

An Algorithm to Predict Life-Threatening Complications using Heart Rate Variability and the Circadian Heart Rate Difference with a Special Interest on COVID-19, SUDEP Children with Congenital Heart Disease and Obesity

Reiner Buchhorn

Caritas-Krankenhaus Bad Mergentheim, Department of Pediatrics, Uhlandstraße 7, Bad Mergentheim, Germany

reiner.buchhorn@ckbm.de

ABSTRACT

Corona virus disease (COVID-19) has been declared as a pandemic by the WHO with a global mortality rate of about 3.4%. More recently the neuroinvasive potential of SARS-CoV2 was emphasized as a potential cause for respiratory failure. Such pathophysiology has been investigated in sudden unexplained death in epilepsy (SUDEP) including functional neuroimaging that demonstrates alterations to networks involved in central autonomic and respiratory control located in the brainstem. For risk stratification in these patients, one method may be heart rate and heart rate variability (HRV) monitoring. **Method:** For a better understanding, we compare HRV monitoring in two cases; 1.) Twenty Holter ECGs of a boy with generalized tonic-clonic seizures up to his death at the age of 10.5 years with special interest on an acute respiratory failure at the age of 5.4 years. 2.) Thirty one Holter ECGs of a 58-year old pediatric cardiologist who survived an infection with COVID-19. During his disease 24-hour Holter electrocardiography (ECG) was performed continuously over 10 days. Moreover, 24-hour Holter ECGs from the last 10 years were available. The derived algorithm that depends on the global heart rate variability and circadian heart rate difference was proofed in 151 healthy children, 26 children with a fatal outcome or transplantation, 151 patients with operated congenital heart disease, 130 obese children and healthy adult data from literature. **Results:** In both cases we observe a decline of the global heart rate variability SDNN together with a loss of the circadian heart rate difference. The derived algorithm differentiate healthy children from children with a fatal outcome. The algorithm identify 7.3% of 151 patients with operated congenital heart disease and 5.4% of children with obesity as candidates for COVID-19 complications. **Conclusions:** A sudden decline of HRV together with a loss of the circadian heart rate difference may indicate a life-threatening complication in critical illness.

Keywords: COVID-19 virus disease; sudden unexplained death in autonomic nervous system; heart rate variability; congenital heart disease

Corona virus disease (COVID-19) has been declared as a pandemic by the WHO with a global mortality rate of about 3.4% (WHO, 2020). COVID-19 is an infection caused by the novel coronavirus (SARS-CoV2). The causes of death for the patients are varied including severe acute respiratory syndrome (1) , thromboembolism, arrhythmia and sudden death(2). More recently the neuroinvasive potential of SARS-CoV2 was emphasized as a potential cause for respiratory failure (3, 4). This pathophysiology has been investigated in sudden unexplained death in epilepsy (SUDEP) including functional neuroimaging that demonstrates alterations to networks involved in central autonomic and respiratory control located in the brainstem (5, 6). Analysis of heart rate variability seems to be a potential biomarker of SUDEP (7, 8).

HRV measures of the heart rate interval's variations - reflecting a complex interplay of thermogenesis, intrinsic mechanisms of pacemaker cells, and parasympathetic and sympathetic tone – may indicate the hit of SARS-CoV2 to the brainstem. Heart rate and HRV parameters' calculations could help to facilitate the identification of patients at risk for life-threatening complications.

Based on this background, we aimed to analyze HRV and heart rate in a 58-year old pediatric cardiologist, who was infected with COVID-19 - clearly proofed by positive PCR test and SARS-CoV2 antibody conversion. These data are compared to a boy who was monitored and resuscitated on the pediatric intensive care unit at the age of 5.4 years with acute respiratory failure after prolonged generalized tonic-clonic seizures– suggested as a fatal breakdown of the central autonomic control.

The derived algorithm that depends on the global heart rate variability and circadian heart rate difference was proofed in 151 healthy children, 26 children with a fatal outcome or transplantation (N=3), 151 patients with operated congenital heart disease, 130 obese children and healthy adult data from literature.

1 Patients

Based upon the HRV analysis of the two cases with acute respiratory failure after prolonged generalized tonic-clonic seizures and COVID-19, we develop an algorithm for risk stratification. The derived algorithm depends on the global heart rate variability and circadian heart rate difference. We proofed this algorithm in patients of our Holter ECG database based upon an ethic vote from 2013 (9) according investigations of routine Holter ECG data: These data are recorded in 151 healthy children, 26 children with a fatal outcome or transplantation (N=3), 151 patients with operated congenital heart disease and 130 obese children. For the investigation of data in healthy adults up to the age of 60 years, we used the original data from H. Bonnemeier et al published in 2003(10).

2 24 hour ECG and analysis of heart rate variability (HRV)

Measurement and interpretation of HRV parameters in the current sample were standardized according to the Task Force Guidelines (11). Cardiac autonomic functioning was measured by 24-hour Holter 12-bit digital ECG (Reynolds Pathfinder II, Spacelabs, Germany; 1024 scans/sec). Daytime and night-time periods were defined according to patient protocols. If we have no protocol of the Holter ECG's from the adult group, we defined the day interval from 7:00 to 22:00 and the night interval from 22:00 to 7:00. All Holter recordings were reviewed by the same experienced cardiologists (RB and CW) and were edited to validate the systems QRS labelling. Measures of HRV were calculated employing only normal-to-normal intervals. QRS-complexes classified as noise were excluded from the data. A minimum of 23 hours of analysable

data and minimally 95% of analysable NN intervals were required for data to be included. For time domain measures, mean RR interval, resulting heart rate and the following HRV parameters were calculated.:

2.1 Heart rate:

The easiest but very important HRV parameter is the average sinus rhythm heart rate, since all other parameters are significantly affected by the heart rate. The circadian heart rate difference was calculated by the subtraction of the mean heart rate at night from the mean heart rate at day.

2.2 SDNN:

Standard deviation of all normal RR intervals in a time frame. This global HRV parameter represents the overall variability of the autonomic nervous system.

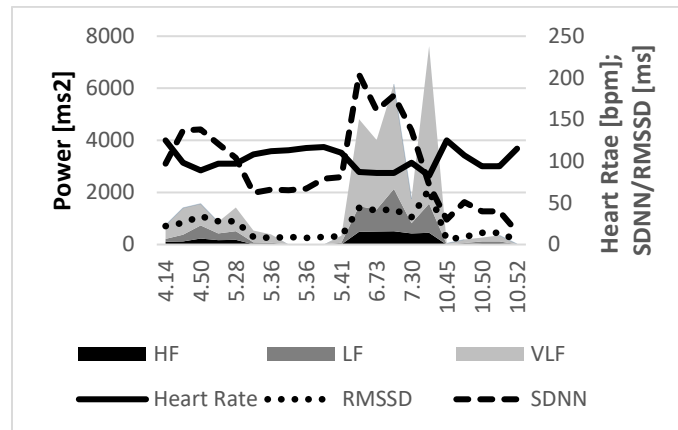
2.3 rMSSD:

Square root of the arithmetic mean of the squared deviation of successive normal RR intervals in a time frame. This parameter is mainly influenced by the parasympathetic nervous system.

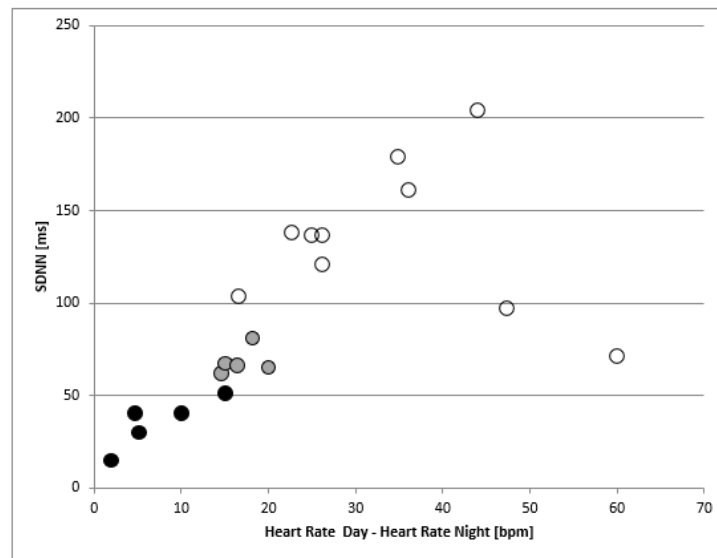
3 Results

Case 1: HRV-monitoring of acute respiratory failure of a 5 years old boy with seizures

Figure 1 shows the 10 years HRV monitoring of a boy with generalized tonic-clonic seizures up to his death at the age of 10.5 years in a palliative setting. The etiology of his seizures and severe mental retardation remains unclear but MR imaging shows progressive brain atrophy that begun in early infancy. If we were aware of the high risk of sudden unexpected death in epilepsy (SUDEP) and the crucial role of autonomic dysfunction in this child, we used 24-hours Holter ECG Monitoring for risk stratification: A total number of 20 Holter ECG's are illustrated in the figure 1+2. The most impressive changes concerned the complete loss of HRV indicated by the Fast Fourier Analysis during acute respiratory failure at the age of 5.4 years comparable to the HRV at the end of his life 5 years later. At the time of this "near" SUDEP, he stayed at hospital to change antiepileptic drug therapy because an increasing number of daily generalized tonic-clonic seizures under valproic acid, vigabatrin and phenobarbital. After a prolonged generalized tonic-clonic seizures during intensive care monitoring he developed severe hypopnea and must be intubated without signs of circulatory failure or heart rhythm disturbances. At this time, he was treated with 120mg/kg/d valproic acid, 10mg/kg/d vigabatrin, 2,5mg/kg/d phenobarbital, 5mg/kg/d topiramate and 10µg/kg/d clonidine. Intoxication was excluded by drug monitoring (valproic acid: 51.5µg/ml Phenobarbital: 20.5µg/ml topiramate: 9.1mg/l clonidine:<0.1µg/l). Because severe lung failure the boy could be weaned from respirator after one week and he survive without additional neurological problems. After this complication, we treat the boy with 3mg/kg L-Dopa beside antiepileptic drug therapy with valproic acid and phenobarbital. The Holter ECG monitoring showed an impressive increase of HRV over 5 years without a further respiratory failure. We plot the relationship between the global HRV indicated by the parameter SDNN and the circadian heart difference in figure 2. This plot clearly differentiates the data during "near" SUDEP and the last 4 examinations within the last months of his life, generated routine monitoring during palliative care.



Legend Fig. 1: HRV monitoring of a boy with generalized tonic-clonic seizures up to his death at the age of 10.5 years. At the age of 5.4 years he develops acute respiratory failure while staying at hospital to change antiepileptic drug therapy. This “near” SUDEP is paralleled by a decline of global HRV indicated by the Fast Fourier analyses and the parameter SDNN as well as the vagus parameter RMSSD.

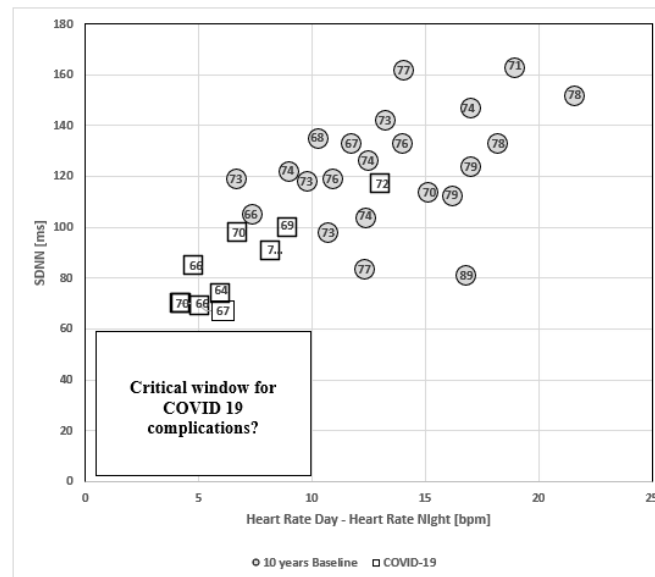


Legend Fig. 2: This plot of the circadian heart rate difference and global HRV parameter SDNN discriminates the acute respiratory failure with 5.4 years (grey circles) and the complete loss of HRV and circadian rhythm at the end of life with 10.5 years (dark circles)

Case 2: HRV-monitoring during COVID-19 of a 58 years old men

After COVID-19 contact, the disease starts after five days with sub febrile temperatures, body pain and losing the sense of taste and smell. The infection is clearly proofed by negative SARS-CoV2 antibodies two days after the contact and a seroconversion 4 weeks later. The SARS-CoV2 PCR was negative again at day 14. During his disease 24-hour Holter electrocardiography (ECG) was performed continuously (Pathfinder, Spacelabs Healthcare, Germany). Moreover, 24-hour Holter ECGs from the last 10 years were available to cause a pre-existing atrial fibrillation. However, after pulmonary vein isolation cardiac dysrhythmias have not reappeared. The global HRV indicated by the parameter standard deviation of normal to normal intervals (SDNN) in a standardized way over 24 hours. Moreover, 24-hour ECGs from the past 10 years

(N=22) and 24-hour ECGs (N=9) which were recorded during COVID-19 infection were used to plot the relationship between SDNN and the circadian heart difference (Figure 3). Seven 24-hour ECGs immediately after pulmonary vein isolation showing an acute stress reaction were excluded. Sinus tachycardia by inflammation as cause of the loss of HRV during COVID-19 can be excluded by the illustration of surprising low mean 24-hours heart rates (figure 3).



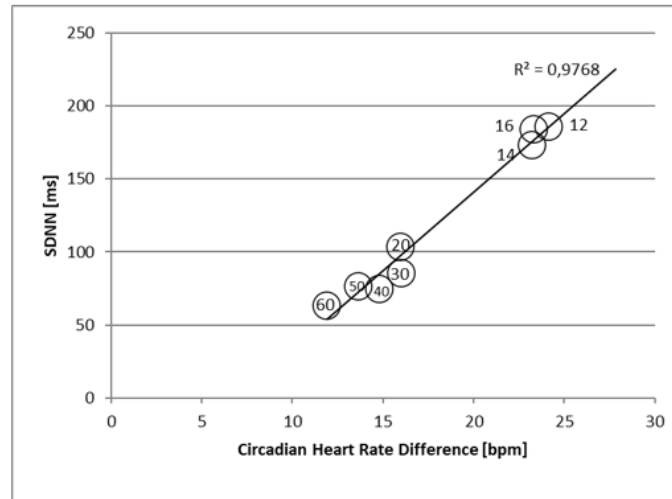
Legend Fig. 3: HRV monitoring of 58 years old men during COVID-19 (open quarters) in comparison to 22 Holter ECGs within the last 10 years. The numbers illustrate the mean 24 hours heart rates. The COVID-19 outlier with a heart rate of 72 bpm at day16 shows the recovery of the autonomic nervous system.

4 Healthy Control

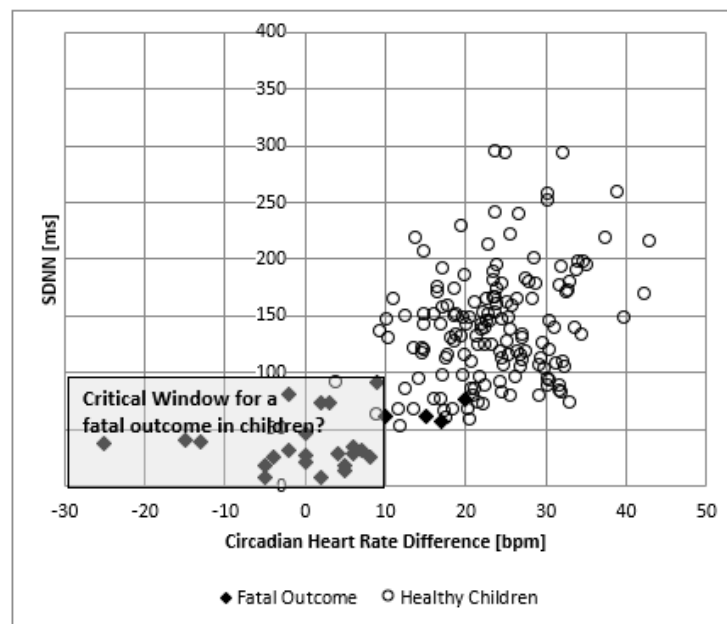
We used the reference values for adults of H. Bonnemeier et al. (10) and our own reference values for children (9) to detect the critical window for life-threatening complications. This plot of the circadian heart rate difference and global HRV parameter SDNN illustrate the means of healthy controls at different ages as indicated in the circles (figure 4). There is a linear relationship in adolescents and adults ($R^2=0.98$). Unfortunately, it is difficult to find the global heart rate variability and circadian heart rate difference data for adults > 60 years.

For the development of an algorithm for children, we used the published Holter ECG data of 151 healthy children (9) and 26 children who died or had heart transplantation (N=3) one year later on average (12 infants, 14 children). The underlying diseases include 9 children with congenital syndromes, 8 children with heart failure, 6 with hypoxic ischemic encephalopathy, and 3 children with oncologic diseases. Most children died in palliative setting of cause an infaust prognosis.

Figure 5 demonstrate the advantage by using two prognostic important parameters: 1) the circadian heart rate difference (12, 13) and 2) the global heart rate variability SDNN(8). Most of all the SDNN failed to differentiate healthy children from children who died one year later average of cause a wide overlap of SDNN values between 50 and 100ms. Most of all infants have no mature circadian rhythm and would be wrong stratified if we only use the circadian heart rate difference. However, we should be careful to use this algorithm for infants if some healthy infants would be stratified as critical ill (figure 5).



Legend Fig. 4: This plot of the circadian heart rate difference and global HRV parameter SDNN illustrate the means of healthy controls at different ages as indicated in the circles. There is a linear relationship in adolescents and adults ($R^2=0.98$). We anticipate a further decline of these parameters in COVID-19 as shown in the patient (figure 3)

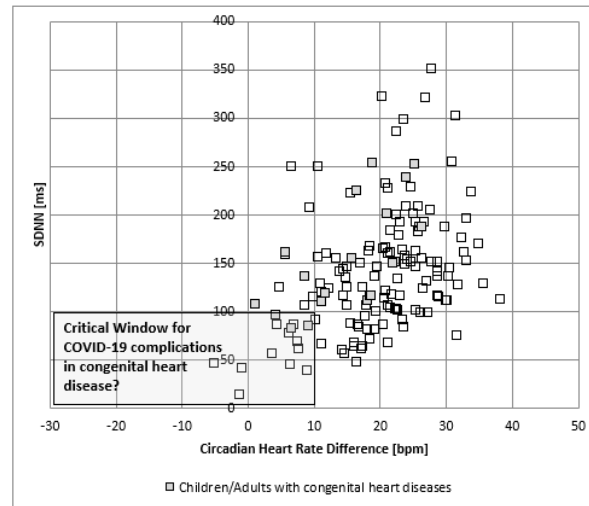


Legend Fig. 5: This plot of the circadian heart rate difference and global HRV parameter SDNN illustrate a group of 151 healthy children and 26 children who died or had heart transplantation ($N=3$) one year later on average. We propose a critical window for a fatal outcome that should not be used for infants (the two circles in the square rectangle are infants).

5 Patients with operated congenital heart disease

In our outpatient clinic of the Pediatrics Department of the Caritas Hospital in Bad Mergentheim, we treat children and adults with congenital heart disease. In our Holter ECG database we found 151 patients with operated congenital heart disease with complete data sets including the heart rates at day and night together with the global 24 hours HRV indicated by the parameter SDNN. The mean age is 11 ± 7 years

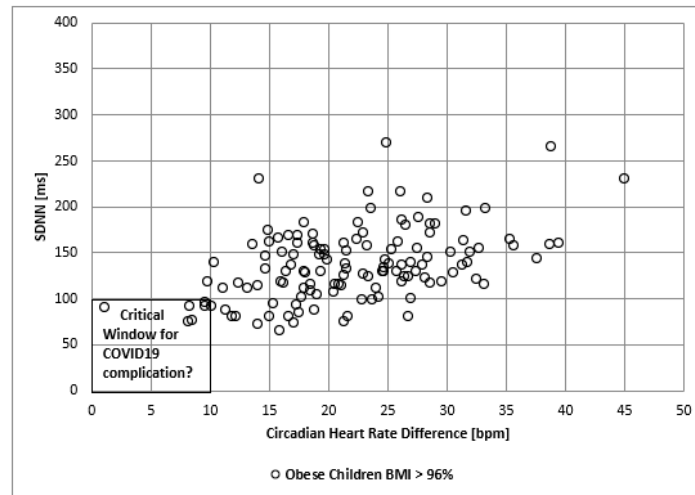
(131 children and 20 adults) and the mean age at operation was 2 years. The plot of the circadian heart rate difference and global HRV parameter SDNN (figure 6) illustrate our patients with congenital heart disease. Most patients are in the normal range of healthy children as shown in figure 5. The young adults with congenital heart disease have higher SDNN on average of cause the age dependent increase of heart rate variability. However, eleven children with operated congenital heart disease [open squares] and three adults [grey squares] with congenital heart disease are within the critical window and probably have an enhanced risk for COVID-19 complications: Three of them had or are listed for heart transplantation and two died recently. Nine suffer from heart failure including three with significant obesity.



Legend Fig. 6: This plot of the circadian heart rate difference and global HRV parameter SDNN illustrate our patients with congenital heart disease. Eleven children with operated congenital heart disease [open square] and three adults [grey square] with congenital heart disease are within this critical window: Three of them had or are listed for heart transplantation and two died recently. Nine suffer from heart failure including three with significant obesity.

6 Obese children

In our outpatient clinic of the Pediatrics Department of the Caritas Hospital in Bad Mergentheim, we treat children with obesity. In our Holter ECG database we found 130 children with a body mass index > 96% who had complete data sets including the heart rates at day and night together with the global 24 hours HRV indicated by the parameter SDNN. The mean age is 12.7 ± 9.9 years and the body mass index was 30.1 ± 4.7 kg/m² on average (99 $\pm$ 1% percentile). The plot of the circadian heart rate difference and global HRV parameter SDNN (figure 7) illustrate our patients with obesity. The global HRV indicated by the parameter SDNN is lower on average as recently published. Most patients are in the normal range of healthy children as shown in figure 5. However, seven children with obesity are within the critical window and probably have an enhanced risk for COVID-19 complications.



Legend Fig. 7: This plot of the circadian heart rate difference and global HRV parameter SDNN illustrate our children with obesity and a body mass index >96%. Seven children with obesity are within the critical window and probably have an enhanced risk for COVID-19

7 Discussion

The two cases show an impressive loss of heart rate variability and circadian rhythm during acute respiratory failure of 5.4 years old boy with a severe epilepsy - interpret as “near” SUDEP - and a 58 years old pediatric cardiologist who survived COVID-19. We anticipate a shared pathophysiology of a brainstem network disruption due to different causes (4, 5) and develop an algorithm for risk stratification based upon global heart rate variability SDNN(8) and circadian heart rate difference(13).

We use the data from healthy controls in different age groups and found a highly significant decrease of global heart rate variability (SDNN) and the circadian heart rate difference ($R^2=0.98$) for age groups greater than 10 years (Figure 4). Global HRV (8) and the circadian heart rate difference (12-14) are age dependent and have a proven impact on prognosis. A further decline of these parameters during COVID-19 - as shown in case 2 - would indicate the risk for complications in the elderly (15). However, as pediatricians we have not the opportunity to proof the algorithm in other COVID-19 patients if we have no children with COVID-19 in our hospital.

We proof this algorithm for risk stratification in children by using our published Holter ECG data of 151 healthy children(9) and 27 children who died or had heart transplantation (N=3) one year later on average. The data clearly differentiate healthy children from children with a worse outcome. We propose a critical window for a fatal outcome that should not be used for infants if some healthy infants would be stratified as critical ill (figure 5). Using this algorithm in our group of 151 patients with operated congenital heart disease, eleven children with operated congenital heart disease and three adults with congenital heart disease are within this critical window (figure 6): Three of them had or are listed for heart transplantation and two recently died. Nine suffer from heart failure including three with a significant obesity – a well-known risk factor for COVID-19 complications(16). The impact of obesity on the plot of the circadian heart rate difference and global HRV parameter SDNN is illustrated in figure 7, showing the data from 130 children with a body mass index >96% from our Holter ECG database. Most patients are in the normal range of healthy children. However, seven children with obesity are within the critical window and

probably have an enhanced risk for COVID-19 complications. In comparison 7.3% of patients with operated congenital heart disease and 5.4% of children with obesity may be candidates for COVID-19 complications.

However, some patients with significant clinical risk factors are not within this critical window based on HRV analysis. The algorithm must be proofed in a prospective study to be able to answer the urgent questions of the patients and their parents based on objective data. Otherwise, we must advise all the adolescents with preexisting chronic disease that they are probably on a higher risk for COVID-19 complications based on single reported cases (17).

Our concept opens new opportunities for risk stratification in the current COVID-19 pandemic in the era of using health technologies in millions of smart watches. Prospectively user-friendly smart watches, mobile ECG devices or chest straps may represent an elegant option in an ambulatory setting to monitor the health risks. Thus, the development of algorithms and advances in machine learning techniques to recognize severe disease like COVID-19 are necessary. To date common algorithms, focus on stress regulation. In the current case 2, the fitness tracker (LifeTrak Zoom HRV™, LifeTrak, USA) and the Samsung Health Galaxy wearable App™ (<https://www.samsung.com/de/apps/samsung-health/>) interpreted the low heart rates as relaxation instead of a COVID-19 infection (Data available from the author on reasonable request) . This incorrect interpretation of the HRV incorrectly reflects the user's health status and must be urgently improved.

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