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Research Article

Physiological Differences between Mood Disorder Phenotypes Based on Heart Rate Variability

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Abstract

Background: Psychiatric conditions have always been diagnosed by clinical interview of patients. Diagnostic accuracy based on this subjective method of psychiatric diagnosis is limited by many factors including skill of the clinician in interviewing psychiatric patients, patient's insight into their symptoms and ability to verbalize distinct characteristics of their symptoms. Use of objective measures for diagnosing psychiatric conditions has not been available to clinicians to improve diagnostic accuracy.

Methods: We performed a retrospective analysis on 24-hour heart rate means and variabilities (standard deviations) of 301 consecutive patients with the diagnosis of either normal, anxiety, depression or mixed. Diagnoses were predicted using multinomial logistic regression analysis. Inter-rater agreement prediction was calculated using Kappa. Mean heart rates of the diagnostic groups were compared simultaneously to the normal cohort using Tukey's range test. Diagnostic accuracy, sensitivity and specificity of the predicted diagnoses compared to the normal cohort were calculated using binomial proportion estimates and ROC curve estimates. Groups were compared to the normal cohort.

Results: Overall Inter-rater agreement was 0.79. Accuracy of diagnosis prediction was 57%. Sensitivities and specificities by diagnoses were: anxiety: 68%, 67%; depression: 35%, 91%; mixed: 0%, 100% (no subjects were diagnosed by the regression as "mixed"). Mean HRs were significantly lower in normal than in the mental illness groups. Standard deviations of the HRs appear to distinguish groups ONLY by the nighttime variation, which is significantly less in the depressed patients than in the normal or anxiety patients. This is especially interesting because it seems to indicate that depressed patients have more consistently higher HRs when compared with anxiety and normal cohort. Equally interesting was the finding of anxiety patients having higher than normal HR, but the same variability as normal patients.

Conclusion: Distinct patterns in mean heart rates and heart rate variability are found that clearly differentiate mood disorder diagnostic groups from normal controls. These reproducible and consistent findings reveal a new opportunity for the improving the accuracy of psychiatric diagnosis through use of these distinct patterns of mean heart rate and heart rate variability.

Keywords: *Depression; Anxiety; Heart Rate; Heart Rate Variability*

Abbreviations

HR: Hear Rate; HRV: Hear Rate Variability; ROC: Receiver Operating Characteristic

Introduction

Psychiatric conditions have always been diagnosed by clinical interview of patients. Diagnostic accuracy based on this subjective method of psychiatric diagnosis is limited by many factors including skill of the clinician in interviewing psychiatric patients, patient's insight into their symptoms and ability to verbalize distinct characteristics of their symptoms. Use of objective measures for diagnosing psychiatric conditions has not been available to clinicians to improve diagnostic accuracy.

Hear rate and hear rate variability (HRV), specifically time and spectral domains, have been employed in psychiatry conditions (especially depression, anxiety, or both as comorbid), as an accurate, reproducible and non-invasive tool for the assessment of autonomic nervous system dysfunction [1-6]. HRV is now widely investigated as a bio-physiological marker for a variety of mental disorders including, unipolar and bipolar disorders, dysthymia, and schizophrenia [1,5-7].

In mental illness, due to multifactorial reasons, diagnosing particular condition is still challenging by experienced clinicians. The presence of comorbid conditions, such as anxiety and depression, always make the clinical diagnosis more difficult and cumbersome. A unique characteristic of HRV when evaluation and monitoring mental illness is the diversity of patterns that exists between behavioral conditions and the response of HRV to the severity of the symptoms [6,8-13].

Concerning HRV in depression, a reduced parasympathetic activity and a shift of autonomic balance toward sympathetic activation have been demonstrated by researchers in the recent past [6,11,12,14]. The severity of depressive symptoms has been correlated with a profound reduction in parasympathetic modulation [6,11,12,14]. In anxiety disorders, including generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, and panic disorder, a reduction in HRV has also been reported [6,16-21]. However, it seems in anxious individual's heart rate changes are more prominent than extreme variations in HRV [21].

Our research demonstrates the value of using autonomic assessment when comparing the patho-physiological profiles of depression and anxiety in order to determine the physiological differences between mood disorder phenotypes.

Materials and Methods

We performed a retrospective analysis on 24-hour heart rate means and variabilities (standard deviations) of 301 consecutive patients with the diagnosis of either normal, anxiety, depression or mixed. Diagnoses were predicted using multinomial logistic regression analysis. Inter-rater agreement prediction was calculated using Kappa. Mean heart rates of the diagnostic groups were compared simultaneously to the normal cohort using Tukey's range test. Diagnostic accuracy, sensitivity and specificity of the predicted diagnoses compared to the normal cohort were calculated using binomial proportion estimates and ROC curve estimates. Groups were compared to the normal cohort.

Results and Discussion

Overall Inter-rater agreement was 0.79. Accuracy of diagnosis prediction was 57%. Sensitivities and specificities by diagnoses were: anxiety: 68%, 67%; depression: 35%, 91%; mixed: 0%, 100% (no subjects were diagnosed by the regression as "mixed"). Mean HRs were significantly lower in normal than in the mental illness groups (Table 1). Standard deviations of the HRs appear to distinguish groups only by the nighttime variation, which is significantly less in the depressed patients than in the normal or anxiety patients. This is especially interesting because it seems to indicate that depressed patients have more consistently higher HRs when compared with anxiety and normal cohort. Equally interesting was the finding of anxiety patients having higher than normal HR, but the same variability as normal patients.

	24hr Heart Rate		Day Heart Rate		Night Heart Rate	
	Mean	SD	Mean	SD	Mean	SD
Condition						
Normal	71.41	7.56	79.14	8.96	63.70	7.49
Anxiety	84.42	9.56	91.81	11.0	77.03	9. 35
Depression	83.66	12.7	90.90	14.6	76.42	11.8
Mixed	85.08	10.9	92.34	12.6	77.82	9.9
Groups Compared using Tukey Test						
Anxiety vs Normal	***	NS	***	NS	***	NS
Depression vs Normal	***	NS	***	NS	***	**
Mixed vs Normal	***	NS	***	NS	***	NS
Depression vs Anxiety	NS	NS	NS	NS	NS	**

Table 1: *Values of heart rate during the day and the night.*
** P < .05, **P < .01, ***P < .001*

The presence study intended to examine the physiological differences between mood disorder phenotypes, specifically anxiety, depression or mixed diagnosis and compared to a normal cohort. Our clinical variances were focused on alterations in heart rate and heart rate variability components. The presence study examined HR and HRV changes in the early stages of the disease, so we avoided the cofounding effects of anti-psychotic or anti-depressive medications. Of notice, diagnosis of anxiety and depression can be challenging for any mental health care provider and when the two disorders coexist diagnostic precision is more complicated.

In our study, we demonstrated that HR and HRV in non-medicated patients were different in the depression group, when compared to anxiety and normal cohort. Depressed patients have more consistently higher HRs when compared with anxiety and normal cohort. Equally interesting was the finding of anxiety patients having higher than normal HR, but the same variability as normal patients. Suggesting that reduction in HRV could be used as a psychophysiological marker between mood disorder phenotypes.

HRV time and spectral domains can be used as intrinsic bio-physiological markers of mental illness [22,23]. These components can accurately, non-invasively, detects cardiac autonomic dysregulation. By means of these factors researchers can identify parasympathetic and sympathetic nervous system over or down modulation in a short term – 24 hours, or over a period of days – longitudinal monitoring [22-32].

It is hypothesized that reduced vagal modulation is accompanied by a subsequent displacement of the sympathovagal balance, this is demonstrated by changes in low frequency/high frequency ratio of HRV- spectral domain. Researchers studied further parameters of HRV- spectral domains such as high frequency power, which estimates parasympathetic activity, and low frequency band which reflects both vagal and sympathetic influences [1,23,33]. Although, Goldstein., *et al*. considers low frequency power to be an index, not of cardiac sympathetic tone, but of baroreflex function during supine rest position [34].

Depressive disorders are associated with sympathetic hyperactivity and reduced vagal control, this is recognized as an independent risk factor of cardiovascular diseases. Similarly, anxiety disorders have been associated with increased risk of cardiovascular morbidity. The latent description for the increased risk of cardiovascular diseases is based on dysregulation of the autonomic nervous system [6,8,11,22].

The cardiovascular signature of depression and anxiety may arise more prominently during sleep stages, due to the sensibility of the heart rate to endogenous dynamic changes across the night like progression of sleep stages, dynamic interactions between homeostatic and circadian processes; these are combined with the fact that sleep minimizes the influence of several external confounders such as fluctuating daytime stress, physical activity and constant cognitive an emotional processing [14,35,36].

Finally, the following clinical theoretical perspectives substantiate our findings. The polyvagal theory initially describes by Porges, it highlights the importance of vagal pathway in attention, emotion expression, social bonding and flexible adjustment to environmental demands. Vagal influences on the heart serve to dampen the sympathetic reaction to stress and to promote calm behavioral states and self-regulation. Without this protective function of vagal tone, which normally disappears or decreases with mental illness, individuals may become vulnerable to anxious apprehension and worry, involving pre-attentive biases to threat information, with rigid and inflexible response patterns, these symptoms are diagnostic traces in patients with anxiety [10,37-45].

Another explanation for decreased parasympathetic tone in anxiety and depression is the inability to disengage threat detection, which serves to perpetuate hyperarousal and worry, even when no real threat exists, which may cause a chronic withdrawal of parasympathetic activity and long-term reduction in HRV [15,37-45].

We understand the limitations of a retrospective analysis, such as: 1) some key statistic factors cannot be measure like control exposure or outcome; 2) we must rely on accurate record-keeping; 3) significant selection biases may affect selection control.

Conclusion

The use of HRV as a transdiagnostic marker has become a novel tool in the psychiatry armamentarium for determination of sympathetic and parasympathetic activity and sympathovagal imbalance. Pathophysiological alterations are likely to alter heart rate dynamics during sleep thereby providing a relevant window to observe multi-systemic characteristic of depression and anxiety. Distinct patterns in mean heart rates and heart rate variability are found that clearly differentiate mood disorder diagnostic groups from normal controls. These reproducible and consistent findings reveal a new opportunity for the improving the accuracy of psychiatric diagnosis through use of these distinct patterns of mean heart rate and heart rate variability.

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Conflict of Interest

Marie Casey Olseth is a part of Medibio's Scientific Advisory Board. The other authors declare that they have no conflicts interests.

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