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Pre-symptomatic Covid-19 detection

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Intro

It has been shown that a negative relationship between heart rate variability and an inflammatory reflex exists[1,5], however, in general heart rate variability parameters are useful indices of bacterial lung[2], gut[3,4] and liver [8,9] infections, but also of neck pain [6,7], eye disorders [10,11], psychiatric disorders[12, 13, 14]. We propose a method for detecting deviations from heart rate variability as an indicator of pre-symptomatic Covid-19 patients, and predict the onset of symptoms to mitigate the spread of the SARS-COV 2 virus within a time window between detection and onset of infectious symptoms.

SARS COV 2 and infections

Although there exists a disagreement among scientists about the origin of the novel pneumonia (Covid19) in Hubei province, China, Andersen K.G, et al [15] considered two possible pathways the virus through natural selection became highly infectious for humans. It appears the SARS COV 2 virus has an high affinity with the human Angiotensin Converting Enzyme type 2 (ACE2) receptor such that the spike protein with its functional furin cleavage site at the S1-S2 boundary can insert 12 nucleotides inside the cell through acquisition of three unique O-linked glycans around the binding site. However, these conclusions were based on simulations, and this polybasic cleavage site has not been observed in other beta coronaviruses.

The ACE2 receptor has been of interest as a pharmaceutical drug target in cardiovascular diseases as the ACE2 receptor is expressed in the gut, kidney, lung, brain, and liver and a key enzymatic constituent of the renin-angiotensin-aldosterone system (RAAS), regulating blood pressure, electrolyte and fluid balance, as well as systemic vascular resistance. ACE2 degrades Angiotensin 2 (Ang2), a peptide with multiple actions that promotes cardiovascular diseases, which cascades to the upregulation of Angiotensin-(1-7) in turn antagonizing the effects of Ang2. However, older patients with hypertension and other related cardiovascular diseases are periodically treated with RAAS and statins blockers, as it was showed that statins enhances ACE2 to such an extent that it contributed in the developing of

cardiovascular diseases. Moreover, recent research suggest to consider clinical effects of inhibiting enzymatic components of the RAAS system that attenuate symptoms of infected Covid19 patients [16]. Interestingly, in ACE2 knockout mice severely impaired myocardial contractility was fully rescued after genetic ablation of ACE, suggesting a protective role of ACE2 counterbalancing the effects of ACE in its enzymatic activity on Ang1 and Ang2[17]. It should be considered that SARS COV 2 viral loading impairs enzymatic ACE2 activity as key component in the RAAS system, and permanent glucose and lipid metabolic myocardial disorders were observed in SARS COV affected[18]. Moreover, new evidence suggests that SARS COV 2 adhesion with ACE2 results in ACE2 membrane withdrawal, subsequently accumulating bradykinin as causative agent for the observed symptoms, such as dry cough. ACE has an inhibitory effect on bradykinin synthesis, as it is a kinogen, and decreases vascular permeability, pain, contraction of non-vascular smooth muscles and vascular disorder symptoms. It seems that the regulatory capacity of ACE2 is inhibited through SARS COV 2 binding, such that ACE's regulatory capacity fails, and subsequent symptoms like hypotension, renal impairment, acidosis, hyperkalemia and increased vessel permeability are observed, which are all risk factors in progressing to the severe phase of Covid19. Increased vessel permeability increases risk to bacterial leakage followed by septic shock, arrhythmia or acute respiratory distress syndrome (ARDS)[19].

Symptoms

The incubation time for the SARS COV 2 virus, defined by the WHO, is two to 21 days, followed by an onset of 1 or more of the following symptoms; fever, a cough, shortness of breath, inability to smell, tiredness, aches, sore throat or a runny nose. On average 7 days after the onset symptoms decrease or worsen into severe and/or critical cases, in which the average of deaths in these cases fall between 2 to 8 weeks after the onset of the first Covid19 symptoms. Although the exact pathology of the disease remains yet to be proven, it is known that most deathly cases are caused through an inflammatory reflex that leads to bilateral interstitial pneumonia following sepsis induced cytokine storm related ARDS symptoms, septic shock, or arrhythmia[19], as the SARS COV 2 binds to ACE2 on epithelial cells in the upper throat and lungs.

Epidemiology

On average in every country affected men tend to dominate the hospital admission, mortality and ICU stay statistics by a factor of 3:1. Moreover, in affected Covid19 patients an increase in age seems to increase hospital admission, mortality and ICU stay, making older men (> 60+ years) at a higher risk than women and persons of a younger age. On average 1 in 3 mortality cases are associated with 1 or more pre-existing medical conditions like cardiovascular, metabolic syndrome (MetS), neurodegenerative and respiratory disorders and cancer. However, pre-existing cardiovascular disorders, such as hypertension, diabetes and heart disorder, seem to be the underlying cause of severe symptoms in 80% of MERS COV infected, a similar beta coronavirus [18]. In a more recent publication of the NHS at least 52% of critically symptomatic Covid19 patients had a history of hypertension and/or coronary heart disease, suggesting that pre-existing cardiovascular disorders in older persons can propel the severity of Covid19 symptoms, and that a healthy cardiovascular system is a determining factor in ICU stay and mortality.

Cardiac baroreflex (LF, HF, HF/LF)

The sensing of carotid and aortic baroreceptors are capable of notably fast processing of blood pressure differences, and subsequently relaying this information afferently in burst-like firing for autonomic processing in order to adaptively respond efferently parasympathetically changing the heart's beat frequency pattern. Measuring the change in time between heartbeats, also known as interbeat - interval (IBI), displays a sine wave, with the slope going up for the increase of heartbeats per minute, opening the possibility for Fourier Transform' frequency domain interpretations of the heart rate variability (HRV). Classification of frequency domains ranges from very low/VLF(0.003-0.04 HZ) to low/LF (0.04-0.15 HZ) and high/HF frequency bands(0.15 > 0.4 HZ) representing Mayer' waves(VLF), sympathetic activation(LF) and parasympathetic activation(HF) of the autonomic nervous system. The mechanical modulation of the sinoatrial node' pacemaking properties always account for blood pressure variance, and are based on cardiac filling, stroke volume and genetic predispositions (VLF). However, the body's response to perceived stress (LF) is slower than the activation of inhibiting properties of the parasympathetic innervation(HF), arguing sympathetic activation of norepinephrine targets

over time are too slow to account for changes in the HRV. The sympathetic outflow in response to decreased blood pressure on short timescales does not influence the LF-band of the HRV sine wave to modulate the heart's rhythm directly, as the LF-band of the HRV sine wave functions as a high pass signal filter for the sympathetic activity originates in 10 second-long Meyer' waves. However, D.P. Williams et al. 2019 showed that the HF-band of the sine wave is strongly inversely correlated with the white blood cell count(WBC) and C-reactive protein(CRP), on which decades of accepted research has been practiced and well-established to be used as inflammatory markers together with Interleukin 6 (IL-6) en 1 (IL-1), Fibrinogen (FIBR) and tumor necrosis factor (TNF). Aurajo et. al 2016 also observed the increase of C-reactive protein to be inversely related to heart rate variability.

Interestingly observed increased LF-band and decreased HF-band spikes in Fourier frequency domains over time are potentially predictive factors of ICU stay, mortality and transitioning phases from asymptomatic to symptomatic in Covid19 patients. The focus of this article is to present a model from the predictive properties of a decreasing LF and HF-band frequency/ratio over time as a measure of a shifted latency in the cardiac baroreflex in an inflammatory reflex expressed in a combinations of symptoms ranging from mild to severe sepsis-induced cytokine storm ARDS symptoms in Covid19 patients. The ability to predict the onset of symptoms in presymptomatic patients heralds the onset of cluster infections if used in a medical setting like a nursing home all the way to mitigating the load of incoming pre-severely septic Covid19 patients on the ICU.

The slight investment in cluster tracking of non-invasive pre-symptomatic risk groups is also economically more beneficial, as it aids in preventing the spread of symptomatic Sars-Cov-2 carriers, thereby for example decreasing the load on healthcare staff. All forms of data that stems from monitoring heart rate, with a 44 kilohertz sensitive sensor while lying or sitting still at least five minutes a day, can be processed through an mobile and/or internet application that handles the reading of and structures the data for creating personalised baselines and aims to predict the onset of symptoms in pre-symptomatic Covid19 risk clusters.

Our intervention method

What we offer is tailored profile statistics of general health detection within a minimal timeframe, which is five to fifteen minutes a day. Adding to that we provide immunity training focused on self-regulating blood pressure variance with breathing and physical exercises increasing adaptive responsivity to inflammation of diseases. ***Our best coaches and advisors are ready to decrease general stress levels and assist you to increase coherent multimodal integration of your psychophysical state***. In return you receive print out ***pdf or csv graphics*** and predictions of your health and well-being, and are able to monitor your increasing robustness against inflammation in your personalised app. There is always a possibility to go 1-on-1 with on of our coaches in personal meetings next to the webinars and presentations provided. Together with the aid of our health professionals, the ***anonymous, non-invasive low cost and time effective sensing of the heart beat*** of individuals in personal/business settings and risk clusters with sensors, and the personalised statistical feedback provides a model where business, personalised healthcare and IT cross edges in a low economic investive environmental deployment.

Contact me, Nigel van der Laan, for a tailored quotation, more information or to have access to the full list of references, and I will happily assist you:

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