MITIGATING THE IMPACTS OF CORONAVIRUS DISEASE USING HEART RATE VARIABILITY

by

Sarah March

A Senior Honors Project Presented to the

Honors College

East Carolina University

In Partial Fulfillment of the

Requirements for

Graduation with Honors

by

Sarah March

Greenville, NC

May 2022

Approved by:

Linda P. Bolin, PhD, MSN, RN, ANP, BCB, FAHA
Department of Nursing Science, College of Nursing

Nicholas Murray, PhD
Department of Kinesiology, College of Health and Human Performance

Abstract

Objective: The primary objective of this literature review is to examine the current state of the science on heart rate variability is currently used to mitigate the impact of the Coronavirus Disease 2019 (COVID-19) pandemic. The secondary objective of this literature review is to discuss future implications based on the identified gaps in current research surrounding Heart Rate Variability (HRV) and COVID-19. This scoping review isn't limited to patients with COVID-19, as it also explores indirect impacts of the pandemic, including Healthcare Worker (HCW) burnout.

Methods: In November of 2022, a scoping review was performed by using one database, PubMed. The key phrase "HRV and COVID-19" was used to search for relevant articles.

Results: 42 articles were collected, of which 16 met the inclusion criteria for relevance. From these 16 articles, four distinct categories were identified. The first category is predicting COVID-19 diagnosis. The second is predicting COVID-19 patient outcomes. The third is monitoring Healthcare Worker (HCW) burnout and guiding HCWs in Triaging and Treating Patients suffering because of the physical and psychological impacts of COVID-19. Finally, HRV shows potential as a remote monitoring system of a large population's health.

Conclusion: More research is needed to determine how and if age as well as the type of variant influences the way COVID-19 can be monitored with HRV. Gaps in the current state of the science are identified as the lack of data on variants and special populations, including pediatrics and certain chronic conditions. This demonstrates the need for future research.

Introduction and Background

In March of 2020, the World Health Organization declared Coronavirus Disease 2019 (COVID-19) a pandemic. Since then, there have been over 250,000,000 cases of COVID-19, leaving five million lives lost.[1] This pandemic has brought consequences of new magnitudes, many of which are still not fully understood. For the purposes of this literature review, the impacts of COVID-19 are limited to physical health and mental health.

The aspects of physical health discussed in this review are transient COVID-19, Post-COVID Conditions, and autonomic dysfunction (AD). Transient COVID-19 is the illness most commonly associated with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic with symptoms of varying severity.[2] Post-COVID Conditions, or "Long COVID", occur when the illness is not short term, but rather persists for at least a month following initial infection.[3] The autonomic nervous system is part of the peripheral nervous system that controls enteric, sympathetic, and parasympathetic nervous systems in the body.[4] Autonomic dysfunction, or dysautonomia is defined as the autonomic nervous system being overactive or underactive.[5]

The aspects of mental health discussed in this review are healthcare worker burnout, misophonia, and general emotional well-being. Burnout, or burn-out, is defined by the World Health Organization as "a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed".[6] The Mayo Clinic notes that burnout can lead to a plethora of additional health concerns, varying from substance use disorders to diabetes.[7] Burnout has become especially concerning during the pandemic, as it is commonly attributed to sparking "The Great Resignation of 2021".[8] While burnout can be present in all careers, its presence in healthcare causes further straining in other aspects of health. Another mental health concern relating to the pandemic is misophonia, which is characterized by specific everyday sounds causing an abnormally negative emotional reaction.[9] Quarantine and social distancing changed a lot of the misophonia population's exposure to sounds.[10] For the purposes of this review, general emotional well-being is being defined as not having detectable stress caused by a negative state of mental health. Emotional well-being is important to track during a pandemic, because psychological stress has a direct effect on the immune system.[11]

Heart Rate Variability's (HRV) ability to measure autonomic nervous system performance makes it particularly versatile in measuring emotional well-being. As mentioned previously, this review defines general emotional well-being as not having detectable stress caused by a negative state of mental health. As explained by Ginty and colleagues, psychological stress has a direct impact on physical health and vice versa.[12] While this study focused primarily on linking psychological stress to cardiovascular disease, it also illustrates the way in which the autonomic nervous system links them.[12] This link explains how HRV is capable of measuring both psychological and physical stress. This is relevant to the use of HRV in mitigating the impacts of COVID-19, because COVID-19 has impacts on both mental health and physical heath. This establishes the need for a metric of stress in all forms of health as a result of the pandemic.

HRV is used as a metric of autonomic nervous system performance because of its role as an indicator of sympathetic and parasympathetic response, which the autonomic nervous system controls.[4] There are multiple ways to represent heart rate variability, however all measurements depend on the change in the time interval between sequential heartbeats over time.[4] For measuring sympathetic and parasympathetic response, the low-frequency band/high frequency band (LF/HF) ratio reflects which system is more dominant in a moment of time.[4] The low-frequency band is affected by both the sympathetic and parasympathetic response, whereas the high-frequency band is specific to the parasympathetic response.[4] This means a low LF/HF ratio indicates parasympathetic dominance, whereas a high LF/HF ratio indicates sympathetic dominance.[13]

Similar to a low LF/HF ratio, the Root Mean Square of Successive Differences (RMSSD) is another measurement that indicates parasympathetic response.[4] This measurement relies on the variability between a single beat interval and the beat interval immediately following the previous interval.[4] Meanwhile the Standard Deviation of NN intervals (SDNN) is less influenced by the parasympathetic nervous system.[4] SDNN measures variability between a single beat interval and the average of all "normal" beats, and recordings of SDNN over the course of 24 hours is generally considered the "gold standard".[4]

Methodology

A scoping review was performed by using one database, PubMed, and the key phrase "HRV and COVID19". The search from early October 2021 to early November 2021, resulted in forty-two articles. Inclusion and exclusion criteria were employed, resulting in sixteen studies of relevance. Those excluded were twenty-six articles not meeting the following criteria: (1) No discussion of heart rate variability, but human rhinovirus or the HRV Transparency Project. (2) No explicit link between HRV with COVID-19, but with a vaccine or general disease sometimes associated with COVID-19. (3) Not in full text English. (4) The full text was inaccessible through PubMed, Elsevier, or Mendeley.

The sixteen remaining articles each related heart rate variability and a direct effect of COVID-19, including physical or psychiatric illness, burnout, hospital protocols, and social distancing. These articles were collated and organized into four categories based on their findings. The four distinct categories were: (1) Using HRV as a Predictive Tool of the Physical Impacts of Transient COVID-19, (2) Explaining COVID-19 "Long Haulers" through HRV and Autonomic Dysfunction, (3) Using HRV and the Psychological Impacts of COVID-19, or (4) Discussing the efficacy of HRV as a Preventive Metric of COVID-19's Impact.

Results

Using HRV as a Predictive Tool of the Physical Impacts of COVID-19

When COVID-19 first emerged, the main populations of concern were those already at risk of severe respiratory illness.[14] By June of 2020, the CDC recognized that COVID-19 also has a disproportionate effect on immunocompromised populations and those at risk of heart disease, infection, and other conditions relating to the autonomic nervous system.[14] Before the CDC even expanded its list of at-risk populations, Kaliyaperumal and colleagues had already started to investigate COVID-19's role in autonomic dysfunction by comparing the HRV of sixty-three patients with COVID-19 and forty-three controls.[15] This case-control designed study involved determining the low-frequency power, high-frequency power, RMSSD, and SDDN from a five-minute EKG before analyzing the data with the seventeenth version of the IBM SPSS statistical software. This study determined that in patients with COVID-19, there was a significant decrease in both low-frequency and high-frequency powers.[15] It also found that the COVID-19 patients had a significant increase in SDNN and RMSSD, indicating increased parasympathetic activity. Since this investigation was completed early in the pandemic's timeline, there is no data on Post-COVID Conditions, pediatrics, or how HRV may vary with newer variants of the SAR-CoV-2 virus. Another limitation of this study is that none of the participants had a severe COVID-19 infection.[15] While further research is needed with a larger sample size, this study highlights the potential for HRV to be used as diagnostic criteria for COVID-19.

One common goal of initial COVID-19 research was to rapidly determine who in the population had been infected or who was at risk of infection. Current methods of testing COVID-19 are usually limited to people who are or know someone who is actively experiencing symptoms or is contagious, as these are the people that consider it necessary to get tested. A study from Natarajan and colleagues in November of 2020 opens the door to using HRV as a predictor of COVID-19 from the comfort of home before symptoms emerge (if at all).[16] Natarajan's research team intended to use wearable devices as a way to assess physiological signs of COVID-19, including HRV. The sample included 2,745 participants who used a Fitbit in the USA or Canada. Participants completed a survey regarding their experience with COVID-19, if they had been diagnosed, and all data was analyzed by Fitbit. This study determined that values for RMSSD began to plummet a few days before symptoms had even started and reached a minimum value right after the onset of symptoms.[16] After symptoms emerged, RMSSD increased consistently until roughly thirteen days following the onset of symptoms, at which time their RMSSD returned to their baseline level. While this study implies RMSSD could predict the COVID-19 prior to the onset of symptoms, a major source of bias is that all symptoms were self-reported. Further research is also needed on if and how newer variants impact HRV differently. Additionally, this study was funded entirely by the Fitbit company.[16]

A study with a similar objective was done by Hirten and colleagues who explored the use of physiological data with a much smaller sample size. This prospective study followed 297 HCWs that wore Apple Watches and used the Warrior Watch Study app.[17] Surveys were also used in this study to monitor COVID-19 symptoms, where participants used an Apple Watch as their wearable device to measure HRV as SDNN. Data were analyzed with a bootstrapping method to compare the different populations within the study's daily circadian rhythms of HRV, which were found by mixed-effect cosinor models. This study found that the circadian pattern of SDNN differed significantly for participants with COVID-19 up to seven days before their diagnosis.[17] While the findings of this study corroborate those of Natarajan and colleagues, this study also relied on self-reported surveys. While this study was not directly funded by any companies that created the materials used, it had a significantly smaller sample size, of which only thirteen participants were diagnosed with COVID-19. Furthermore, this study didn't account for fluctuations in sleeping patterns, possible differences in pediatrics, or how newer variants may impact HRV differently.[17] Further research would also benefit from collecting more diverse HRV data (not just SDNN) throughout the day.

Regardless of the implications of both studies, each shows the ability of HRV to reduce the impact of COVID-19 before the illness gets the chance to fully take root in a community. Using HRV as an early warning sign of COVID-19 illness would allow for quicker testing and quarantine turn-around, further preventing the spread of COVID-19 without sacrificing other aspects of the population's health.

HRV can also be used as a predictive metric beyond transient COVID-19. Tiger Technologies Warfighter Monitor (WFM) was used to measure HRV as SDNN in seventeen participants for the study published by Hasty's research team.[18] This study attempted to demonstrate that HRV could be used to predict increases in C-reactive protein (CRP), which is directly related to the progression of COVID-19. Data was analyzed with the twenty-fourth version of the IBM SPSS statistical software. This article explains that sharp spikes in CRP correlate with preceding sharp drops in SDNN.[18] Since CRP is a protein associated with inflammation, this study also indicates that HRV may be useful in predicting cytokine storms before they happen in patients with COVID-19. Further research with a larger sample size is needed, especially to determine what may cause false negatives and positives.[18]

Explaining COVID-19 "Long Haulers" through HRV and Autonomic Dysfunction

As mentioned earlier, one major long-term impact of transient COVID-19 is Post-COVID Conditions. Barizien and colleagues aimed to use the nociception level (NOL) index, which is dependent on HRV, to demonstrate that dysautonomia could occur in Post-COVID Conditions.[19] This study divided their sample population into three groups and followed the changes in the NOL index of each participant. NOL Index is an objective measurement to quantify a patient's physiological response to pain. The three groups were comprised of (1) patients with "Long COVID" and fatigue, (2) patients with "Long COVID" and no fatigue, and (3) control patients. Data analysis was performed with the SAS statistical software version 9.4, repeated-measures mixed-models, a Kruskal–Wallis test and a Chi-squared test. No significant difference in the NOL index between the two "Long COVID" groups was noted, but both differed significantly from the control group.[19] Further research with a larger sample size that includes a more diverse range of age and severity of illness is needed to determine if these findings are reliable and if newer variants cause differing results. A future study that includes participants with transient COVID-19 would allow for a better understanding of how autonomic dysfunction changes based on the severity and length of illness.

Another study with a larger sample size from Milovanovic and colleagues also investigated AD in patients with COVID-19, more specifically how COVID-19 impacted the cardiovascular system.[20] In this case control, observational study, 116 patients were grouped into one of three categories: (1) severe COVID-19, (2) mild COVID-19, or (3) negative for COVID-19. Severe COVID-19 was defined as COVID-19 with pneumonia, whereas mild COVID-19 was without. HRV was measured using a Task Force Monitor© to obtain an EKG. Data was analyzed with the fifteenth version of the IBM SPSS statistical software. This study determined that AD was present in more than half of the patients with severe COVID-19 and in over seventy percent of patients with mild COVID-19.[20] This study was interrupted by a shortage of resources at the peak of the pandemic, so further research is needed to see if the patients with AD experience worse outcomes.[20] Depending on the results of future research that includes more variants and participants, it may be determined that patients are at a lower risk of developing Post-COVID Conditions if AD can be prevented or reduced in transient COVID-19. Even if not, HRV as a tool to determine AD in patients with COVID-19 gives HCWs a better glimpse into the status of their patient, improving patient care.

Four different studies from the research teams of Aragón-Benedí, Pan, Mol, and Tanwar corroborate the ability of HRV to predict COVID-19 patient outcomes. Using HRV to demonstrate higher levels of AD in patients with COVID-19 are dependent on the severity of the illness was the goal of the prospective pilot study completed by Aragón-Benedí and colleagues.[21] The HRV of fourteen participants with COVID-19 was measured with an Analgesia Nociception Index monitor (ANIm). All participants were on mechanical ventilation. Data was analyzed with U-Mann-Whitney and Wilcoxon tests and Kendall's tau-b correlation test. Despite the small sample size, the study was still able to determine that ANIm values of 80 or higher had positive predictive and negative predictive values of 87.5% and 100%, respectively.[21]

Pan and colleagues had a similar objective, to relate autonomic functioning to severity and outcomes in patients with COVID-19.[22] Thirty-four participants were separated into two groups based on the severity of their COVID-19 illness. Each participant had their HRV collected via EKG upon diagnosis with COVID-19 and again upon their first negative test. Data analysis was completed using a Pearson Chi-Square, a Fisher's exact, a Mann–Whitney, the Wilcoxon signed rank, or an unpaired or paired t-test. Similar to the previous study, this investigation was limited by sample size, but found that patients with more severe COVID-19 also had more severely impaired HRV. This study also found that patients with COVID-19 took longer to recover if their HRV indicated AD.[22]

The relation between COVID-19 and AD was examined by Mol's research team, who used vagus nerve activity to predict COVID-19 patient outcomes.[23] 271 participants were involved in this retrospective cohort study, which used HRV to indicate vagus nerve activity from ten-second EKGs. Data was analyzed using the twenty-fourth version of the IBM SPSS statistical software. HRV values for SDNN were determined to be a reliable indicator of survival, but it is only accurate when a patient is over the age of seventy.[23] Both SDNN and RMSSD were reliable indicators of ICU referral. Since the vagus nerve is a part of the autonomic system, the study demonstrates how AD is contributing to negative patient outcomes. Only ten-second EKGs were used, so more research is needed to determine if LF and HF power could also act as predictors of patient outcomes. Future research should also be done to determine if newer variants or certain ages made patients have different AD and COVID-19 outcomes. [23]

Relating HRV to AD and COVID-19 was taken a step further by Tanwar and colleagues, as they aimed to create an algorithm to predict the onset or worsening of COVID-19.[24] HRV was collected from smart bands (Apple Watch, Fitbit, and Garmin), and analyzed by Welltory using a hidden Markov Model. This sample size of 186 was far larger than the two previously mentioned studies. It was determined that the onset or worsening of COVID-19 could be a direct cause of steady declines in HRV values.[24] This further corroborates the potential of HRV as a remote metric of COVID-19 outcomes. Additional research is needed to determine if these findings are consistent in populations who have been diagnosed with COVID-19 more than once, as well as with newer variants.

While all four articles varied in their exact objective and findings, they all support that HRV (1) may indicate a direct relationship between autonomic dysfunction and COVID-19 severity, and (2) can assist in triaging patients by predicting patient outcomes. Future research in relating the severity and length of COVID-19 to autonomic dysfunction. A major implication of the findings of future research is that Post-COVID Conditions may in part be caused by autonomic dysfunction that occurred during a patient's initial experience with transient COVID-19.

HRV and the Psychological Impacts of COVID-19

The impact of COVID-19 is not limited to physical health. The CDC's Morbidity and Mortality Weekly Report from August 14, 2020, reported an increase in mental health concerns relating to COVID-19, varying from individual mental health conditions like anxiety and depression to suicidal ideation and substance use as a method of coping.[25] Czeisler and colleagues also found that essential workers had higher increases of certain mental health concerns than nonessential workers or those who were unemployed.[25] This is especially concerning, as the population's resiliency during the pandemic is dependent on workers whose own resiliency is being strained by said pandemic. Similar to COVID-19, HRV isn't limited to measuring physical stress. This means HRV can assist in reducing both the physical and psychological impacts of COVID-19, like by preventing burnout and promoting emotional well-being.

Synchronously, there was another, smaller study of 361 participants in New York City investigating HRV in relation to HCW stress.[26] A secondary objective of this study by Hirten and colleagues ("Factors Associated...") was to compare HRV's circadian rhythm in groups with differing levels of resiliency and emotional support. Similar to the study by Hirten's research team mentioned earlier ("Use of Physiological Data..."), this prospective, observational cohort study used Apple Watches to measure HRV (as SDNN) and the Warrior Watch Study app to have participants complete surveys. Instead of quantifying physical symptoms, the surveys in this study quantified "perceived stress, resilience, emotional support, quality of life, and optimism".[26] Data was analyzed using cosinor and bootstrapping models. This study found that both strong resiliency and emotional support were associated with smaller changes in SDNN throughout a 24-hour period.[26] Further research is needed to determine if there are still discrepancies in HRV as a result of COVID-19 when an individual has low resiliency or emotional support. If future research doesn't find that there are discrepancies, patient resiliency and emotional support could serve as primary indicators of outcomes for COVID-19 patients.

One common goal of current COVID-19 research is to find ways to rapidly determine who in the population has been infected or at risk of infection. Gupta's research team from India aimed to do this for the psychological side of COVID-19's impacts by developing machine-learning models to predict burnout in over 1,500 HCWs through monitoring HRV.[27] In this study, burnout was defined as a score of three or higher on the Mini-Z-burnout-item survey and HRV was collected from 12-lead electrocardiograms (ECGs). A variety of logistic regression analyses and the sixteenth version of SPSS statistical software was used for data analysis. Of the six machine-learning models developed, the "tree based extra tree classifier" model had the highest levels of accuracy and sensitivity (both over 77%) for predicting burnout from RMSSD and SDNN.[27] Even with a large sample size, it is important to note that this was only one study out of India from mid to late 2020, meaning more research needs to be done to see if these results are similar to findings in other countries and if newer variants of coronavirus have had any impact on burnout. Possible sources of bias in this study include that the primary investigators have received funding from Acadia Pharmaceuticals, Janssen and Janssen, Pfizer, Medscape, and Clinical Exercise Physiology Association. The results of this study opens the door to a plethora of opportunities for HRV to reduce the impact of COVID-19. Beyond merely monitoring and predicting burnout in individual HCWs, it could also provide quantitative insight into the effectiveness of hospital systems' methods to reduce burnout on a greater scale and reduce the mass exodus of HCWs throughout the USA.[27]

Promoting psychological wellbeing during the pandemic includes monitoring preexisting mental health conditions. One mental health condition that worsened for many during the pandemic is misophonia.[9] In Spain, there was a prospective, longitudinal study to determine how and if HRV could be used to mitigate worsening misophonia caused by quarantine and social distancing.[10] From March 14, 2020 to June 21, 2020, Ferrer-Torres and colleagues measured the HRV of participants with moderate to extreme misophonia before and after three confinement periods. Misophonia was diagnosed with the Amsterdam Misophonia Scale and measured HRV with emWave® technology. Data was analyzed with IBM SPSS software from the HeartMath tool and the Wilcoxon signed rank tests.[10] HRV following triggering auditory stimuli was found to be significantly lower when following periods of confinement.[10] Additionally, participants were able to use HRV as an indicator for determining if their condition was worsening, allowing them to have interventions sooner. Unfortunately, this was a small sample size and only in Spain, so additional studies are needed to determine if these results are replicable in larger sample sizes in other parts of the world and if pediatrics would have similar results. A major implication from the results of this study is that HRV can vary depending on psychological stress.[10] COVID-19 likely causes psychological stress on patients, which indicates additional metrics would be necessary to differentiate changes in HRV from psychological or physiological stress. However, each form of stress can have an impact on the other, meaning regardless of the type of stress, HRV is an excellent tool for measuring changes in stress including those related to the COVID-19 pandemic.[12] This means that HRV can still be used as an early warning sign of COVID-19 related stress, allowing interventions to happen sooner for those who need them.[10]

Efficacy of HRV as a Preventive Metric of COVID-19's Impact

Misophonia isn't the only condition that impacts HRV. During the pandemic, there were also studies to note how the pandemic may have changed the relationship between HRV and certain chronic illnesses. Andreu-Caravaca's research team used HRV to investigate how the pandemic has affected "cardiac autonomic function in people with Multiple Sclerosis (MS)".[28] This prospective, observational study used a Polar H7 to measure the HRV of seventeen participants (all with MS) before and after quarantine. Data was analyzed with the third version of Kubios HRV software and a Shapiro-Wilks test. This study determined that quarantine had no impact on the HRV of people with MS.[28] A major implication of these findings is that people with certain chronic illnesses may not have fluctuations in HRV as a result of COVID-19. This may be because their chronic illness already causes autonomic dysfunction. Further research is needed on the role of chronic illness impacting the efficacy of HRV as a metric for COVID-19.[28]

Junarta and colleagues also addressed the concern of chronic illness impacting the efficacy of HRV as a metric of COVID-19 by looking at the relation between HRV and chronic atrial fibrillation in patients hospitalized for COVID-19.[29] In this retrospective review, SDSD, RMSSD, and pNN50 were all calculated from EKGs that were obtained from 82 participants, roughly half of which developed COVID-19. Kaplan-Meier curves, log-rank test, and the STATA/SE program version 16.1 were used for data analysis. This study's findings indicate that HRV will still be impacted by COVID-19, regardless of if a patient has chronic atrial fibrillation.[29] More research is needed to see if this remains true with other chronic conditions that impact the autonomic nervous system, as well as in different age categories and with newer variants of COVID-19. However, this study demonstrates HRV's efficacy in at least one subgroup of the population with chronic illness. Even if HRV isn't as accurate in certain populations due to chronic illness, HRV might still be able to be used to monitor said chronic illness and reduce stress on HCWs.[29]

Despite HRV's possible limitations in certain populations, its biggest advantage may be how it could be used to remotely monitor COVID-19's spread through a population. Capodilupo's research team completed a study that established how quarantine and social distancing influenced HRV.[30] For this retrospective analysis, HRV data was obtained from almost 5,500 participants through a smart fitness band (WHOOP strap) over roughly four months. The first two months acted as a baseline while the following two months acted as the experimental data. Separate general linear mixed models were completed to analyze the data. This study found that their metric for HRV increased during the quarantine period.[30] While this may indicate changes in a population's average HRV as a result of COVID-19 are due to psychological stress, 2019 also saw a similar increase in HRV. It is also notable that the primary investigator of this project is employed by WHOOP, Inc. The findings focused on the impact of social distancing on HRV, but this study also demonstrates HRV's efficacy as a metric that can be used remotely on a large population. Further research is needed with different types of smart watches to determine if an algorithm that uses HRV to track the spread of COVID-19 would be accurate.[30]

Conclusion

In summary, the sixteen articles found in this scoping review from early October 2021 to early November 2021 demonstrate the potential of HRV to mitigate the impacts of COVID-19 by predicting COVID-19 diagnosis, predicting COVID-19 patient outcomes, monitoring Healthcare Worker (HCW) burnout, guiding HCWs in Triaging and Treating Patients suffering because of the physical and psychological impacts of COVID-19, and remotely monitoring the health of large populations. HRV shows potential for reducing the impacts of transient COVID-19, Post-COVID Conditions, and autonomic dysfunction (AD). Future research is needed to determine how and if newer variants of SARS-CoV-2 impacts HRV as well as how and if age influences the way COVID-19 can be monitored with HRV.

Works Cited:

1. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. Accessed November 17, 2021. https://covid19.who.int/

2. Basics of COVID-19 | CDC. Accessed November 17, 2021. https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19/basics-covid-19.html

3. Post-COVID Conditions | CDC. Accessed November 17, 2021. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html

4. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*. 2017;5:258. doi:10.3389/FPUBH.2017.00258

5. Dysautonomia Information Page | National Institute of Neurological Disorders and Stroke. Accessed November 17, 2021. https://www.ninds.nih.gov/Disorders/All-Disorders/Dysautonomia-Information-Page

6. Burn-out an “occupational phenomenon”: International Classification of Diseases. Accessed November 17, 2021. https://www.who.int/news/item/28-05-2019-burn-out-an-occupational-phenomenon-international-classification-of-diseases

7. Job burnout: How to spot it and take action - Mayo Clinic. Accessed November 17, 2021. https://www.mayoclinic.org/healthy-lifestyle/adult-health/in-depth/burnout/art-20046642

8. The Great Resignation Didn’t Start with the Pandemic. Accessed April 27, 2022. https://hbr.org/2022/03/the-great-resignation-didnt-start-with-the-pandemic

9. Palumbo DB, Alsalman O, de Ridder D, Song JJ, Vanneste S. Misophonia and Potential Underlying Mechanisms: A Perspective. *Frontiers in Psychology*. 2018;9(JUN):953. doi:10.3389/FPSYG.2018.00953

10. Ferrer-Torres A, Giménez-Llort L. Sounds of Silence in Times of COVID-19: Distress and Loss of Cardiac Coherence in People With Misophonia Caused by Real, Imagined or Evoked Triggering Sounds. *Frontiers in Psychiatry*. 2021;12. doi:10.3389/FPSYT.2021.638949

11. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res*. 2014;58(2-3):193-210. doi:10.1007/S12026-014-8517-0

12. Ginty AT, Kraynak TE, Fisher JP, Gianaros PJ. Cardiovascular and autonomic reactivity to psychological stress: Neurophysiological substrates and links to cardiovascular disease. *Auton Neurosci*. 2017;207:2-9. doi:10.1016/J.AUTNEU.2017.03.003

13. Shaffer F, Meehan ZM, Zerr CL. A Critical Review of Ultra-Short-Term Heart Rate Variability Norms Research. *Frontiers in Neuroscience*. 2020;14. doi:10.3389/fnins.2020.594880

14. CDC Museum COVID-19 Timeline | David J. Sencer CDC Museum | CDC. Accessed November 17, 2021. https://www.cdc.gov/museum/timeline/covid19.html

15. D K, K R, M A, S R. Characterization of cardiac autonomic function in COVID-19 using heart rate variability: a hospital based preliminary observational study. *J Basic Clin Physiol Pharmacol*. 2021;32(3):247-253. doi:10.1515/JBCPP-2020-0378

16. A N, HW S, C H. Assessment of physiological signs associated with COVID-19 measured using wearable devices. *NPJ Digit Med*. 2020;3(1). doi:10.1038/S41746-020-00363-7

17. RP H, M D, L T, et al. Use of Physiological Data From a Wearable Device to Identify SARS-CoV-2 Infection and Symptoms and Predict COVID-19 Diagnosis: Observational Study. *J Med Internet Res*. 2021;23(2). doi:10.2196/26107

18. Hasty F, García G, Col ;, et al. Heart Rate Variability as a Possible Predictive Marker for Acute Inflammatory Response in COVID-19 Patients. *MILITARY MEDICINE*. 186. doi:10.1093/milmed/usaa405

19. N B, M LG, S R, P T, F H, A V. Clinical characterization of dysautonomia in long COVID-19 patients. *Sci Rep*. 2021;11(1). doi:10.1038/S41598-021-93546-5

20. Milovanovic B, Djajic V, Bajic D, et al. Assessment of Autonomic Nervous System Dysfunction in the Early Phase of Infection With SARS-CoV-2 Virus. *Frontiers in Neuroscience*. 2021;15. doi:10.3389/FNINS.2021.640835

21. Aragón-Benedí C, Oliver-Forniés P, Galluccio F, et al. Is the heart rate variability monitoring using the analgesia nociception index a predictor of illness severity and mortality in critically ill patients with COVID-19? A pilot study. *PLoS ONE*. 2021;16(3). doi:10.1371/JOURNAL.PONE.0249128

22. Pan Y, Yu Z, Yuan Y, et al. Alteration of Autonomic Nervous System Is Associated With Severity and Outcomes in Patients With COVID-19. *Frontiers in Physiology*. 2021;12. doi:10.3389/fphys.2021.630038

23. MBA M, MTA S, FHM van O, et al. Heart-rate-variability (HRV), predicts outcomes in COVID-19. Tolkacheva EG, ed. *PLoS One*. 2021;16(10):e0258841. doi:10.1371/JOURNAL.PONE.0258841

24. Tanwar G, Chauhan R, Singh M, Singh D. Pre-Emption of Affliction Severity Using HRV Measurements from a Smart Wearable; Case-Study on SARS-Cov-2 Symptoms. Published online 2020. doi:10.3390/s20247068

25. Czeisler MÉ, Lane RI, Petrosky E, et al. Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic — United States, June 24–30, 2020. *MMWR Morbidity and Mortality Weekly Report*. 2020;69(32):1049-1057. doi:10.15585/MMWR.MM6932A1

26. Hirten RP, Danieletto M, Tomalin L, et al. Factors Associated With Longitudinal Psychological and Physiological Stress in Health Care Workers During the COVID-19 Pandemic: Observational Study Using Apple Watch Data. *Journal of Medical Internet Research*. 2021;23(9). doi:10.2196/31295

27. Gupta MD, Jha MK, Bansal A, et al. COVID 19-related burnout among healthcare workers in India and ECG based predictive machine learning model: Insights from the BRUCEE- Li study. *Indian Heart Journal*. Published online October 2021. doi:10.1016/J.IHJ.2021.10.002

28. Andreu-Caravaca L, Ramos-Campo D, Manonelles P, Abellán-Aynés O, Chung LH, Rubio-Arias JA. Effect of COVID-19 home confinement on sleep monitorization and cardiac autonomic function in people with multiple sclerosis: A prospective cohort study ☆,☆☆☆,☆☆. *Physiology & Behavior*. 2021;237:113392. doi:10.1016/j.physbeh.2021.113392

29. Junarta J, Riley JM, Pavri BB. Describing heart rate variability in patients with chronic atrial fibrillation during hospitalization for COVID-19. *Journal of Arrhythmia*. 2021;37(4):893. doi:10.1002/JOA3.12569

30. ER C, DJ M. Changes in health promoting behavior during COVID-19 physical distancing: Utilizing wearable technology to examine trends in sleep, activity, and cardiovascular indicators of health. *PLoS One*. 2021;16(8). doi:10.1371/JOURNAL.PONE.0256063