# Alterations of oscillatory relationships of plethysmographic signal in patients with COVID-19

# Alterations of oscillatory relationships of plethysmographic signal in patients with COVID-19

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*Abstract*— **The aim of this study was to investigate possible alterations in the relationship between peripheral and central circulation dynamics caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.**

*Clinical Relevance*—**Results show how coronavirus disease 2019 can affect the energy of the Low Frequency band [0.04-0.15]Hz of the plethysmographic signal.**

## I. Introduction

The Coronavirus disease 2019 (COVID-19) is a condition caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The novel coronavirus SARS-CoV-2 manages to infect the human body mainly by binding to epithelial cells in the oral and nasal cavity. In particular, this infection is widely distributed in the respiratory tract and in other tissues such as skin and arterial and venous endothelium [2], [3]. Among the non-respiratory complications, a high prevalence of cardiovascular diseases were found in patients with COVID-19 [4]. The timely assessment of the microcirculation of patients with COVID-19 can be very important because it is correlated with the severity of the disease and prognosis in the acute phase [3], [5]. Furthermore, the evaluation of microcirculation can be important in order to avoid the long effects of Covid-19 [5], [6]. Photoplethysmography (PPG) technique was used in order to carry out the evaluation of microcirculation. PPG technique is a non-invasive, low cost and user-friendly method easy to perform even remotely, concurring in detecting the disease and its severity [7]. The aim of this study was to verify the correlation between central dynamics (heart) and the peripheral ones (microvessels). In order to achieve this result, the frequency signal power in three different frequency bands was evaluated. As for the analysis of central dynamics, the perfusion peaks of the raw signals were extracted and analyzed. The peripheral part, the raw PPG signals were studied directly. The three bands of interest were: very low frequency (VLF: 0-0.04 Hz), low frequency (LF: 0.04-0.15 Hz) and high frequency (HF: 0.15-0.4 Hz). Usually, LF power has been related to sympathetic system (SS), while HF power to parasympathetic system (PS) [8]. In particular, to evaluate the central dynamics, Hearth Rate Variability (HRV) technique was adopted. It is well known that HRV is a surrogate measure of cardiac autonomic tone [9]. Since HRV measures normal-to-normal (NN) interbeat interval (IBI) variations, it reflects complex interactions among physiological processes such as feedback, intrinsic mechanisms of pacemaker cells, thermogenesis, and the PS and SS [10].

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## II. Methods

This study included a total of 143 subjects assigned to Control (50) and Covid (93) groups. The Covid group was, in turn, divided into Group 1 (47) and Group 2 (46) on the basis of the severity of the disease, in particular on the basis of ventilation support and/or oxygen therapy required for the treatment of respiratory failure caused by COVID-19. Control group, referred as group 0, was composed by healthy workers operating at the San Giuseppe hospital (Empoli - Italy) while groups 1 and 2 were composed by patients admitted to the same hospital. The study was approved by the local ethics committee (approval No. CEAVC19059), and each subject gave informed consent before participating according to the Declaration of Helsinki. A blood perfusion signal was measured from each subject using the PPG technique. The acquisition instrument consisted of a finger pulse oximeter, a Mindray monitor and a Raspberry Pi 3 for data storage. Energy in the three frequency bands considered was separately estimated using the classical Fast Fourier Transform (FFT) technique. The analysis of the peripheral dynamics was carried out by the direct application of the FFT on the raw signal $s_n$, after removal of its mean value for all patients $n$. The energy on each of the three frequency bands was computed as the sum of the FFT amplitudes in the corresponding frequency band:

$$P^r_{i,p} = \sum_{f \in i} S_p(f) \tag{1}$$

where $S_p(f)$ is the FFT of the signal $s_p$, $f$ is the frequency, and $i = \{VLF, LF, HF\}$. Finally, the three values were normalized with respect to the total signal power in the frequency band up to 0.4 Hz:

$$P_{i,p} = \frac{P^r_{i,p}}{\sum_j P^r_{j,p}} \tag{2}$$

The analysis of central dynamics is based on the methodology used for analyzing HRV. The raw PPG signal was processed, using the Pan Tompkins algorithm for extracting the pulse peaks, identifying PP intervals. While Pan Tompkins algorithm is specifically designed for ECG signal, it can successfully handle also PPG signals. In particular, low and high pass filter cut-off frequencies were adjusted to PPG signal characteristics, respectively 3/fs and 0.2/fs where fs is the sampling frequency of the signals, 60 Hz. Despite

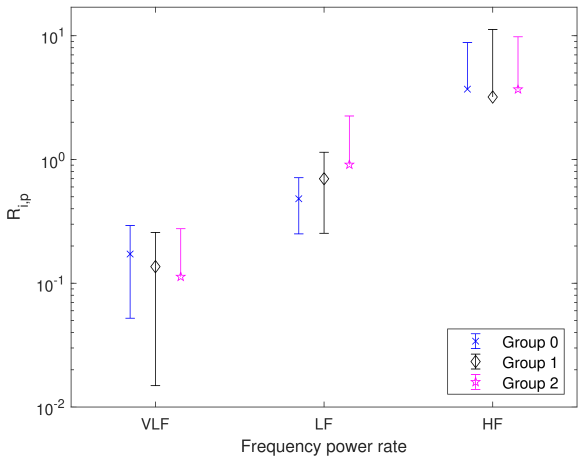


Fig. 1. Frequency power rate for each group. The $\times$ symbol represents the median value for the Group 0, the $\diamond$ symbol represents the median value for the Group 1 and the $\star$ symbol represents the median value for the Group 2. Whiskers represent the MAD value of the relative frequency power rate value.

usually HRV analysis is carried out on short-term time series of P-P intervals [8], in this work the raw PPG signals were directly considered. The PP sequence was fed as input to Kubios software toolkit (Kubios Oy, 2021) for extracting HRV parameters. Among other HRV-related parameters, the toolkit provides an estimate of the total power energy $C_i$ in the three above-defined frequency bands, again normalized with respect to the total power in the frequency band up to 0.4 Hz. The relation between the driving force (cardiac pump) and the peripheral signal (PPG) provides an insight on the responsiveness of the circulatory system at each given frequency. In particular, the ratio between the energy signal at peripheral level, and the energy, in the same frequency band, present in the cardiac signal may be used as an approximation of a transfer function, or gain, in the selected frequency band. Thus, for each patient $p$, we evaluated the ratio $R_{i,p} = P_{i,p}/C_{i,p}$, with $i = \{VLF, LF, HF\}$. A student t-test was performed for assessing the presence of significant variations among healthy and patients with Covid-19.

## III. Results

Figure 1 shows the distribution of the proposed parameter $R_{i,p}$ in the different groups, expressed by means of error bars. The figure reports the median and Median Absolute Deviation (MAD) for each frequency band and subjects group. Given the large difference between VLF and HF ratios, the figure is drawn in logarithmic scale.

Results indicate the relative power in the higher frequency bands is larger than in the VLF region. The effect of the severity of SARS-CoV-2 infection appears to be higher in the LF band than in the other two regions of the spectrum. In particular, we observed an increase in the energy related with LF band, directly correlated with the severity of the disease. This is in agreement with the literature, in fact as reported in [11], Covid-19 may activate the SS through increased production and release of Angiotensin II. On the contrary, we observed a small decrease on the VLF band, while no visible trend can be observed on the HF range. It is worthy of attention, however, that this variation may be partially related to the normalization of the power components. Statistical analysis, reported in Table I, confirms a significant difference between the values of $R_{LF}$ of controls and both groups of patients with Covid-19. Conversely, no statistically significant differences were present among other frequency bands.

TABLE I

P-values of statistical comparisons between healthy and patients groups for each frequency band.

| Frequency band | 0 vs 1 | 0 vs 2 |
|---|---|---|
| *VLF* | 0.269 | 0.613 |
| *LF* | 0.025* | 0.007* |
| *HF* | 0.726 | 0.969 |

* indicates statistically significant differences ($p < 0.05$).

## IV. Conclusion

The results of the study suggest that patients with Covid-19 may show an higher peripheral contribution to energy in the LF band respect to healthy controls. Overall, this result suggests that peripheral activity is stimulated by SARS-CoV-2 infection; the LF frequency band, indeed, includes the activity related to vasomotory activity, that is an expression of oscillations in the microcirculation [12].

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