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Heart rate variability measured by Trasndermal Optical Imaging (TOI) as a pre-diagnostic factor and outcome in patients with SARS / COV2

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Introduction

SARS / COV2 infection has become an epidemiological challenge which is taking lives every day. Todate, there are 4,782,539 infections and 317,566 deaths. The commitment to the implementation of technological tools that allow academic and scientific support for discernment in detection of possible cases, timely diagnosis and monitoring becomes an urgent need. Therefore, tools have been developed to establish the use of technological resources that have the possibility of supporting the population and the scientific community for the detection and control of cases.[1,2]

The exponential curve of infections and deaths does not stop and it is vitally necessary to optimize the sensitivity of possible cases and timely detection, which otherwise, in its continuous epidemiological delay, can lead to higher expenses in the health system, collapse and increase in morbidity and mortality of the Colombian population.

General Objectives To

1. Identify possible cases of COVID 19 in the Colombian population by metrics of heart rate variability through transdermal optical images.
2. Monitor confirmed cases with COVID 19 in the Colombian population by metrics of heart rate variability through transdermal optical images.

Specific objectives

1. Provide adequate follow-up to each of the defined cases of COVID-19 in the Colombian territory.
2. Generate early detection strategies for symptoms suggestive of COVID-19 in individuals who are working post-quarantine or those who are in preventive isolation.
3. Generate strategies to avoid the collapse of the intensive care units of the different hospital institutions in the scenario of the SARS / COV2 pandemic that affects the Colombian territory.
4. Propose the outpatient monitoring of patients diagnosed with COVID-19 through integrated digital tools.

5. Reduce the burden of patients who consult for suspected symptoms of COVID 19 and who may not be infected in order to avoid unnecessary exposure.
6. Take advantage of the different options offered by the various cellular devices (cameras) for monitoring patients with symptoms suggestive of COVID-19
7. Promote the use of transdermal optical images to detect patients with COVID-19
8. Progressively improve the quality to detect asymptomatic patients infected with SARS / COV2
9. Implement as a diagnostic predictive tool for COVID-19 the use of transdermal optical images.
10. Proposing as an aid diagnoses monitoring of heart rate variability as an indicator of possible SARS-COV 2 / COVID-19 infection.
11. Generate national studies that involve the use of transdermal optical images for the medical evaluation of subjects with SARS / COV2.
12. Highlight the importance of technological devices to carry out the early detection of patients infected with SARS / COV2.
13. Analyze the degree of heart rate variability in patients infected with SARS / COV2.
14. Compare the levels of heart rate variability by transdermal optical images between infected, suspected or healthy
15. patients. Become a diagnostic tool for patients suspected of COVID-19 in care centers in the country that do not have sufficient infrastructure resources.

16. Improve the accuracy of Transdermal Optical Imaging through data collection in Colombian patients and analyze the degree of heart rate variability in this population.
17. Implement the use of Transdermal Optical Imaging at care sites where access to evidence of Confirmation of infection are not available

Justification

SARS / COV2 infection has established itself as a pandemic with great diagnostic difficulty due to the variability and wide range of constellations in its symptoms and signs. Likewise the ambiguous possibility of generating high complications regardless of any race, sex and age group. Although some clinical and prognostic risk factors are well established, cases in which morbidity and mortality do not appear without these criteria continue. [1-3]

There is growing evidence that the use of technology has increasingly allowed the greatest diagnostic approach and adequate monitoring. However, the implementation of novel technology requires years of research and this scenario is not possible in the face of an emerging infection that does not take time. This is due to the low diagnostic sensitivity already described in multiple studies by only taking into account the classic symptoms such as fever higher than 38 ° C, persistent dry cough, persistent dyspnea, dynamia and asthenia, which can lead to overlapping diagnoses and consultation unnecessary to medical attention centers, which supposes a risk of contagion of not becoming positive or of its dissemination[1-5] Additionally, there is another symptom that goes outside this rule, such as gastrointestinal, neurological, cutaneous and osteo-symptoms. articular. [1-5]

On the other hand, we have seen the ability that asymptomatic carriers and presymptomatic individuals can clear the virus for up to 21 days, which can potentially infect people who come into contact. It is reported that the incubation period estimated varies from 3 to 6 days, with a mean of 5.2 days and even no evidence indicating that a variable incubation period in the range of 1 to 14 days [1-27]

The above summary indicates that it is too difficult to estimate the prevalence of asymptomatic cases in the population. The best evidence so far comes from the Diamond Princess cruise ship, which was quarantined with all passengers and crew members repeatedly screened and closely monitored.[1-27] A model study found that approximately 700 people with confirmed infection (18%) were Asymptomatic However, a Japanese study of evacuated citizens from Wuhan City estimates that the rate is closer to 31%. [1-27] The first data from an isolated town of 3,000 people in Italy estimate that the figure is higher, between 50% and 75%. A Chinese study of 36 children diagnosed with COVID-19 found that 10 (28%) of the patients were asymptomatic, so the possibility that children could play an important role in transmission is currently considered given their significant probability of being asymptomatic[1-27]

In a recent study published in Nature Medicine, a total of 2,618,862 participants reported their potential COVID-19 symptoms in a smartphone-based app. The ten symptoms consulted (fever, persistent cough, fatigue, shortness of breath, diarrhea, delirium, skipped meals, abdominal pain, chest pain and hoarse voice) doing stepwise logistic regression adjusting for age, sex and BMI, the only symptoms The ones that presented positive predictive values were the loss of taste and smell and despite them they were not significant.[5]

For approximately 30 decades, research has been carried out with the variability of heart rate as a tool that adds to the predictions for the evaluation and monitoring of the autonomic nervous system and how it interacts and integrates harmoniously with each of our systems, such as cardiovascular, immunological, endocrinological and even musculoskeletal. The first investigations were carried out in the pediatric population. In the last 20 years, research has progressed significantly in the adult population and this is recorded in various systematic reviews and meta-analyzes.[28-48] ***This evidence is summarized in the state of the art below and as each of them it is possible to answer every question that arises on the stage for the early detection of asymptomatic, pre-symptomatic individuals and monitoring of those diagnosed with COVID-19 for their adequate follow-up.***

State of the art

What is heart rate variability?

The variability of heart rate (HRV) is defined as the variation between each heart beat measured in time and in frequency according to the physiological variables that are integrated into the stimulus received by the autonomic nervous system from other systems such as cardiovascular, endocrinological and immunological.[28-48] This concept, often introduced as reflections imbalances within the autonomic nervous system and you are basto the increasing evidence for increased activation of the sympathetic ortone, parasympathetic*as well as their levels ofco-activation,* pero HRV probably more than an indicator of possible disturbances in the autonomous system. [28-48] In this regard, some disturbances trigger not reciprocal, but parallel changes of vagal and sympathetic nervous activity.[28-48] HRV has been considered as a surrogate parameter for the complex interaction between the brain, the nervous autonomic system , the peripheral nervous system and cardiovascular system and as the biology of this system focuses on interactions between other systems with the help of computer modeling, artificial intelligence and time series analysis, beyond others, reflecting its robustness and sensitivity. [28-48] Increased variability is generally considered associated with good health, while decreased variability can mean pathological changes. [28-48]

These changes in heart rate variability can be explained in each of its metrics. **(Table 1)** and how these respond harmonically with the changes that take place in the autonomic nervous system and how it receives signals from different systems such as the cardiovascular, nervous, endocrinologist and immune systems.[28-48] Infection, injury, or trauma causes an inflammatory reaction in the body that aims to restore homeostasis. The host's inflammatory response is based on a complex combination of different immune mechanisms that contribute to the neutralization of invading pathogens such as **COVID 19**, restoration of injured tissues, and wound healing. The first steps in inflammatory reactions involve the release of pro-inflammatory mediators, especially interleukin (IL) IL-1, IL 6, and tumor necrosis factor (TNF) but also adhesion molecules, vasoactive mediators, and reactive oxygen species. This first release of proinflammatory cytokines is initiated by activated macrophages and is considered crucial to trigger the local inflammatory response, as is well known in the case of **COVID 19.** [28-48]

However, excessive production of cytokines proinflammatorysuch as TNF, interleukins IL6, IL-1B1, generate more damage, as in the case of the cytokine storm caused by **COVID 19.** Thus, immune reactions cause tissue damage, hypotension , disseminated intravascular coagulation and high death rate. Therefore, the inflammatory response must be balanced, which is based on the almost simultaneous release of anti-inflammatory factors such as IL-10 and IL-4 cytokines, soluble TNF receptors, and transforming growth factor (TGF-beta). If local inflammation increases, TNF and IL-1β begin to circulate in the blood and other body fluids. This has important consequences for the CNS because these molecules are also signal molecules for the activation of brain-derived neuroendocrine immunomodulatory responses. [28-48]

There is evidence after systematic reviews and meta-analyzes on the statistically significant correlation with heart rate variability in an inverse relationship between the HRV metrics of the frequency domain and PCR and IL-6.[37,38] These associations persisted after adjustment for other risk factors such as smoking, hypertension, diabetes, high-density lipoprotein (HDL), and depression. Additionally IL-6 was inversely correlated with SDNN ($r = -0.36$), with total power of the heart rate signals and ULF ($r = -0.37$ and$r = -0.43$, respectively). On the other hand, the power of LF has been found to correlate more closely with circulating levels of TNF-α than the HF component, while multiple linear regression analysis showed that TNF-α was a stronger predictor of HRV. lower than circulating norepinephrine levels. The evidence concludes that TNF-α overexpression and subsequent loss of β-adrenergic responsiveness contribute to decreased HRV. [28-48biomarkers]

Inflammation and heart rate variability

Angiotensin-converting enzyme 2 (ACE2) is a potent negative regulator of the renin-angiotensin-aldosterone system, as it degrades angiotensin II that has a vasoconstrictive, proinflammatory and fibrosis-promoting action , and converts it to another form of angiotensin called Ang (1-7) and Ang (1-9) which has vasodilatory, anti-proliferative and apoptotic effects. In addition to systemic effects on blood pressure regulation, ACE2 has regulatory effects on the pathological changes observed in various organs, including the heart, kidney, and lungs. (Pedersen et al, 2020; Li Y et al, 2020; Fu Y et al, 2020). [28-48] SARS-CoV2 binds with ECA2, leading to systemic deprivation of ACE2. These receptors are highly expressed in the vascular endothelium of the vascular system of the lung, kidney and heart. However, any cell that expresses this receptor is a potential target in which case where the protective immune response is exceeded, the virus will spread and mass destruction of the affected tissues will occur, predominantly in the organs with the highest expression of ACE2. [28-48] However, in asymptomatic cases still without generating this entire chain of events, if it is clear that the virus requires the cellular infrastructure for its replication and this necessarily leads to the use of ECA2 with its consequent imbalance of the renin-angiotensin-aldosterone axis, the activation of proinflammatory molecules that stimulate the autonomic nervous system, which is reflected through changes in the metrics in the HRV and which are mentioned in a synthesized form below.[28-48]

Regarding C-reactive protein (CRP) levels are correlated with the level of inflammation, and its concentration level is not affected by factors such as age, sex, and physical condition. PCR levels can activate complement and improve phagocytosis, thus eliminating pathogenic microorganisms that invade the body. PCR levels can be used for the early diagnosis of pneumonia. [28-48] In fact, completely asymptomatic patients with **COVID-19** have been seen to present radiological changes consistent with pneumonia, which explains that these same patients mount an immune response that necessarily depends on the production of acute phase reactants such as C-reactive protein and pro cytokines. -inflammatory that end up explaining the imaging changes (Wang L. 2020; Xiaomin Luo et al. 2020). [28-48] It goes without saying that it has been found as an important index for the diagnosis and evaluation of serious infectious lung diseases.[28-48]

Additionally, it has been seen how CRP positively correlates with lung injury and disease severity. This suggests that in the early stage of COVID-19, CRP levels might reflect lung injury and disease severity (Xiaomin Luo et al. 2020; Wang L. 2020). [28-48] On the other hand, the natural logarithm of the CRP levels has been correlated in studies carried out by Psychari et al. 2007, with inverse associations with the following logarithmic indices transformed from HRV in time and in the frequency domain: SDNN, standard deviation of all normal RR intervals, ($r = -0.40$, $p < 0.001$); SDANN index, standard deviation of average normal RR intervals for 5-minute segments, ($r = -0.46$, $p < 0.001$); SDNN index, mean of the standard deviation of all normal RR intervals for 5-minute segments ($r = -0.41$, $p < 0.001$); total power (TP) ($r = -0.38$, $p < 0.001$); high frequency power (HF) ($r = -0.31$, $p < 0.01$); low frequency power (LF) ($r = -0.45$, $p < 0.001$). The strong inverse relationship between PCR and SDNN, SDANN, SDNN, LF, and TP persisted after adjustment for left ventricular function. In a similar study, a negative correlation was reported between the frequency components of CRP and HRV, while a decrease in HF potency (reflecting vagal tone) was found in the high PCR quartile, compared to the highest. low.[28-48]

The reduction of HRV and LF / HF is related to a pro and anti-inflammatory response mediated by inflammatory markers and how it is increased during sepsis, especially in patients with viral infections. [28-48] Furthermore, the severity of the disease is positively associated with serum IL6 and IL-10 concentrations and inversely changes with the variability of heart rate signals. [28-48] Other substantial findings correspond to the inverse association with fibrinogen levels, although less consistently than with the leukocyte count, D-dimer, PCR, and IL-6, when the co-variables are taken into account (Tan, L. 2020 ; Kim HG, 2018; Williams DP et al., 2019).

On the other hand, stress scores (based on HRV, specifically the inverted z-score of pNN50) have been found with standardized levels of neutrophils, monocytes, and lymphocytes (each as a z-score of the percentage of immune cells obtained from blood samples), as well as a statistically significant positive correlation between stress and neutrophil count ($r = 0.21$, $p < 0.01$). [28-48] Other data of interest show a statistically significant negative correlation between stress and monocytes ($r = –0.16$, $p < 0.05$) as well as lymphocytes ($r = –0.18$, $p < 0.05$) (Kim HG, 2018; Williams DP et al ., 2019). [28-48]

Strikingly, patients who have required admission to the Intensive Care Unit have significantly higher levels of IL-6, IL-10 and TNFα, which is inversely related to the CD4

+ and CD8 + lymphocyte count, confirming studies in previous animal models regarding that cytokine storm lowers adaptive immunity to SARS-CoV infection (Tan, L. 2020; Pedersen SF., 2020; Luo H, 2019). [28-48] In this sense, Fourier spectral analysis in the frequency domain has often been used as a prognostic tool for predicting the outcome of the patient in the ICU. In a study, involving 52 patients from an adult ICU, a progressive decrease (downward trend) in the power densities of the Low Fourier Frequency (LF) and Very Low Frequency spectra was found to be a marker significant impairment and mortality (Williams DP et al. 2019; von Känel R, 2011; Papaioannou V, 2013). [28-48] Likewise, it is currently known that patients with COVID-19 show higher plasma levels of proinflammatory cytokines along with chemokines such as IFN-, IL-1, IP-10 and MCP-1, while severe cases that have required hospitalization. in the ICU they had higher concentrations of TNF-α, G-CSF, MCP-1, IP-10, IL-8, IL-10 and MIP-1A, which reflects the adequate correlation with the described literature (Herold T et al. 2020; Papaioannou V, 2013; Williams DP et al., 2019; Luo H, 2019).

The fact that these pro-inflammatory molecules rise requires other biomarkers that initiate this successive chain of signals such as amyloid protein A, which allows the release of interleukin 6, among others (Huang C, 2020). [28-48] These markers have previously been highlighted in healthy individuals and their correlation with HRV has been studied, finding a negative association between their levels, thus positioning heart rate variability as a scientific and robust possibility for integration.[28-48]

Transdermal Optical Imaging (TOI) Technology

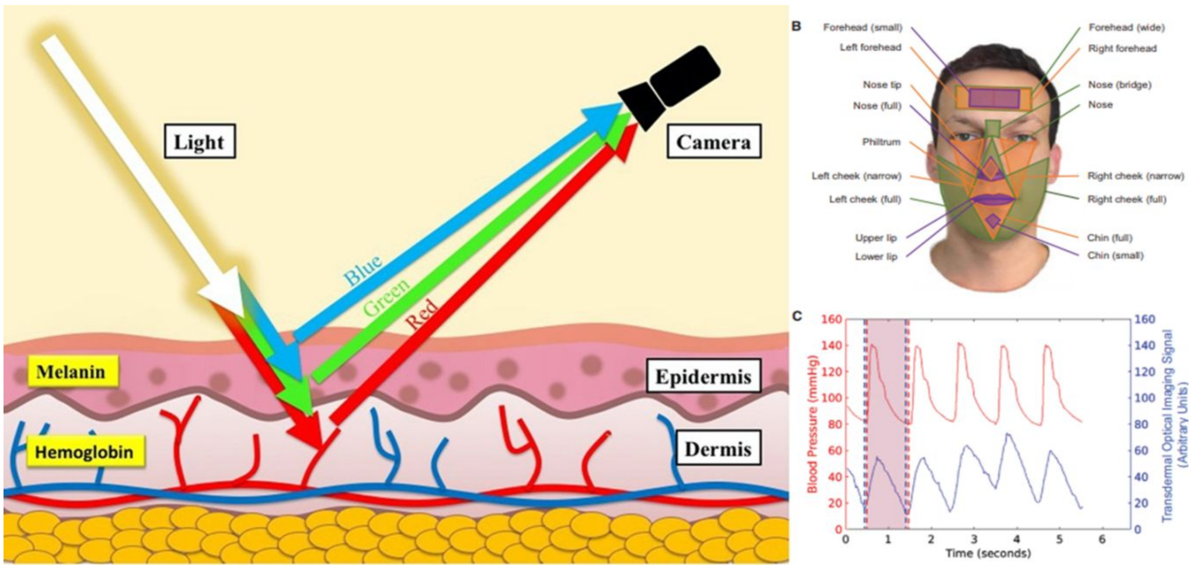
The advent of the increase in the computing capacity of humanity and the methodology of error backpacking have led neural networks, an algorithm from the field of machine learning to take a new impulse, optimizing the times of the process of training through descent of the gradient[49], enabling the variation of the parameters of the neural network efficiently, leaving behind the limitations of the perceptrons, precursors of the neural networks that had important limitations.[50]

Scientific research has allowed new methodologies to analyze patterns to be incorporated through the use of these neural networks, offering the world revolutionary solutions, within it the TOI technology of optical transdermal images. [42]

TOI technology uses a conventional digital camera to process people's faces, analyzing facial blood flow information to obtain heart rate and HRV.[40-42]

During a video capture process, changes in blood flow can be established, this is possible due to changes in the amount and color signatures of the light reflected by the facial skin. [40-42] Changes in facial blood flow can be used to establish cardiovascular metrics since the movement of blood in the face has an obvious connection to the cardiovascular system and is part of the principles that we see in, for example, photoplethysmography, technology that using optical parameters, they infer cardiovascular activity. [40-42]

Machine Learning has been applied to the interpretation of blood flow variation in order to establish cardiovascular and blood pressure parameters, giving humanity the ability to measure these parameters, for example with conventional video cameras, for example from a remote location in a contactless manner.[40.42]



Transdermal optical image signal extracted, signal extraction regions and comparison with the blood pressure signal. View corresponding signal hemoglobin using transdermal technology optical image (a). Seventeen regions of interest of different sizes are found on the forehead, nose, cheek, lip, chin, and filtrum (b). Blood pressure pulse characteristic. Taken, adapted and authorized from Hong Luo et al (2029).

TOI technology has managed to demonstrate that it is possible to calculate cardiovascular HRV metrics from facial image processing that may have the applicability described as a strategy for detecting and monitoring infectious diseases within them COVID19. [40,42]

Conclusions:

The possibility of equipping millions of people by reusing the hardware of their cell phones to take HRV metrics opens up new possibilities to face the challenge of COVID19, both in diagnostic and evolutionary stages of diagnosed people, as well as a strategy of information for decision-making by governments and companies in the process of opening up to economic activities, supported by objective data such as infection markers inferred from a deterioration in a continuous period of time of HRV metrics such as SDNN.

Final recommendations

We propose to provide the necessary technology so that government entities, companies or entities can incorporate TOI as a deterioration tracking strategy over a period of time of HRV following the following recommendations:

1. Through their cell phone or webcam.
2. Measurements of at least 30 seconds.
3. For several consecutive days and at the same approximate time.
4. After going to the bathroom.
5. It must have been at rest for at least 5 minutes before the measurement.

Track these measurements over time to establish the probability of deterioration of the HRV indicator for several consecutive days as a system for early detection and monitoring of COVID infection19.

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ID Variable	Variable	Descripción
BP_DIASTOLIC	Presión arterial diastólica	La presión arterial diastólica es la cantidad de presión en las arterias braquial cuando está diástole , medida en milímetros de mercurio (mmHg). los niveles de presión arterial diastólica: por debajo de 60 mmHg se considera hipotenso
BP_DIASTOLIC_CONF	Confianza presión diastólica de la sangre	La confianza en la predicción de la presión arterial diastólica (0-100%). 0% significa que no hay confianza en la predicción para la presión arterial diastólica. 100% significa absoluta confianza en la predicción para la presión arterial diastólica.
BP_HEART_ATTACK	Riesgo de ataque cardiaco	Riesgo de ataque cardiaco es la probabilidad (expresada en porcentaje) para que pueda experimentar un ataque al corazón en los próximos 10 años. Esta puntuación de riesgo se basa en el método de Framingham y deriva de un algoritmo desarrollado en base a los datos del formulario estudios prospectivos que siguieron a los participantes en términos de su salud cardiovascular desde hace más de diez años.
BP_MAP	La presión arterial media	La presión arterial media (MAP) es la presión media en las arterias de una persona durante un ciclo cardíaco, medida en milímetros de mercurio (mmHg).
BP_MAP_CONF	Mean Arterial confianza Presión	La confianza en la predicción de la presión arterial media (0-100%). 0% significa que no hay confianza en la predicción para la presión arterial media. 100% significa absoluta confianza en la predicción para la presión arterial media.
BP_PP	La presión del pulso	Presión de pulso (PP) es la diferencia entre la presión arterial sistólica y diastólica, medida en milímetros de mercurio (mmHg). Representa la fuerza que el corazón genera cada vez que se contrae.
BP_PP_CONF	La confianza de la presión del pulso	La confianza en la predicción de la presión de pulso (0-100%). 0% significa que no hay confianza en la predicción para la presión del pulso. 100% significa absoluta confianza en la predicción para la presión del pulso.
BP_RPP	Carga de trabajo cardiaco	Carga de trabajo cardiaco, o más precisamente la carga de trabajo del miocardio, es una medida de la tensión puesta sobre el músculo cardiaco. Cardiaca carga de trabajo se puede calcular usando la fórmula: Heart Rate (bpm) x la presión arterial sistólica (mmHg). Cuando se mide en reposo, este índice se puede utilizar como un indicador de la salud cardiovascular. Por ejemplo, una persona que hace ejercicio con regularidad puede tener una menor carga de trabajo cardiaco que otra persona que tiene un estilo de vida sedentario. Durante el ejercicio físico intenso, el trabajo cardíaco puede aumentar, pero debe disminuir después del ejercicio.

BP_SYSTOLIC	Presión arterial sistólica	La presión arterial sistólica es la presión máxima en las arterias braquial durante la contracción del músculo del corazón, medida en milímetros de mercurio (mmHg). los niveles de presión arterial sistólica: por debajo de 90 mmHg se considera hipotensor
BP_SYSTOLIC_CONF	La confianza de la presión arterial sistólica	La confianza en la predicción de la presión arterial sistólica (0-100%). 0% significa que no hay confianza en la predicción para la presión arterial sistólica. 100% significa absoluta confianza en la predicción para la presión arterial sistólica.
BP_TAU	Capacidad vascular	Capacidad Vascular, o Tau, es una medida de la elasticidad de los vasos sanguíneos. Capacidad Vascular se puede calcular usando la fórmula: R (Resistencia Vascular) x C (Arterial Compliance) Cuando se mide en reposo, este índice se puede utilizar como un indicador de la salud cardiovascular, ya que está fuertemente correlacionada con la rigidez vascular. Una persona con un alto Tau tiene una mejor salud vascular que una persona con una baja Tau. Además, ciertas actividades transitorias y eventos fisiológicos pueden conducir a cambios inmediatos en Tau (por ejemplo, beber alcohol, fumar).
HR_HERTZ	Heart Rate 140 (Hz)	La frecuencia cardíaca en Hz. Medible Rango: 40-140bpm (0.67-2.33Hz).
HRV_SDNN	HR variabilidad (SDNN)	La desviación estándar de los intervalos NN (SDNN) es una medida de la variabilidad del ritmo cardíaco (HRV). intervalos NN se refieren a intervalos de latido a latido. Es el intervalo de tiempo entre cada latido del corazón. SDNN es la desviación estándar de los intervalos de tiempo entre cada latido del corazón, expresado en milisegundos (ms).
IHB_COUNT	Los latidos del corazón irregulares	El número de latidos que faltan durante un minuto.
MSI	Índice de estrés	Índice de estrés según lo determinado por las características de variabilidad del ritmo cardíaco. El rango es [1,0 a 5,9], mayor es el valor, mayor es el estrés.
SNR	Relación señal-ruido (SNR)	El flujo de sangre señal SNR largo de la duración de la medición con ventana móvil cuando la duración de la medición sobre 30s.

Tabla 1. Características de cobertura en métricas de variabilidad de la frecuencia cardiaca y demás variables cardiofisiologicas integradas a TOI