Cardio respiratory coupling: A potential biomarker for the early detection of respiratory distress in COVID-19 affected patients.

Dabbu Suman[1], Ram Reddy B[2]& Bhanu Prasad Marri[3]

[1]*Department of Biomedical Engineering, University College of Engineering(A), Osmania University,Hyderabad, Telangana, India.*
[2]*Department of Physiology, Apollo Institute of Medical Sciences & Research, Hyderabad, India.*

Abstract:

Background & objectives: The world is facing SARS-COVID-19 pandemic. It is caused by a novel pathogenic virus which is highly contagious and spread across the globe and affecting millions of people leads to death. As per the clinical studies reported, most of the COVID19 patients who are under critically ill condition are suffering from the respiratory failure associated with cardiac dysfunction. COVID 19 directly impacts the lungs, where it damages the alveoli by accumulation of plasma protein on the alveolus wall. As a result, the lining gets thickened, and leads to hypoxia. State public health departments of Maharashtra and Kerala have reported that happy hypoxia or silent hypoxia as the prime killer among the higher mortality of COVID19. Silent hypoxia is asymptomatic, in which the patients suddenly go into the respiratory distress. Usually, these patients are under artificial ventilation through the continuous positive airway pressure. Sudden positive airway pressure compresses the capillaries which results in increase in the intravascular thrombosis, release of inflammatory biomarkers leading to the cytokine storm. Among these cases the mortality rate was reported as 80-90%. This paper reviews the works related to the cardiorespiratory coupling of covid patients, and the literature on the physiology studies were meagre.

The objectives of the study were to detect the silent hypoxia or early detection of respiratory distress, which plays a vital role in prevention of the mortality of the COVID19 patients.

The objectives of the study are

1. To find the degree of coupling between HRV and Respiratory signals through the time and frequency domain bivariate analysis.
2. To study the efficacy of CRC for the early detection of respiratory distress in COVID19 patients.
3. To validate the hypothesis through the statistical analysis.

Methods: The approaches most commonly applied to detect direct and indirect couplings between time series are Granger causality, nonlinear prediction, entropy, symbolization, phase synchronization. These are mostly focused on nonlinear approaches. Usually, nonlinear methods are used to study the interactions of a complex signal and linear methods are used to represent biological signals in the frequency domain. The HRV and Respiratory signals can be used to establish the cross-coupling behavior of the cardiac and respiratory systems through the bivariate analysis of the signals.

Results: Various features of the bivariate analysis can be derived from the HRV and respiration signals. These features include Granger causality, Partial directed coherence (PDC), Directed transfer function (DTF), Entropy, Cross-conditional entropy, Transfer entropy, Joint symbolic dynamics, Phase synchronization. The extent of correlation and synchronization of the CRC analyzed can be found from the derived features.

Interpretation & conclusions: Statistical analysis may be done for the test of significance and validation of the hypothesis. Hence, the degree of coupling may be established as a potential biomarker for the early detection of the respiratory failure by comparing those parameters against the samples under assessment. The Cardiorespiratory coupling certainly helps the clinicians in assessing electrophysiology of the COVID19 patients and provides an insight into early detection of respiratory failure and can be used for the management and therapy.

Key Words: COVID-19 -hypoxia- cardio-respiratory coupling-HRV-bivariate analysis- SARS-CoV-2

SARS COVID-19 is a novel corona virus affecting millions of people across the globe and leading to the death, WHO statistics shows that 127,349,248 COVID-19 cases have confirmed among which 2,787, deaths were reported as on 31th March 2021. In view of the severity of the disease, research in the diagnosis, therapy, and management of COVID19 has gained much prominence during the last one year. A study was conducted on the 100 inpatients diagnosed with COVID-19 at University college of London hospitals, U.K. The Sera was collected and cytokine testing was performed to obtain the clinical parameters and statistical analysis was carried out to test the significance. This study has reported that the COVID19 enters through the nasal cavity and targets the respiratory epithelial cells and alveolar macrophage. This leads to increased immune response leads to cytokine storm affects the vital organs of the human body causes multiorgan failure and leads to death. [2].

A study shows that the COVID-19 cases are classified in to four categories depending on the severity of the disease. Among these, few patients suffered from uncomplicated illness without the evidence of pneumonia in the radiographic findings, where as those with mild disease are suffered from fever with respiratory symptoms detected pneumonia through the radiographic images. Severe disease was demonstrated in patients with respiratory distress with increased respiratory rate (RR>30), decreased Partial pressure of oxygen (PO2<93%) at rest, and decreased inspired oxygen fraction (PaO2/FiO2<=300 mm of Hg). Critically ill patients suffered from respiratory failure supported with the mechanical ventilation, leads to multi organ failure and septic shock. [3].

An abundant clinical report on coronavirus disease 19 (COVID19) have focused on the laboratory investigations which revealed that decreased CD3,CD4 or CD8, elevated T-lymphocyte counts, while blood cell count, neutrophil count were associated with the disease.[4]. Elevation of these inflammatory biomarkers were used to analyze the progression and severity of the disease in developing into the sepsis. Detection of these biomarkers involves in the qualitative measurements through the clinical investigations usually takes time and lacks in giving the physiological information about the functioning of cardiac and respiratory function. A recent study shows that the higher concentration levels of neopterin is observed among the severe cases of COVID compared to those with the mild symptoms. It was also reported that these levels maintained for longer time in the severe cases, and decreased during the recovery period of those with mild symptoms and critically ill patients.[5]. A study was conducted on 1091 covid-19 positive cases and 32 clinical investigations were performed to detect the severity of the disease through the potential biomarkers. It is found that there is a significant correlation betweenincreased levels of PCT, thrombocytopenia,D-Dimer, LDH,lymphopenia, and COVID-19 severity. These results shows that these parameters can be used as the potential biomarkers for identifying the severe cases of COVID-19 and appropriate action towards their therapy and management is possible [6].

An investigation reported that few COVID-19 patients are labelled with 'happy hypoxia' or 'silent hypoxia'. These patients havecomplained of dyspnea and the expected symptoms of respiratory distress are absent. This study has postulated the underlying mechanism and interaction of neurologicalandrespiratorycomponents that could investigate the silent hypoxemia and provides a path for the future investigations. This study has also given the future directions regarding the investigations of respiratory sensationandneuronal control of breathing in COVID-19 patients. The study of silent hypoxaemia requires the understanding of respiratory physiology, central neural regulation of breathing, sensory feedback, principles of gas exchange, and respiratory sensation. [8].

The research on detection of silent hypoxemia or respiratory distress can be done through the Cardio Respiratory Coupling (CRC) from the Heart Rate Variability and respiration signals. CRC is very crucial in finding the interactions of cardiac and respiratory systems which are under the control of autonomic nervous system.Cardiorespiratory coupling (CRC) comprises differentphenomena resulted from common rhythms, shared inputs, and complementary functions.

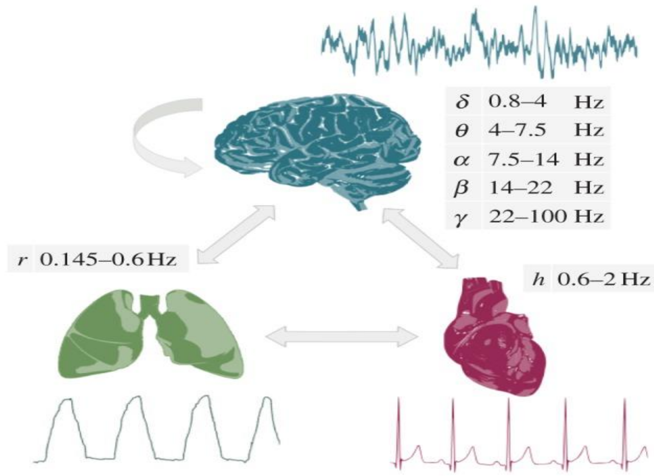
A study was conducted on rats to find the extent of autonomic control of brain over respiration under the hypoxia condition. This study has reported that the Cardio Respiratory Coupling can aid in finding the neural control for the enhanced Sympathetic Neural Activity was associated under the chronic intermittent hypoxia. This study shows that there exists a correlation of hypoxia and autonomic control system, which can be detected by using CRC.[10].

National Status:

In India 1,21,49,335 COVID-19 confirmed cases were reported, and out of which 1,62,468 lost their lives up to 5th March, 2021. [1].A study was conducted on the extent of the spread of COVID-19 from the 20 sewage samples in the Mumbai city. The samples were collected during the initial period (before 6th march, 2020) and later stages of COVID-19(during 11-15th May, 2020). It was found that all the samples collected during the initial phase of COVID-19 are negative, and all samples of later stages were tested positive. [11]. An article has reported that the COVID-19 enters the brain through the olfactory bulb and attacks the deeper parts of the brain including the brain stem and hypothalamus, thereby attacks the respiratory center. This results in the respiratory distress, hence this study has proposed to investigate the neurological symptoms and the neurological control of respiration. [7].

A study has proposed the role and use of the CT chest in the detection of COVID-19. Usually, CT is not recommended during the screening purpose, but it is a potential tool during the therapy for monitoring the extent of infection of lungs and severity of infection. [12].

An article reviews the extent of spread of COVID-19 and its impact on the patients with cardiovascular disorders. Though the COVID-19 primarily affects the lungs, it has the implications on the cardiac function because of the interdependence of the cardiovascular system and respiratory systems. COVID-19 Patients with pre-existing cardiac morbidities are at a higher risk, hence managing these patients with the appropriate guidelines and cognizant about novel emerging



technologies coming worldwide. [13].Most of the research studies are based on the detection of inflammatory biomarkers for the detection of COVID-19, but nobody is working on the electrophysiology studies of the cardiorespiratory system through the CRC. Hence, this study proposes the cardio Respiratory Coupling for finding the early detection of respiratory distress in the patients suffering from COVID19.

Methodology

Data Collection: This study requires the physiological data such as the heart Rate Variability, and Respiration signals of the COVID-19 patients and normal subjects. Hence data collection plays a crucial and challenging role.

The HRV and Respiratory signals can be used to establish the cross-coupling behavior of the cardiac and respiratory systems through the bivariate analysis of the signals. Various features of the bivariate analysis can be derived from the HRV and respiration signals. These features include Partial directed coherence (PDC), Granger causality,Cross-conditional entropy, Directed transfer function (DTF), Entropy, Transfer entropy, Phase synchronization,Joint symbolic dynamics. The extent of correlation and synchronization of the CRC analyzed can be found from the derived features.

ISSN 2229-5518

The capacity/efficiency to measure direct and indirect couplings between different biological time series such as HRV and Respiration may be implemented. Bivariate approaches are usually appliedfor the investigation of systems like the above. Bivariate, multivariate approaches can be used for the improvement in characterization of causal or non-causal interrelationships if there are more than two signals in assessment. Actually, the Cardiorespiratory and Cardiovascular time series (e.g.,blood flow,electrocardiogram, diastolic and systolic blood pressure, respiratory frequency, plethysmogram, and respiration flow) are mostlystationary for very short periodsor else non-stationary and noisy. By applying the linear & nonlinear time-series analysis approaches we can assess the causality and coupling of the signals which implies the different biological systems. Usually, nonlinear methods are used to study the interactions of a complex signal and linear methods are used to represent biological signals in the frequency domain.

Granger causality: It is a method to find the causality of the two simultaneous measured time varying signals. It can be such as HRV and respiration. It uses the HRV and Respiration data sets to find features patterns of correlation. It gives the statistical framework of one signal as the causal for the other signal and predicts the extent of causality in assessment. In Granger causality, the linear regression models can be fitted with following observations.

$$Z_1(t) = \sum_{j=1}^{p} A_{11,j} Z_1(t-j) + \sum_{j=1}^{p} A_{12,j} Z_2(t-j) + E_1(t) \quad \text{---(1)}$$

$$Z_2(t) = \sum_{j=1}^{p} A_{21,j} Z_1(t-j) + \sum_{j=1}^{p} A_{22,j} Z_2(t-j) + E_2(t) \quad \text{--- (2)}$$

All linear methods analyse the Granger Causality (GC) by the multivariate autoregressive (MAR) model by the parametric approach and are divided and assessed the GC in the time and frequency domain methods. In time domain the GC would be estimated by the linear prediction theory of least means square criterion with the test of significance for the causality. After obtaining the GC values the F-test and Wald test can be performed to find the test of significance across the samples.

Partial directed coherence (PDC): GC in the frequency domain can be calculated from thedirected transfer function (DTF) and Partial directed coherence (PDC). These techniques can be applied on the HRV and respiration signals with a fact that these signals are non-stationary signals. PDC is n-dimensional autoregressive approach with order p detects the direct and indirect information related to the causality between the two signals. PDC exclusively detects the direct coupling and interaction among the signals of multivariate dynamic systems. PDC values of HRV to Respiration and respiration to HRV signals in assessment can be found. The PDC ranges between 0 and 1, in this way, the direct influence from process HRV to process respiration is inferred by PDC≠0. When HRV does not cause Respiration at frequency *f*, then PDC=0 andwhen all causal influences originating from HRV at frequency *f* are directed towards Respiration then PDC=1.

Directed transfer function (DTF): DTF find the extent of correlation between the HRV and respiration signals. It enables to identify the direct and indirect causal interactions between the HRV and respiration signals. Thisled to a differentiation among the direct and indirect causal interactions or both may bepossible.

Entropy: Entropy is used to obtain the commonly accepted transfer of information among the signals. Entropy of the subjects in assessment will be obtained from the HRV and respiration signals. It actually gives the prediction of uncertainty among the cardiac and respiratory systems, and it is a way to establish the CRC. Greater value of the entropy shows the higher uncertainty and lower predictability. If $S(x)$ represents a measure of uncertainty of a time series and denotes the statistical properties of a time series *y*based on probabilities.

$$S(x)=\Sigma Pr(y)\log Pr(y) \quad \text{----(3)}$$

Where $Pi(x)$ is probability distribution of r^{th}bin of the time series *y*.

Cross-conditional entropy: Cross-conditional entropy (CE) is used to find the degree of coupling between two time-varying signals. CE approximates the complexity among the signals that may obtainthe degree of Cardio-Respiratory coupling. CE uses the sorting & mixed patterns of the two signals by the probabilistic approach and measures the causality from the prediction theory.

Transfer entropy: Transfer Entropy (TE) is based on the information that theoretical approach to distinguish between the responding elements and driving elements and it finds the asymmetries in the interaction among the bivariate signals like HRV & Respiration signals. This may quantify the degree to which the dynamics of cardiac and respiratory systems. Information flow among the cardiac and respiratory systems can be obtained from TE, the influence of one system over the other system estimated by the transition probabilities.

Joint symbolic dynamics: Joint Symbolic Dynamics (JSD) isa tool for the analysis of short-term dynamics of time-varying signals by simulating the characteristics of complex systems through simplified representation. JSD uses the symbols for the analysis of bivariate signals such as HRV and respiration signals for finding the Cardio respiratory coupling. It takes the short term beat-to-beat changes, and assess the overall all short-term cardio respiratory interactions to give the extent of cardio respiratory coupling. JSD is characterized by three symbols based on a threshold and clusters the coupling in to eight word symbols HRJSD for estimating cardiorespiratory coupling. In extension to the JSD the symbolic coupling traces(SCT) may assess the structural patterns and brings the direction of time-delayed interactions in a short-term bivariate signal.

Phase synchronization: Phase synchronization isdefined as the obtaining a relation between the phases (Φ_1, Φ_2) of the interacting signals, but the amplitudes are uncorrelated and chaotic. This technique is applicable to the cardio-respiratory signals such as HRV & respiration as they are inter dependent. The extent or the degree of coupling can be assessed by the phase synchronization. It obtains if the interaction is unidirectional or bidirectional and also measures the degree of asymmetry of bidirectional coupling. Among the two signals HRV and Respiration if the HRV signal is driven by the respiration signal the evolution of phase of HRV depends on phase of respiration. Prediction of the phase of HRV from its old values may be improved by only considering the prehistory of phase of Respirationif the Respiration signal drives the HRV signal. The converse of this phenomenon is also true, hence the phase coupling of HRV and Respiration may establish the degree of cardio respiratory coupling.

$$\Phi_{1,2}=\omega_{1,2}+\varepsilon_{1,2}f_{1,2}(\Phi_{2,1},\Phi_{2,1})+\xi_{1,2}$$

$\varepsilon_{1,2}$&$\omega_{1,2}$ helps in finding the strength of degree of coupling, $\xi_{1,2}$ denotes the noisy signals, $\omega_{1,2}$ are the natural frequencies of the HRV & respiration and functions $f_{1,2}$ is 2π periodic.

Results& Conclusion

Various features of the bivariate analysis may be found from the HRV and respiration signals. The features that can be derived from the bivariate analysis are Partial directed coherence (PDC), Granger causality,Cross-conditional entropy, Directed transfer function (DTF), Entropy, Transfer entropy, Phase synchronization, Joint symbolic dynamics.

These parameters of the samples under assessmentmay be compared for the test of significance through the statistical tools. Thus, degree of cardio-respiratory coupling can be estimated and established from the parameters which shows significant difference among the samples under assessment. Since the Cardiorespiratory coupling was used in the detection of cardio-pulmonary disorders, this hypothesis also would test the Cardio-respiratory coupling andmay be establish it as a potential biomarker for the early detection of the respiratory failure &respiratory distress. The Cardiorespiratory coupling certainly helps the clinicians in assessing electrophysiology of the COVID19 patients and provides an insight into early detection of respiratory failure and can be used for the management and therapy.

Discussion

Importance in current status:

Among the mortality cases of COVID-19, it was reported that the ‘silent hypoxia ‘or ‘happy hypoxia' was present without any symptom. This leads to the sudden respiratory distress and brings the patient into hypoxia and leads to the death. Hence the early detection of respiratory distress of COVID19 patient's plays a vital role in saving the lives. The Cardio respiratory coupling is based on the fact that the functioning of respiratory and cardiovascular systems are inter dependent and controlled by the autonomic nervous system. Cardio-respiratory coupling plays (CRC) an important role in synchronization of the cardiac and pulmonary systems by overlapping of brainstem networks through the autonomic control system. Many studies revealed that the degree of sympathetic and para-sympathetic nervous systems can be analyzed through the CRC. Hence CRC is used for the early detection of respiratory distress. The study postulates that the deterioration in the CRC disrupts the synergy between cardiac and respiratory systems that leads to cardiorespiratory dysautonomia. Quantitative methods for the understanding of normal and pathophysiological conditions (COVID19) that respectively leads to CRC and cardiorespiratory dysautonomia. The Cardio Respiratory Coupling of COVID patients test the degree of coupling through the bivariate analysis of HRV & respiratory signals, and provides an insight in to the early detection of respiratory distress. The degree of coupling would emphasize the interaction between the cardiac and respiratory systems and control mechanism through the autonomic nervous system. The CRC coupling would be altered in the COVID-19 patients with those who are also with silent hypoxia, this can be detected in advance before the patient goes into hypoxic death. Hence this would a way for the early detection of silent hypoxia and can save millions life. It also throws an insight into the electrophysiology study of the COVID-19 patients which is highly required.

Significance:

This study aims at finding the CRC of the COVID19 patients through the Heart Rate Variability (HRV) and Respiration signals to derive the time and frequency domain features which signifies the extent of synergy between the cardio-pulmonary systems. This would certainly help the clinicians in assessing electrophysiology of the COVID19 patients and provides an insight into the early detection of respiratory failure and can be also used for the management and therapy.

Environmental impact assessment and risk analysis:

This project requires the approval ofInstitutional Ethical Committee as it involves in the data collection from human participants. Institutional Ethical Committee approvals shall be taken once it is considered in the upcoming meetings. There is no impact on the environment in achieving the objectives of the project

Acknowledgment:

The collaboration with the Apolloinstitute of medical sciences helps in the data collection and analysis.Authors acknowledge the support provided by the following:

Prof.Ram Reddy B, a Professor of physiology, Apollo institute of medical sciences, with 35 years of research experience in electrophysiology is essential in the design and implementation of the study for the data collection from the COVID patients. He has contributed a lot to the research in the cardiac electrophysiology, genetics and DBS related to cardio-respiratory disorders. Apart from data collection he will assist in the comparison of results to get the clinical correlation.

Dr.Dabbu Suman, an assistant professor, in Biomedical engineering department having 14 years of research and academic experience in biomedical signal processing, neurological signal processing, and cognitive science will be responsible for the design and development of DAQ for the acquisition of HRV and respiration signals. He will be also involved in the data collection, feature extraction and analysis through statistical tools to validate the results.

Financial support & sponsorship: This work is partly funded by the DST-PURSE, Govt. of India, under the Grant C-DST-PURSE-II/52/2020 dated 5/12/2020. The authors would like to thank the TEQIP (Technical Education and Quality Improvement Program) Phase-II of World Bank initiative to promote technical education in India, for the extended financial support in terms of equipment, Software procurement. We would also express our sincere gratitude to the NPIU (National Project Implementation Unit) & SPFU (State Project facilitation Unit) of TEQIP for motivating us to improve our research and development activities..

Conflicts of Interest: None.

References

[1].W.H.O statistics on COVID-19.

[2]. Keddie, S., Ziff, O., Chou, M. K. L., Taylor, R. L., Heslegrave, A., Garr, E., … Lunn, M. P. (2020). *Laboratory biomarkers associated with COVID-19 severity and management. Clinical Immunology, 221, 108614.* doi:10.1016/j.clim.2020.108614

[3]. Giovanni Ponti, Monia Maccaferri, CristelRuini, Aldo Tomasi, TomrisOzben Biomarkers associated with COVID-19 disease progression Crit Rev Clin Lab Sci. 2020: 1–11. Published online 2020 Jun 5. doi: 10.1080/10408363.2020.1770685.

[4] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

[5] T. Herold, V. Jurinovic, C. Arnreich, et al., Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19, J Allergy Clin Immunol 146 (1) (Jul 2020) 128–136, https://doi.org/10.1016/j.jaci.2020.05.008 (2020.04.01.20047381).

[6] E.A. Coomes, H. Haghbayan, Interleukin-6 in COVID-19: a systematic review and meta-analysis, Rev Med Virol. 26 (e2141) (Aug 2020) (2020.03.30.20048058).

[7] European center for disease prevention and control, Case Definition for Coronavirus Disease 2019 (COVID-19), as of 29 May 2020, 2020.

[8] World Health Organisation, Blueprint Novel Coronavirus COVID-19 Therapeutic Trial Synopsis, 2020

[9].Huang, YC., Lin, TY., Wu, HT. *et al.* Cardiorespiratory coupling is associated with exercise capacity in patients with chronic obstructive pulmonary disease. *BMC Pulm Med* **21,** 22 (2021). https://doi.org/10.1186/s12890-021-01400-1

[10]. Dick TE, Hsieh YH, Dhingra RR, et al. Cardiorespiratory coupling: common rhythms in cardiac, sympathetic, and respiratory activities. *Prog Brain Res*. 2014;209:191-205. doi:10.1016/B978-0-444-63274-6.00010-2

[11].Deepa Kailash Sharma, Uma Prajwal Nalavade, Kamlesh Kalgutkar, Nivedita Gupta, Jagadish Mohanrao Deshpande, *SARS-CoV-2 detection in sewage samples: Standardization of method & preliminary observations, Indian Journal of Medical Research 2020*

[12]. Mandeep Garg , Nidhi Prabhakar , AshuSeith Bhalla , Aparna Irodi , Inderpaul Sehgal , Uma Debi , Vikas Suri , Ritesh Agarwal , Laxmi Narayana Yaddanapudi , Govardhan DuttPuri&Manavjit Singh Sandhu, *Computed tomography chest in COVID-19: When & why?* , Indian J Med Res Epub ahead of print DOI: 10.4103/ijmr.IJMR_3669_20.

[13]. Yash Paul Sharma, Sourabh Agstam , Ashutosh Yadav , Anunay Gupta & Ankur Gupta, Cardiovascular Manifestations of COVID-19: An evidence-based narrative review, Indian J Med Res Epub ahead of print DOI: 10.4103/ijmr.IJMR_2450_20.