Derangement of Cardiovascular Regulatory Mechanisms in COVID-19 Patients in Intensive Care Unit and its Association with Mortality

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Abstract

The uncontrolled hyper-inflammation in critically ill patients with COVID-19 might be associated with a dysfunction of the cardiovascular regulatory mechanisms. In order to estimate the involvement of cardiovascular control in limiting the risk of mortality in COVID-19 patients we assessed the degree of asynchrony between heart period (HP) and systolic arterial pressure (SAP) variability at rest in supine condition (REST) and during an orthostatic challenge, namely the modified head-up tilt (MHUT), in 18 COVID-19 patients (age: 62 ± 10 yrs, 15 men) admitted in intensive care unit (ICU) for pneumonia. The patients were distinguished in two groups, i.e. survivors (SURVs) or non survivors (noSURVs) according to the outcome. Asynchrony between HP and SAP was assessed via a model-free nonlinear marker in the information domain, i.e. cross-sample entropy (CSampEn). Neither demographic indexes nor time domain markers could separate the two groups and this result held regardless of the experimental condition. Conversely, CSampEn could and, more precisely, noSURVs subjects had a significantly larger HP-SAP asynchrony when compared to SURVs in response to MHUT. We conclude that measures of the derangement of the cardiovascular control might be helpful to stratify the risk of mortality in COVID-19 critically ill patients.

1. Introduction

Since the pandemic started in early 2020, critically ill patients suffering from COVID-19 pneumonia have become the main challenge in intensive care unit (ICU) around the world [1]. The severe illness is associated with a dysregulated immune response, leading to an uncontrolled hyper-inflammation, i.e. the so-called "cytokine storm" [2]. On one hand, this systemic infection impairs multiple systems, including the autonomic nervous system (ANS) [3]. On the other hand, a low ANS activity might accelerate the uncontrolled hyper-inflammation probably due to a deficient parasympathetic protective role [2]. Indeed, indexes derived from the variability of heart period (HP) have been suggested to anticipate the cytokine storm [4] and to be associated with prognosis and mortality [1].

A previous study utilized the modified head-up tilt (MHUT) [5] carried out in ICU, to probe the residual cardiovascular control in critical patients [6]. Since in healthy subject orthostatic stimulus [7,8] and, more specifically, MHUT [5], increases the degree of association between HP and SAP variability by evoking a significant baroreflex response, the missing increase of HP-SAP coupling strength during orthostatic challenge, or even a decrease, could be taken as an indication of an impaired baroreflex control. We hypothesized that MHUT could be helpful to stratify the mortality risk in COVID-19 patients admitted in ICU as well. The degree of HP-SAP uncoupling was assessed in the information domain via cross-sample entropy (CSampEn) [9]: the greater the CSampEn, the stronger the uncoupling between HP and SAP variability, the more deranged the cardiovascular control.

Thus, this study aims at characterizing the cardiovascular control via CSampEn between HP and SAP variability in critically ill COVID-19 patients at rest in supine position (REST) and during MHUT carried out in ICU. The group was divided into survivors (SURVs) and non-survivors (noSURVs) according to the mortality outcome.

Table 1. Time domain markers in SURVs and noSURVs at REST and during MHUT.

Index	SURVs		noSURVs	
	REST	MUHT	REST	MHUT
μ_{HP} [ms]	829.63 ± 246.66	827.28 ± 240.78	860.44 ± 173.27	859.15 ± 169.5
σ^2_{HP}[ms^2]	235 ± 278.55	304.75 ± 433.17	245.91 ± 435.65	401.34 ± 829.75
μ_{SAP} [mmHg]	110.93 ± 20.62	108.72 ± 20.3	119.29 ± 16.03	107.67 ± 22.78
σ^2_{SAP} [mmHg^2]	6.3 ± 6.35	16.84 ± 21.81	10.34 ± 16.67	11.16 ± 8.91

REST = at rest in supine position; MHUT = modified head-up tilt; ICU = intensive care unit; SURVs = survivors to ICU stay; noSURVs = non-survivors at the ICU stay; HP = heart period; SAP = systolic arterial pressure; μ_{HP} = HP mean; σ^2_{HP} = HP variance; μ_{SAP} = SAP mean; σ^2_{SAP} = SAP variance.

2. Methods

2.1. Experimental protocol

Experimental protocol was devised to probe cardiovascular control mechanisms in ICU [6]. The study was performed according to the Declaration of Helsinki and the ethical review board of "L. Sacco" Hospital, Milan, Italy, approved the protocol. All conscious patients gave their written informed consent. Close relatives or legal representatives of unconscious patients provided written informed consent.

We enrolled 18 critically ill patients with COVID-19 pneumonia (age: 62±10 yrs, 15 men). They were divided into SURVs (8 patients; age: 58±9 yrs, 8 males) and noSURVs (10 patients; age: 65±8 yrs, 7 males). During the patient's first day in ICU, electrocardiogram (ECG) and invasive arterial pressure (AP) were acquired from the patient's monitor (IntelliVue MX800 Patient Monitor, Philips, Best, The Netherlands). Signals were sampled at 250 Hz. Recordings were made at rest in supine position (REST) and during MHUT. This orthostatic maneuver was carried out at the ICU bed as follows [5]: patients' bed was tilted to 15° as a rigid body, then the inclination of back rest was increased to reach 60°, while the inclination of the thigh rest was adjusted to 0°. Both data acquisition sessions lasted 10 minutes with MHUT always starting after REST. The first 3 minutes of recordings during MHUT was not analyzed to avoid nonstationary conditions.

2.2. Beat-to-beat series extraction

From the ECG signal, we computed the HP as the time distance between two consecutive R-peaks. On the AP signal, we detected the *n*th SAP as the maximum value of AP within the *n*th HP. The series were manually inspected and a maximum of 5% of values was corrected in case of misdetection or isolated arrhythmic events via linear interpolation. Sequences of 250 consecutive values were selected at REST and during MHUT. Time domain markers such as mean and variance of HP and SAP were computed and labelled respectively μ_{HP}, σ^2_{HP}, μ_{SAP} and σ^2_{SAP}. They were expressed in ms, ms^2, mmHg and mmHg^2, respectively.

2.3. CSampEn

Given two stochastic process realizations $x = \{x_n, n = 1, \ldots, N\}$ and $y = \{y_n, n = 1, \ldots, N\}$ of length N, we define $\boldsymbol{x}_i^- = [x_{i-1} \cdots x_{i-m}]$ the pattern formed by m past value of x and $\boldsymbol{x}_i = x_i \oplus \boldsymbol{x}_i^-$ the (m+1)-dimensional vector obtained by concatenating x_i and $\boldsymbol{x}_i^-$ with i=1, …, N–m. Similarly, we set $\boldsymbol{y}_j^- = [y_{j-1} \cdots y_{j-m}]$ and $\boldsymbol{y}_j = y_j \oplus \boldsymbol{y}_j^-$ with j=1, …, N–m. We define the probability that $\boldsymbol{y}_j$ lies in the neighborhood of the reference vector $\boldsymbol{x}_i$ of size r as $p(\|\boldsymbol{y}_j - \boldsymbol{x}_i\| \le r)$, where r is the tolerance in the computation of the neighborhood and $\|\cdot\|$ is the Euclidean norm and, similarly, $p(\|\boldsymbol{y}_j^- - \boldsymbol{x}_i^-\| \le r)$ as the probability that $\boldsymbol{y}_j^-$ lies in the neighbourhood of $\boldsymbol{x}_i^-$ of size r. CSampEn [9] was defined as

$$\mathrm{CSampEn}(m, r, N) = -\log\left(\frac{\langle p(\|\boldsymbol{y}_j - \boldsymbol{x}_i\| \le r)\rangle}{\langle p(\|\boldsymbol{y}_j^- - \boldsymbol{x}_i^-\| \le r)\rangle}\right), \quad (1)$$

where $\langle\cdot\rangle$ performs the average over all reference vectors built over x. The series were first normalized to have zero mean and unit variance before the computation of CSampEn. According to the standard settings, we assigned m = 3 and r = 0.2 [10].

2.4. Statistical analysis

The demographic characteristics of SURV and noSURV groups were compared via unpaired t test, or Mann-Whitney rank sum test, or χ^2 test as appropriate. Two-way repeated measures analysis of variance (Holm–Sidak test for multiple comparisons, one factor repetition) was used to check the significance of the differences between groups (i.e. SURVs and noSURVs) within the same experimental condition (i.e. REST or MHUT) and between experimental conditions within the same group. Results are reported as mean ± standard deviation.

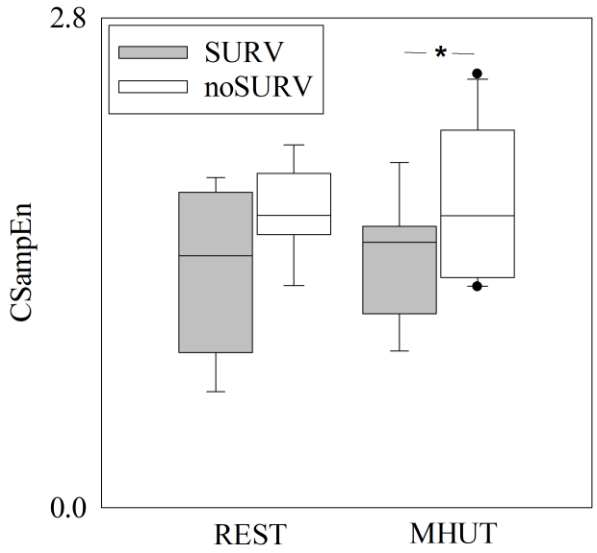

Figure 1. The grouped box-plot graph shows CSampEn as function of the experimental conditions (i.e. REST and MHUT) in SURV (grey box) and noSURV (white box) groups. The symbol * indicates a significant difference versus SURVs with $p<0.05$.

Statistical analysis was carried out using a commercial statistical program (Sigmaplot, v.14.0, Systat Software, Inc., Chicago, IL, USA). A $p<0.05$ was always considered as significant.

4. Results

Demographic and clinical variables were not significantly different between SURV and noSURV groups. Table 1 reports the time domain indexes in SURV and noSURV groups. None of the time domain markers exhibited differences across groups and/or experimental conditions.

The grouped box-plot graph in Figure 1 shows CSampEn as a function of the experimental condition in SURVs (grey box) and noSURVs (white box). Both at REST and during MHUT CSampEn increased in noSURVs compared to SURVs and this raise was significant only during MHUT. Within the same group (i.e. SURV or noSURV) the effect of the challenge was not significant.

5. Discussion

The main findings of the study is as follows: noSURVs patients have a significantly larger asynchrony between HP and SAP during the orthostatic challenge compared to SURVs as measured via CSampEn. This result indicates a missed ability of noSURVs to activate residual cardiovascular regulatory mechanisms.

5.1. CSampEn Assessed During MHUT Can Stratify Mortality Risk in COVID-19

In healthy subjects during orthostatic stressor it is well-known that the gain of the relationship from SAP to HP (i.e. the baroreflex sensitivity) [11,12] and the degree of association along the baroreflex pathway increases as measure via transfer entropy from SAP to HP [7,8], thus suggesting a greater involvement of cardiovascular control mechanisms to cope with the reduction of the venous return and stroke volume. This result was confirmed even in the case of a postural stimulus of a less relevant intensity as it is the case of MHUT [5]. In critical patients in ICU for respiratory failure with similar demographical indexes and mortality rate as the present group we observed a decrease of the degree of association between HP and SAP variability as measured via HP-SAP squared coherence function [6]. This result indicates that patients in ICU features a depressed ability to control SAP changes and measures of the degree of association between HP and SAP variability might be useful to typify the residual ability of cardiovascular control mechanisms to react to stimuli. Therefore, we hypothesized that the risk of mortality of COVID-19 patients admitted in ICU for pneumonia could be stratified according to a marker of asynchrony between HP and SAP variability following a postural stressor (i.e. MHUT). According to this hypothesis, a group of COVID-19 patients admitted in ICU was divided into SURVs and noSURVs and a nonlinear marker of HP-SAP asynchrony in the information domain, namely CSampEn [8], was computed. If the hypothesis was true, the effect of the MHUT on the two groups would be different and noSURVs might be characterized by a greater difficulty in coping with the orthostatic challenge. In agreement with the hypothesis, during MHUT CSampEn was significantly larger in noSURVs than in SURVs. This result indicates that the noSURV group has less internal regulatory resources than the SURV one when a stressor requiring a coordinated HP-SAP response is applied. Remarkably, none of the demographic indexes and time domain markers was able to differentiate the SURV and noSURV groups, thus indicating an independent potential of CSampEn to stratify the mortality risk. The difference between noSURV and SURV groups might be attributed to the atypical dysregulated immune response triggered by COVID-19 and activation of inflammatory pathway that might have produced a greater derangement of cardiovascular control mechanisms and integrative autonomic center activity in noSURVs. Finding markers stratifying the mortality risk such as CSampEn between HP and SAP variability following MHUT could raise the attention of the clinicians toward a specific class of patients, otherwise indistinguishable from the entire population admitted in ICU, that needs a specific and more prompt pharmacological anti-inflammatory therapy.

5.2. On the use of CSampEn in ICU

We selected a model-free nonlinear method for the assessment of the asynchrony between HP and SAP variability such as CSampEn [9], because in a previous work, conducted in ICU on patients with respiratory failure, we observed that model-free nonlinear bivariate approaches were more powerful than model-based linear bivariate methods [6] in stratifying mortality risk within the same experimental condition. This ability might derive from the possibility of accounting complex nonlinear interactions without imposing any specific model structure [10]. Future work should test different model-free nonlinear bivariate approaches such as those based in symbolic dynamics that were found particularly useful in [6].

6. Conclusions

We conclude that the analysis of the association between HP and SAP variability following MHUT via CSampEn is a valid tool to stratify the risk of mortality in COVID-19 patients admitted in ICU. We suggest that the greater the HP-SAP asynchrony during postural stressor, the more limited is the response of internal regulatory reflex, the worse the prognosis. CSampEn and MHUT could be utilized as a part of the monitoring of COVID-19 to assess the effect of the cytokine-storm that might be responsible for the observed derangement of the cardiovascular control mechanisms and autonomic integrated responses to stimuli. Future developments should limit the impact of confounding factors on the conclusions. The enlargement of the sample size could favor the achievement of this goal by allowing us to implement a more direct, and joint, competition of CSampEn with other clinical variables via *ad hoc* statistical models. For example, in the present group, even though not significantly different, the age of SURV and noSURV groups is borderline to significance. The assessment of the independent predictive value of HP-SAP CSampEn compared to age is one of the key issues of future studies.

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