Heart Rate Variability- A Predictive Tool for Analysis of Autonomic Dysfunction in Covid-19 Vaccinated Individuals

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Abstract

Objective: To determine the association between gender and HRV values in COVID-19 vaccinated participants and the difference in HRV in male and female COVID-19 vaccinated individual as compared to standard value of HRV in healthy individuals

Method: An experimental, randomized control study was carried out in the department of physiology of Wah Medical College, Wah Cantt, Pakistan for 3 months (April 2021 to June 2021). A total 100 vaccinated students of 1st year and 2nd year MBBS were divided into 2 groups, Female (Nf= 50) and Male Group (Nm= 50). Then were further divided into three groups: (Group 1-HRV in above normal range), (Group 2- HRV in below normal range), and (Group 3- HRV in normal standard range).

Results: 64.0% females had HRV value within standard reference range whereas 36.0% were below the range. 44.0% males had HRV value within standard reference range, 28.0% were below the range and 28.0% were above range. There was significant association ($p < 0.001$) between gender and HRV values in COVID-19 vaccinated participants. The average HRV of male and female COVID-19 vaccinated individuals were significantly different ($p<0.001$). The HRV of female vaccinated individuals was significantly different where no difference was found in male vaccinated individuals, when compared with standard values.

Conclusion: COVID-19 vaccinated females are more prone to disturbance in autonomic modulation as compared to males vaccinated individuals, thus at momentarily risk of cardiovascular events.

Keywords: COVID-19, Heart rate variability, Gender, Vaccine

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Introduction

COVID-19 virus, first identified in China in December 2019, was communicated globally imprudently.[1-2] For more than one year, authorities across the world have encountered multifaceted challenges to battle this ailment. Due to an imperative necessity to thwart the further blowout of COVID-19 infections, the conservative measures for consent of new vaccines could not be trailed, and these vaccines were given as an emergency endorsement.[3] This creates a solid motive for gathering detailed scientific evidence for these vaccines by monitoring the adversative responses reports in the population, after vaccination.[4-6]

Most vaccines work by exposing the body's combat system to antigens and generate a comparable immune response as if it was exposed to the actual virus.[7] Thus, after getting a vaccine, augmented inflammation levels caused by stimulation of our immune system may lead to a short-lived unevenness in the autonomic innervation of the heart. Decrease in parasympathetic action and extreme sympathetic activation effect the functions of ANS, thus causes cardiovascular dysfunction, arrhythmias and sudden death.[8]

Heart rate variability (HRV) is an easily manageable, accessible, and noninvasive physiological tool, regulated by the autonomic nervous system (ANS). It is used

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for decades to evaluate general well-being in various clinical settings.[9] Decrease in HRV below the normal range is risk factor for disruption in normal cardiac events like such as arrythmias, angina, myocardial infarction and can be a warning of an impending cardiac complication. It helps to diagnose earlier than other currently employed laboratory tests.[8,9]

Presently, there is dispersed information regarding the disparate events about the reporting and scrutiny of adverse measures following the COVID-19 vaccination. This study analyzes whether there is any association between gender and HRV values in COVID-19 vaccinated participants and there is difference in HRV of male and female covid-19 vaccinated individual as compared to standard value of HRV in healthy individuals. Hence, by using heart rate variability as a predictive tool, we will try to analyze that whether the COVID-19 vaccination is associated with cardiac illness state evolution or not. In addition, this study helps to generate a safety signal for COVID-19 vaccines at an early stage and form the foundation of other studies for creating and assessing the safety data of COVID-19 vaccines.

Material and Method

This cross-sectional experimental randomized control trial was conducted in Department of Physiology, Wah Medical College, Wah Cantt after getting approval from ethical review board.

A total of hundred students from first year and second year MBBS were enrolled in the study via random sampling. The study was proceeded after informed and written consent from the participants. Data was collected within 20 days after complete vaccine protocol. The students who received inactivated COVID-19 vaccines were included in the study. Equal number of male and female participants were included/To control the factor of gender in our study, we used the equal allocation stratification technique. Students who were less than 17 years or more than 21 years and who have history of hypertension, or any other cardiac disease were excluded from the study. Students taking anti-asthmatic drugs, cold medicine, decongestant, antihypertensive drugs, anti-depressants, anti-anxiety, or thyroid medicines were also excluded from the study. Students after 20 days of vaccination was not included in the studies. Subjects were requested to avoid coffee, tea, cola drinks, and smoking for 12 hours before data collection procedure. Heart rate variability was obtained during deep breathing in early morning by Lead II electrocardiographic recording for 1 minute using an electrocardiograph.

For measuring heart rate variability, we used the commonly used time domain method by RMSSD which is the square root of the mean squared differences of successive NN intervals.[10]

The root mean square of successive differences between normal heartbeats (RMSSD) was obtained by first calculating each successive time difference between heartbeats in milliseconds(ms). Then, each of the values was squared and the result was averaged before the square root of the total was obtained.[11] The RMSSD reflects the beat-to-beat variance in heart rate and is the primary time-domain measurement used to estimate the vagally mediated changes reflected in HRV.[10]

The normal value of heart rate variability in young healthy adults if measured by time domain method (RMSSD) is 42+15ms.[12,13] Individuals with HRV less than 27ms were considered to have low heart rate variability and was allocated the Group 1, Group 2 individual with HRV more than 57ms were considered to have high HRV and individuals with HRV more than 27ms and less than 57ms were considered to have normal HRV and were allocated in Group 3.

Data was collected on data collection proforma (given in Annexure A) and then was analyzed by using Statistical Package for the Social Sciences (SPSS 20.0 version software program). Covid-19 vaccination was an independent variable and Heart rate variability was dependent variable.

Results of COVID-19 vaccinated participants are divided into 2 sets of Female (Nf=50) and Male Group (Nm= 50). Then result of each set is further divided into three groups; (Group 1-HRV in above range), (Group 2- HRV in below range), and (Group 3- HRV in normal standard range) and were expressed in terms of percentage. Chi square test was applied to test the significant association between gender and HRV values in COVID-19 vaccinated participants. Independent sample T test was applied to observe the gender difference in the variance and average HRV of COVID-19 vaccinated individuals. One sample T test was applied to observe the difference in HRV of male and female COVID-19 vaccinated individual when compared to standard value of HRV in healthy individuals. P value of < 0.05 was regarded as significant.

Results

The HRV values in females (Nf= 50) and males (Nm=

50) were expressed in Table 1.1 Results after applying Chi Square test displayed that p value is <0.001 that showed a significant association between gender and HRV values in COVID-19 vaccinated participants.

The mean HRV values in male and female students were 48.6639 + 4.43ms and 31.1422 + 0.94ms respectively. Table-2 shows that the variance for HRV of male COVID-19 vaccinated individuals is statistically different from HRV of female COVID-19 vaccinated individuals. Table-3 showed that it means there is no significant difference in HRV of male COVID-19 vaccinated individual as compared to standard value of HRV in healthy individuals. However, the HRV of female COVID-19 vaccinated individual as compared to standard value of HRV in healthy individuals was found significantly different.

Table 1: *Heart Rate Variability (HRV) of COVID-19 Vaccinated Individual*

		HRV of Covid-19 Vaccinated Individual		
		Above	Below	Normal
Participants Of COVID-19 Vaccinated Individual Count (N=100)	Female Participants Of COVID-19 Vaccinated Individual (%)	0.0%	36.0%	64.0%
	Male Participants Of COVID-19 Vaccinated Individual (%)	28.0%	28.0%	44.0%

Table 2: *Comparison of Variance of HRV of Male and Female COVID-19 Vaccinated Individuals*

		Levene's Test for Equality of Variances		Significance	
		F	Sig.	One-Sided p	Two-Sided p
HRV values of COVID-19 vaccinated individuals	Equal variances assumed	24.830	<.001	<0.001	<0.001
	Equal variances not assumed			<0.001	<0.001

Table 3: *Comparison of HRV of Female and Male COVID-19 Vaccinated individuals with standard reference value*

	Significance
HRV values Female COVID-19 Vaccinated individuals	<.001
HRV values Female COVID-19 Vaccinated individuals	.070

Discussion

Investigational evidences recommend that autonomic indicators such as heart rate variability (HRV) is advantageous and suitable way of estimating the autonomic modulation.[14] Low HRV has been documented as a solid pointer of risks linked to adversative proceedings, indicating the importance of autonomic nervous system in sustaining health.[14-16] Our study showed a notable association between gender and HRV values in COVID-19 vaccinated participants and showed a significant difference between the average HRV of male and female COVID-19 vaccinated participants. Our findings were similar to the results of Umetani et al., (1998) and Lutfi & Sukkar., (2011) that showed that there were gender variances in autonomic modulation. The underlying mechanisms of the gender difference in cardiac autonomic function are still not clea.[17,18] However, Umetani et al., (1998) and Koenig & Thayer., (2016) proposed that the detected gender differences show lower parasympathetic activity in female and this view is supported by the fact that females have an increased heart rate as compared to males.[17,19]

Our study showed that HRV in female COVID-19 vaccinated individual is significantly low as compared to standard HRV value in healthy individuals.[12,13] It is probably due to the fact that the vaccine may generate an inflammatory provocative response that is controlled by the autonomic nervous system.[8,9] This association is mediated to a large degree by the vagus nerve.[9] The vagus nerve not only plays an imperative role in regulation of inflammation but also acts as a bidirectional street between the brain and the rest of the body as it is also forming the autonomic innervation of the heart.[9,10] Therefore, after getting a vaccine, augmented inflammation levels caused by stimulation of the immune system may lead to a short-lived irregularity in the autonomic innervation of the heart.8 Therefore, it can be hypothesized in the light of our findings that vaccinated females are more prone to disturbance in autonomic modulation as compared to males vaccinated individuals. These results were similar to results of Lanza GA et al., (2011) that showed that vaccine for Influenza A virus also induce cardiac autonomic dysfunction and may momentarily increase the risk of cardiovascular events.[20] However, our study showed no significant change in HRV of male vaccinated participants, rather showed dominant parasympathetic activity in the form of high HRV. Lutfi & Sukkar., (2011) study also showed significantly higher HRV values in males as compared

to females.[18] In addition, the results of Umetani et al., (1998) also revealed lower HRV in female compared with male subjects at age less than 30 years old.[17] Khan, Hussain & Aleem., (2010) study showed that population of Pakistan have increased parasympathetic activity further strengthened our results.[13] However, pros of vaccine administration are way more than the cones and a study with bigger sample size is required to be done to determine further validity and reliability of our results. Furthermore, follow up data can also help in further strengthening or nullifying our findings.

Conclusion

Our study showed that COVID-19 vaccinated females are more prone to disturbance in autonomic modulation as compared to males vaccinated individuals, thus at momentarily risk of cardiovascular events.

Conflict of Interest *None*

Funding Source *None*

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. New England Journal of Medicine. 2020 Feb 20;382(8):727–33.
2. Gorbalenya A, Baker S, Baric R, Groot R. Severe acute respiratory syndrome-related coronavirus: The species and its viruses–a statement of the Coronavirus Study Group. 2020 [cited 2022 Apr 1]; Available from: https://digital.csic.es/handle/10261/212994
3. COVID-19 vaccine tracker | RAPS [Internet]. [cited 2022 Apr 1]. Available from: https:// www. raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker
4. Lee E, Cines D, … TG-A journal of, 2021 undefined. Thrombocytopenia following pfizer and Moderna SARS-CoV-2 vaccination. ncbi.nlm.nih.gov [Internet]. [cited 2022 Apr 1]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8014568/
5. Torjesen I. Covid-19: Norway investigates 23 deaths in frail elderly patients after vaccination. 2021 [cited 2022 Apr 1]; Available from: https:// www.bmj.com/content/372/bmj.n149/rapid-responses? int_source=trendmd&int_medium=cpc&int_campaign=usage-042019
6. Wilkins AL, Kazmin D, Napolitani G, Clutterbuck EA, Pulendran B, Siegrist CA, et al. AS03- and MF59-adjuvanted influenza vaccines in children. Frontiers in Immunology. 2017 Dec 13;8(DEC).
7. Iwasaki A, Cell SO-, 2020 undefined. Why and how vaccines work. Elsevier [Internet]. [cited 2022 Apr 1]; Available from: https://www.sciencedirect.com/science/article/pii/S009286742031237X
8. Bonaz B, Sinniger V, Pellissier S. The vagus nerve in the neuro-immune axis: Implications in the pathology of the gastrointestinal tract. Frontiers in Immunology. 2017 Nov 2;8(NOV).
9. Williams D, Koenig J, Carnevali L, Brain AS-, behavior undefined, and undefined, et al. Heart rate variability and inflammation: a meta-analysis of human studies. Elsevier [Internet]. [cited 2022 Apr 1]; Available from: https://www.sciencedirect.com/science/article/pii/S0889159118304665
10. neurochemistry GM-J of, 2011 undefined. The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. Wiley Online Library [Internet]. 2011 Jan [cited 2022 Apr 1];116(2):164–76. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1471-4159.2010.07109.x
11. Thayer J, Yamamoto S, cardiology JB-I journal of, 2010 undefined. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Elsevier [Internet]. 2009 [cited 2022 Apr 1]; Available from: https://www.sciencedirect.com/science/ article/pii/S0167527309014879
12. Goldenberg I, Goldkorn R, Shlomo N, Einhorn M, Levitan J, Kuperstein R, et al. Heart rate variability for risk assessment of myocardial ischemia in patients without known coronary artery disease: The HRV-DETECT (heart rate variability for the. Am Heart Assoc [Internet]. 2019 Dec 17 [cited 2022 Apr 1]; 8 (24). Available from: https://www.ahajournals.org/doi/abs/10.1161/JAHA.119.014540
13. Khan M, Hussain M, Physiology SA-PJ of, 2010 undefined. Heart rate variability in healthy population. pjp.pps.org.pk [Internet]. 2010 [cited 2022 Apr 8];6(2). Available from: http:// www.pjp.pps.org.pk/ index. php/PJP/article/view/807
14. Carlos L, Vanderlei M, Pastre CM, Hoshi RA, Dias De Carvalho T, Fernandes De Godoy M. Basic notions of heart rate variability and its clinical applicability. SciELO Brasil [Internet]. 2009 [cited 2022 Apr 8]; 24(2): 205–17. Available from: https://www.scielo.br/pdf/rbccv/ v24n2/v24n2a18.pdf
15. Ranpuria R, Hall M, … CC-ND, 2008 undefined. Heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV. academic.oup. com [Internet]. [cited 2022 Apr 8]; Available from: https://academic.oup.com/ndt/article-abstract/ 23/ 2/ 444/1852216

16. Wen T, Chung-Kwe W, of FY-AJ, 2007 undefined. Relationship between electrolytes and heart rate variability parameters in end-stage renal failure patients before and after hemodialysis. jag.journalagent.com [Internet]. [cited 2022 Apr 8]; Available from: https://jag.journalagent.com/z4/download_fulltext.asp?pdir=anatoljcardiol&plng=tur&un=AJC-05095

17. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. J Am Coll Cardiol. 1998 Mar;31(3):593–601.

18. Lutfi M, sciences MS-I journal of health, 2011 undefined. The effect of gender on heart rate variability in asthmatic and normal healthy adults. ncbi.nlm.nih.gov [Internet]. [cited 2022 Apr 8]; Available from: https:// www. ncbi.nlm.nih.gov/pmc/articles/pmc3521833/

19. Koenig J, Reviews JT-N& B, 2016 undefined. Sex differences in healthy human heart rate variability: a meta-analysis. Elsevier [Internet]. [cited 2022 Apr 8]; Available from: https://www.sciencedirect.com/science/article/pii/S0149763415302578

20. Lanza GA, Barone L, Scalone G, Pitocco D, Sgueglia GA, Mollo R, et al. Inflammation-related effects of adjuvant influenza A vaccination on platelet activation and cardiac autonomic function. Wiley Online Library [Internet]. 2011 Jan [cited 2022 Apr 12]; 269(1): 118–25. Available from: https://onlinelibrary.wiley.com/doi/ abs/10.1111/j.1365-2796.2010.02285.x

Authors Contribution

SI: Conceptualization of Project

SI, AS, KS: Data Collection

SI: Literature Search

SI: Statistical Analysis

SI: Drafting, Revision

SI, SI: Writing of Manuscript