interestingly, in female group, all HRA indices (GI, PI and EI) can differentiate depressed subjects from non-depressed ones. These results need further investigation in large cohort of depressed populations.

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