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Original article

A Non-Invasive Tool to Quantify Autonomic Dysfunctuion: A Prognostic Indicator in Covid-19

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Abstract

Background: The Outbreak of SARS-CoV-2 has caused a major pandemic posing a threat to the millions of lives all over the world. The evidence shows that there is a relation between the autonomic nervous system and coronaviruses and likewise, levels of inflammatory markers - C-reactive protein (CRP) and autonomic dysfunction. Autonomic dysfunction is elicited using heart rate variability which in turn quantified using autonomous regulatory index (ARI). Hence this study was conducted to determine if ARI measured using patented NEUROCOR Precision HRV® Solution instrument could be used as a non-invasive measure of autonomic dysfunction among COVID-19 subjects. ***Materials & Methods:*** An exploratory study was conducted among randomly selected 22 COVID-19 male patients aged more than 18 years, admitted to COVID ward, Victoria Hospital, Bengaluru for 5 days, using ANS Recorder, a non-invasive heart rate variability recorder heart rhythm data were collected, one test per day continuously for 5 days and a patented NEUROCOR Precision HRV® Solution, an ANS Analysis Software instrument was used to record, analyze and interpret the heart rate variability in terms of ARI and CRP levels were measured. Data was analyzed using SPSS version 18.0. A P value of < 0.05 was considered statistically significant. ***Results:*** The occurrence of autonomic dysfunction in COVID-19 patients using the Patented NEUROCOR Precision HRV® Solution was found to be among 50.0%. The median scores of average ARI indices were significantly lesser among those with higher health risk (28.39) compared to those with lower health risk (65.95) ($P<0.05$). The Median ARI index showed a weak negative correlation ($r = -0.13$, $P>0.05$) with CRP ($P>0.05$). ARI index showed a significantly excellent predictive ability in detecting the higher health risk with the areas under the curves (AUC) being 0.93 with an optimal cut-off of 40.85 with maximum sensitivity and specificity of 100.0% and 93.0%. ***Conclusion:*** Autonomous Regulatory Index (ARI) index with significantly excellent predictive ability in detecting the higher health risk can be used as a non-invasive measure of autonomic dysfunction among COVID-19 subjects.

Keywords: ***SARS-COV-2, COVID-19, inflammation, autonomic dysfunction, autonomous regulatory index, sympathetic nervous system, parasympathetic nervous system.***

Introduction

SARS-CoV-2 is a novel corona virus that has led to a great disaster impacting the whole world through disruption of lives, economies and societies [1]. Regardless of international efforts in containing its spread, SARS-CoV-2 has spread to 213 countries, resulting in more than 5 million cases and nearly 400,000 deaths [2]. Though the major target of this disease is learned to be a respiratory system, resulting in acute respiratory insufficiency and failure, it has been noted to affect pan systems viz., cardiac, renal, hemodynamic, hematological and neurological systems in critically-ill COVID-19 patients leading to multi- system injury. Among the patients requiring mechanical ventilation the mortality rates have been noted to be more than 50%. Hence early identification of the patients at high risk and prevention of the occurrence of such multi-system injury is of prime importance [3].

Besides this, corona viruses are known to travel retrograde to the autonomic center in the brainstem via synaptic connections from mechano- and chemo-receptors located at the lungs and lower respiratory tract, potentially contributing to respiratory failure. Though such actions implicate the connection of corona viruses to the autonomic nervous system, the effect of COVID-19 on the autonomic nervous system is not very well established. Lo YL et

al., in their study, have documented autonomic dysfunction among 50% of recovered SARS-patients [4-7].

The literatures brings out the fact of autonomic nervous system bearing control over short and long-term regulation of homeostasis and even inflammation. Autonomic modulation has been described to be associated with a sympathetic interference in acute and chronic inflammation in its earlier stages and is also believed to activate the vagal inflammatory reflex in longer processes to regulate innate immune responses and cytokine functional effects. Hence identifying and controlling pro-inflammatory responses associated with inflammatory conditions can help in devising novel therapeutic options linked to autonomic modulation for diseases. Both the sympathetic and parasympathetic nervous systems are known to sense the inflammation and influence the development and severity of inflammatory processes in animal models. It has also been linked to many diseases/ conditions viz., rheumatoid arthritis, obesity, sepsis, burn injuries, etc. [8]. These alterations in the sympathetic and parasympathetic nervous system are correlated with higher levels of C- reactive protein (CRP), an inflammatory marker [8]. Goldstein DS et al., have elucidated biomarkers of extended autonomic system (EAS) activation to correlate with clinical and pathophysiologic data and predict outcome in COVID-19 [9]. Heart Rate Variability (HRV) has been considered to reflect the state of autonomic nervous system regulation for a long time [10]. C-reactive protein, an inflammatory marker is known to be associated with decreased HRV [11]. In this study, we have considered the autonomous regulatory index [ARI] as one of the key HRV parameters in assessing autonomic dysfunction. The current study was conducted to assess if ARI measured using patented NEUROCOR Precision HRV® Solution instrument could be used as a non-invasive measure of autonomic dysfunction among COVID- 19 subjects.

Objectives

- To assess the occurrence of autonomic dysfunction in COVID-19 patients using the Patented NEUROCOR Precision HRV® Solution
- To determine its correlation with the C-reactive protein.

Methodology

It is an exploratory study conducted among randomly selected twenty-two COVID-19 male patients aged more than 18 years, admitted to COVID ward, Victoria Hospital, Bengaluru through a computer generated random number table. This tertiary care hospital is the first dedicated COVID-19 hospital and referral center in Bangalore. This study was conducted for a period of 21-06-2020 to 26-06-2020.

The study tools used in our study consisted of an ANS Recorder - TELMED GmbH (Germany) which is a 3-Channel ECG Device, gel-based use and throw electrodes, Hrdayin mobile application - an android application, android based smart Phone and a patented NEUROCOR Precision HRV® Solution, an ANS Analysis Software instrument bearing a patent number EU Patent EP 2745 770 Al was used to recording, analyze and interpret the heart rate variability in terms of Autonomous Regulatory Index (ARI).

This study tool assesses holistic health in 6 minutes of non-invasive test and it helps in predicting current health status, immediate foreseen risks and hence makes a way to intervene appropriately. It will also help to diagnose other possible chronic disorder and stress among the study subjects. It also helps to identify the probability of sudden cardiac death and mortalities.

This study was conducted in collaboration with the team of doctors, BMCRI, headed by Pulmonologist in association with the Non-Profit Research Center for Innovative Neurotechnologies (ZNFgGmbH) and its spin-off FINTEC GmbH, Germany. The Integration mobile application with ANS recorder and backend software was developed by HRDAYIN MobihHealth LLP, Bangalore and M/s. Agillere Technologies, has taken the lead role in initiating this study of HRV/ANS analysis on COVID- 19 patients in Bengaluru, India.

Study Procedure

(a) **(b)**

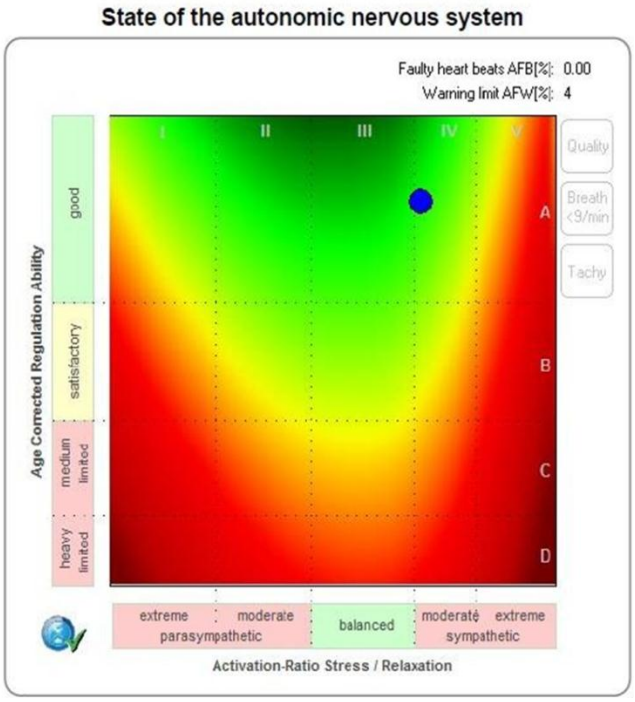
Fig-1 (a) & (b): a) Neurocor ANS recorder & b) 3-way chest lead electrodes

Using ANS Recorder (Figure 1 & 2), a non-invasive heart rate variability recorder heart rhythm data was collected for 22 patients, taking one test per day continuously for 5 days. It was connected to the chest and was paired with mobile via Bluetooth. The collected data sent to the server gets analyzed with time and frequency domain analysis based on a unique patented highly sensitive algorithm built by Dr. Ralf Arne Wittling.

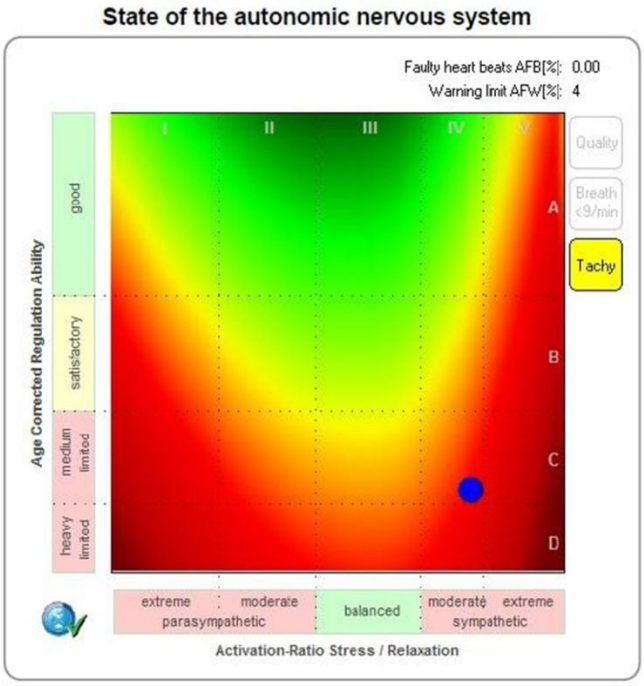
A colour-coded plot was obtained by plotting autonomous regulatory level along the Y-axis and sympathovagal balance along X-axis [**Graph 1**]. The interpretation of the same is as follows:

1. Area from yellow to green signifies ‘good’ to ‘very good’ combined autonomous state respectively
2. Orange to red marked area signifies ‘average’ to ‘bad’ autonomous overall condition
3. Deep red area, especially the combination of very hard sympathetic activation at the same time very low autonomous-nervous regulation level indicates a detailed medical diagnostic.

Heart rate variability was measured by an important key parameter ARI and others like RR- interval, total power (TP), Standard Deviation of RR interval (SDRR) and Root Mean Square Standard Deviation of RR interval (RMSSD)Low Frequency (LF), Very Low Frequency (VLF).



Graph-1: Zone graph indicating the state of autonomic regulation in healthy person



Graph-2: Zone graph indicating the state of autonomic regulation in person with depression

Operational Definition: For the purpose of analysis and interpretation, ARI was considered an important key parameter to measure heart rate variability. [REF]

Autonomous regulatory index (ARI): It is a single value in the sense of a health index of the autonomic nervous system which shows an exponential regressive interrelation between the autonomic total activity and the sympathovagal balance and is expressed in percentage.

A low autonomous regulatory capacity in combination with a high sympathovagal balance causes a low ARI and indicates a high health risk. An ARI index of 0-30 is low, 30-60 is medium and 60 - 100 is high.

Outcomes

High health risk: All those who needed special attention or close monitoring were considered to be at higher health risk for the early diagnosis and intervention.

Low health risk: All those who were stable and recovering were considered to be at lower health risk.

Statistical Analysis

All the collected data were entered into an excel sheet. The continuous data viz., age, autonomous regulatory indices (ARI), serum C-reactive protein levels were expressed in means and standard deviations and the discrete data viz., gender, outcomes of health risk and death were expressed in proportions. The data were presented in the form of tables and graphs where ever necessary. The difference in the medians of ARI and means of CRP were compared among the groups of those with low and high health risk as assessed by our study tool NEUROCOR Precision HRV® Solution using Mann-Whitney U and independent t-tests respectively. The correlations of ARI and serum CRP levels were analyzed using Spearman's correlation coefficient. The area under the receiver operating characteristic (ROC) curve for the assessment of the predictive abilities of ARI and serum CRP levels in detecting the high health risks were constructed by plotting the sensitivities for all individual cut-off values versus the corresponding (1-specificity). The best cut-off values considering both maximum sensitivity and specificity to predict the high health risks were calculated using Youden's index. The analysis was done using SPSS version 18.0. A P value of <0.05 was considered as statistically significant.

Results

Most of the study subjects were aged more than 50 years (12/22, 54.5%) [**Table 1**]. The mean age of the study subjects was 47.82±18.09 years and the youngest one among the study subjects was 19 years old and the oldest was 80 years. Hundred percent of the subjects were males as included under the inclusion criteria of the study. As the data on the autonomous regulatory index (ARI) could be recorded only among eighteen patients, further analysis was conducted among eighteen only.

Autonomous regulatory index and autonomic dysfunction

Fifty per cent of the study subjects had low ARI scores and higher health risk of developing cardiac abnormalities and 33.3% had moderate ARI scores and moderate health risk wherein four among six study subjects (66.7%) with moderate scores needed special attention or close monitoring and the remaining two were stable and were in the recovery phase with their respective median ARI scores of 49.01 and 59.32. Those with high ARI scores had low health risk and were stable and recovered with one exception of a study subject aged 51 years and showed ARI of 80.09 who might be having a pre-existing cardiac problem. Hence the occurrence of autonomic dysfunction was found to be among 50.0% of them. [**Table 2**]

The median scores of average ARI indices were significantly lesser among those with higher health risk (28.39) compared to those with lower health risk (65.95) (P<0.05). [**Table 3**]

Autonomic regulatory index and C-reactive protein levels (CRP):

The median ARI index showed a weak negative correlation (r = -0.13, P>0.05) with C- reactive protein levels (CRP) indicating

lower the ARI indices, the higher will be the CRP levels. However, they were not found to be significant (P>0.05). [**Graph-1**]

ARI index had a significantly excellent predictive ability in detecting the higher health risk with the areas under the curves (AUC) being 0.93 with SE of 0.07 at 95% CI ranging from 0.79 to 1.06 (P<0.05). However, the CRP levels had satisfactory predictive ability with AUC being 0.63 with SE of 0.16 at 95% CI ranging from 0.31 to 0.96 (P>0.05). At the optimal cut- off of 40.85, the maximum sensitivity and specificity of 100.0% and 93.0% could be achieved. [**Graph 2: 2(A) & 2(B)**]

Table 1: Demographic profile of the study subjects

Demographic details	n	%
Age-group		
< 25	02	9.1
26-50	08	36.4
>50	12	54.5

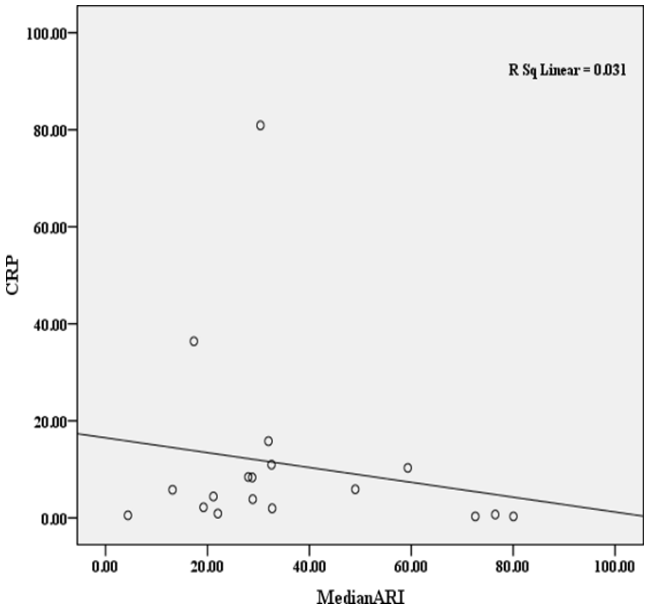
Table 2: Distribution of categories of ARI and their respective health risks [Autonomic dysfunction]

ARI categories (ARI scores)	Respective health risks	n (%)
Low (0-30)	High	09 (50.0)
Moderate (30-60)	Moderate	06 (33.3)
High (60-100)	Low	03 (16.7)

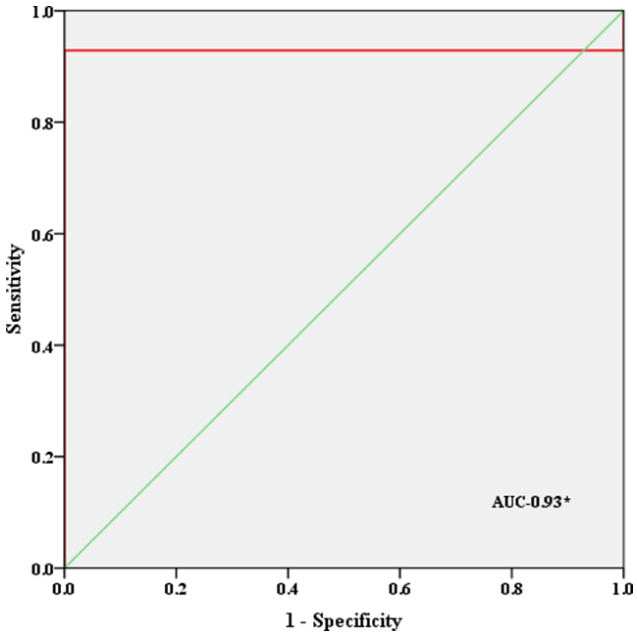
Table-3: Comparison of median ARI indices among the study subjects

Health risk	N	Median ARI indices [Range]	Mean ranks	U-value (*P*-value)
Low	04	65.95 [49.01 – 76.48]	15.50	12.00 (0.01)*
High	14	28.39 [4.39 – 80.05]	7.79	

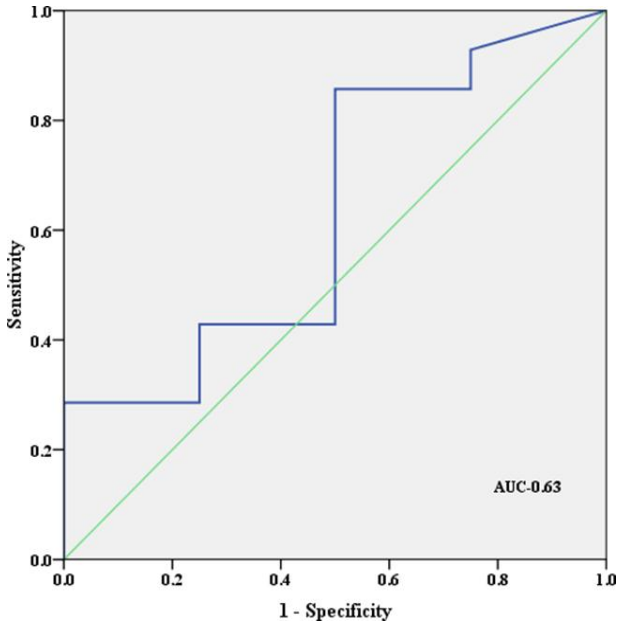
**indicates statistically significant difference at P<0.05*



Graph-1: Correlation of Median ARI index with CRP levels



2 (A)



2 (B)

Graph-2: ROC curves for (A) Median ARI index (B) CRP levels with health risk

Discussion

The autonomic nervous system maintains whole-body homeostasis. HRV is a measure of autonomic health with the Autonomic regulatory index [ARI] used as a key parameter to measure the HRV. The degree of HRV variation is an indicator of the severity of disease and is related to the presence of illness and pathologic conditions (inflammation) [12]. Hence in this study we assessed the occurrence of autonomic dysfunction in COVID 19 patients using the Patented NEUROCOR Precision HRV® Solution and determined its correlation with the C- reactive protein.

In the current study majority of the study subjects were more than 50 years (54.5%) with mean age of 47.82±18.09 years (range 19 - 80 years). 100.0% of the subjects were males. Parashar R et al studied the age-related changes in autonomic functions and found that sympathetic responses & para-sympathetic responses decline significantly with increasing age group and sudomotor

responses gets partially interrupted in the elderly age group [13]. Vita G et al studied the relationship between aging and autonomic control of heart rate and blood pressure and concluded that there is age-dependent degradation of the mechanisms involved in the cardiovascular reflexes [14].

The majority of the subjects with COVID 19 in the present study had low ARI scores and higher health risk of developing cardiac abnormalities. Nemechek P in his study on pulse rate variability as a biomarker of COVID-19 infection observed that a high degree of variability in HR indicates a healthy person with a well-functioning autonomic nervous system and low inflammation whereas a low degree of HRV indicates autonomic nervous system dysfunction and is associated with elevated levels of pro-inflammatory cytokines and worse outcomes in a variety of medical conditions including myocardial infarction, diabetes, metabolic syndrome, end-stage renal disease, chronic liver disease, hypoxic lung disease, congestive heart failure, hypertension, and obesity [12] which is in accordance to this study findings with median scores of average ARI indices being significantly lower among those with higher health risk compared to those with lower health risk.

The rate of occurrence of autonomic dysfunction among COVID-19 patients was found to be among 50.0% which is a unique finding in this study which recommends importance of monitoring autonomic dysfunction in terms of ARI index to detect heart rate variability which in turns helps in assessing the prognosis and better manage COVID 19 patients.

The median ARI index showed a weak negative correlation with CRP levels but not significant whereas Lanza GA et al studied that in patients with unstable angina, high levels of serum CRP levels are significantly associated with decreased HRV showing negative correlation, suggesting a possible pathophysiologic link between cardiac autonomic dysfunction and inflammatory activity [15]. Similarly Nemechek P correlated degree of HRV suppression with severity of illness and increased time to clinical stability after admission [12].

CRP has shown promise in clinical settings as an independent discriminator of COVID- 19 severity upon hospital admission according to chest CT severity and was also a predictor of adverse outcomes and mortality comparable to this study where CRP levels had satisfactory predictive ability with AUC being 0.63 [16].

In this unique study we noted that ARI index was found to have a significant excellent predictive ability in detecting a higher health risk (AUC- 0.93) and the optimal cut-off value was 40.85, with maximum sensitivity and specificity of 100.0% and 93.0%. Nemechek P also suggested that HRV may act as a surrogate for CRP levels in predicting negative outcomes in COVID-19 patients and low HRV was associated with a sixfold increase in the likelihood of pneumonia [12].

Limitations of the study: As the study was an exploratory study, it was conducted among small sample size selected by purposive sampling. Further studies with larger sample size including both genders would be suggested to ensure generalizability.

Conclusions

- The occurrence of autonomic dysfunction in COVID-19 patients using the Patented NEUROCOR Precision HRV® Solution was found to be among 50.0%.
- Autonomic regulatory index (ARI) index had a significantly excellent predictive ability in detecting the higher health risk in COVID-19 patients.
- The median scores of average ARI indices were significantly lesser among those with higher health risk compared to those with lower health risk.
- The median ARI index showed a weak negative correlation with C-reactive protein levels (CRP) indicating lower the ARI indices, the higher will be the CRP levels but it was not statistically significant.

Ethics approval and consent to participate

Ethics committee of Bangalore medical college & research institute and reference number: BMCRI/PS/02/2020-21

List of abbreviations

CRP-C-reactive protein -
ARI- Aautonomous regulatory index
AUC-areas under the curves
HRV- Heart rate variability
ECG- Electrocardiography
ROC-receiver operating characteristic
SDRR-Standard Deviation of RR interval
RMSSD- Root Mean Square Standard Deviation of RR interval)
LF-Low Frequency
VLF-Very Low Frequency

Conflicts of Interest

None

Funding Statement

Not got any funds for study, study done for academic purpose

Author's Contribution

AR-Concept and design of the study; JR, SR-prepared first draft of manuscript; S- Interpreted theresults; DP-reviewed the literature and manuscript preparation andrevision of the manuscript; RR, VN- Statistically analysed and interpreted; VV-preparation of manuscript ;, SH, CR- Concept, coordination, review of literature and manuscript preparation.

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