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Assessment of Sepsis in the ICU by Linear and Complex Characterization of Cardiovascular Dynamics

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***Abstract*— Sepsis is one of the pathological conditions with the highest incidence in intensive care units. Sepsis-induced cardiac and autonomic dysfunction are well-known effects, among others, caused by a dysregulated host response to infection. In this context, we investigate the role of complex cardiovascular dynamics quantified through sample entropy indices from the inter-beat interval, systolic and diastolic blood pressure time series as well as the cross-entropy between heartbeat and systolic blood pressure in patients with sepsis in the first hour of intensive care when compared with non-septic subjects. Results show a significant ($p<0.05$) reduction in the probability of being septic for a unitary increase in entropy for systolic and diastolic time series (odds equal to 0.038 and 0.264, respectively) when adjusting for confounding factors. A significant ($p<0.001$) odds ratio (0.248) is observed also in cross-entropy, showing a reduced probability of being septic for an increase in heartbeat and systolic pressure asynchrony. The inclusion of our measures of complexity also determines an increase in the predictive ability (+0.03) of a logistic regression model reaching an area under the receiving operating and precision recall curves both equal to 0.95.**

Clinical relevance **The study demonstrates the ability of information theory in catching a reduction of complex cardiovascular dynamics from vital signs commonly recorded in ICU. The considered complexity measures contribute to characterize sepsis development by showing a general loss of the interaction between heartbeat and pressure regulation. The extracted measures also improve the ability to identify sepsis in the first hour of intensive care.**

I. INTRODUCTION

According to the third international consensus definitions for sepsis and septic shock [1], sepsis is defined as a dysregulated host response to infection. Sepsis is considered one of the major problems in intensive care units (ICU) where its final stage, called septic shock, reports a mortality of 38.9% among 47% of patients that met the criteria according to the third definition of sepsis [3], [1]. A sepsis incidence of about 48.9 million of cases was observed in 2017 with an average mortality of 19.7% [2]. To this extent, the recognition of sepsis is of primary importance and it was also highlighted in the Surviving Sepsis Campaign Guidelines [4] as well as in [5], [6] which strengthen the need for timely treatment and initiation of antibiotic therapies as starting sepsis management procedures to be performed in the early hours of sepsis development or recognition.

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Sepsis is known to strongly affect cardiovascular functioning, leading to strong impairment of both myocardial and autonomic functions. Recently, Wang [7] reviewed the most common causes of sepsis induced cardiovascular dysfunction, describing it as a global dysfunction of the whole heart which also induces autonomic depression of both sympathetic and vagal branches of the autonomic control system. Also an impairment of the link between heart activity and blood pressure is evidenced. Previous studies identified a reduction in heart rate variability (HRV) measures induced by sepsis in adults [8], [9], [10] and particularly in non-linear measures like the exponent of the detrended fluctuation analysis and entropy. Such measures indeed provide estimates of the non-linear interactions between the heart activity and the underlying mechanisms. However, to our knowledge, only a few studies expanded this analysis to the blood pressure time-series (BPTS) [11], [12], [13], which investigated the association of blood pressure variability (BPV) with illness severity and the ability of complexity measures from BPTS in predicting sepsis, vasopressor independence at 24-h and 28-day mortality. The analysis of complex interactions between heart activity and blood pressure result to be less investigated in septic subjects. The well-known key role of the autonomic control system in regulating the cardiovascular activity resulted indeed to be strongly impaired by sepsis. Therefore, this study proposes the assessment of both entropy features derived from pressure signals and cross-entropy measure between heart activity and blood pressure to characterize and predict sepsis in the ICU, when compared to other patients in critical conditions. The role of these additional features in identifying septic patients is assessed by focusing on the improvement that their inclusion produced on a previously developed sepsis identification pipeline [14] which showed high performances using simple linear models among others.

II. METHODS

A. Cohort Selection

The study includes data publicly available on PhysioNet [15] gathered from the MIMIC-III database [16], which contains electronic health records (EHR) of patients entering the ICU at the Beth Israel Deaconess Medical Center in Boston, MA. A subset of the MIMIC-III database, i.e. 10,282 patients, is also matched with the corresponding available recordings of vital signs continuously recorded at the patients' bedside.

In order to derive a population including both septic and non-septic patients (also referred to as control in this study),

we first aligned patients according to the admission in the ICU and we extracted the first 1-hour recordings of each patient's stay. According to this procedure, we can mimic in the most realistic way possible the condition of a patient that enters the ICU and is put under the surveillance of the proposed monitoring tool.

ICU data are known to be characterized by the presence of different sources of noise, consequently, the following inclusion criteria were applied to select the waveforms with the highest quality:

- Presence of contemporaneous ECG (I,II,III or 'V' leads) and arterial blood pressure recordings (ABP).
- More than 50% of both signals should be available.
- Patients with 18<age<90.

Finally, waveforms were subjected to manual inspection in order to remove those with more than 50% of additional noise like signal saturations, electrodes disconnections and motion. A total of 142 high quality waveforms were extracted, resulting in 71 septic and 71 control subjects.

Septic subjects were identified according to the third definition of sepsis [1], by defining septic patients as those with a prescription of antibiotics, acquisition of body fluid culture, and an increase in sequential organ failure assessment score (SOFA) greater than two points [17]. We computed SOFA score at the admission, identifying as septic patients whoever met the defined criteria between -24 and +24 hours from the admission in ICU.

B. Data Processing and Feature Engineering

Extracted waveforms were preprocessed and annotated in order to extract fiducial points from both ECG and ABP waveforms. R peaks were identified from ECG with an internally developed algorithm and synchronized with the extracted systolic, diastolic and onset fiducial points from the ABP signal. The obtained time-series were processed in order to remove ectopic beats and artifacts, and to extract HRV features. A closed-loop point process modelling approach was used in order to extract features representing the linear interactions between the cardiovascular and autonomonic nervous systems, according to our previous work [14].

1) Entropy Features: In addition to the previously introduced set of features in both time and frequency domain, we derived and investigated the role of non-linear features from the extracted pressure and pulse arrival time series. Specifically, we computed the sample entropy for both systolic, diastolic and pulse arrival time time-series according to Richman et al. [18].

Briefly, considering a time series of *N* points $\{u(j) : 1 \leq j \leq N\}$, $\mathbf{x}_m(i) = \{u(i+k) : 0 \leq k \leq m-1\}$ are the *N-m+1* vectors of *m* points obtained for $\{i | 1 \leq i \leq N-m+1\}$ whose reciprocal distance is defined as $d[x(i), x(j)] = max\{|u(i+k) - u(j+k)| : 0 \leq k \leq m-1\}$. In this context, the probability that two sequences will match for *m* points, $B^m(r)$ can be defined starting from $B_i^m(r) = B_i/(N-m+1)$, with B_i the number of vectors $\mathbf{x}_m(j)$ within *r* of $\mathbf{x}_m(i)$, where $1 \leq j \leq N-m, j \neq i$ and consequently, $B^m(r) = \sum_{i=1}^{N-m} B_i^m(r)/(N-m)$. Similarly, the probability that two sequences will match for *m+1* points, $A^m(r)$, is derived from $A_i^m(r) = A_i/(N-m+1)$ with A_i the number of vectors $\mathbf{x}_{m+1}(j)$ within r of $\mathbf{x}_{m+1}(i)$, where $1 \leq j \leq N-m, j \neq i$, thus obtaining $A^m(r)$ as $A^m(r) = \sum_{i=1}^{N-m} A_i^m(r)/(N-m)$. Richman et al. estimate the sample entropy as

$$SampEn(m, r, N) = -ln(A^m(r)/B^m(r)) \qquad (1)$$

$m = 2$ and $r = 0.2$ were considered for the analysis. Cross-SampEn was then extracted by simply measuring the distance between the vectors $\mathbf{x}_m(j)$ and $\mathbf{x}_{m+1}(j)$ obtained from the first series *u* with respect to vectors $\mathbf{y}_m(j)$ and $\mathbf{y}_{m+1}(j)$ obtained from a second series $\{v(j) : 1 \leq j \leq N\}$, $\mathbf{y}_m(i) = \{v(i+k) : 0 \leq k \leq m-1\}$, thus defining the distance between **x**(i) and **y**(i) as $d[x(i), y(j)] = max\{|u(i+k) - v(j+k)| : 0 \leq k \leq m-1\}$.

Inspired by the hypothesis of a strong effect of sepsis on the coupling between heart rate and arterial blood pressure, we evaluated the cross sample entropy between RR interval series and systolic pressure series (*XEn_RR-SAP*) to assess changes in the non-linear interaction between these two systems. The considered time-series were centralized and normalized before the estimation of cross sample entropy.

C. Statistical Analysis and Classification

Statistical difference between the two groups was assessed, for each entropy feature and for extracted time indices, through a generalized linear model correcting for confoundings (age, gender, undergoing treatment of vasoactive agent and sedative, undergoing mechanical ventilation, hypertension and diabetes).

Finally, we tested the role of entropy features from blood pressure and pulse arrival time series as well as RR-SAP cross-entropy in predicting sepsis by including them in the whole set of features whose performances were already assessed in our previous study [14]. The improvement was evaluated with a logistic regression model which was trained with a set of 80% observations and tested on the remaining 20%. A stratified hold-out partition was performed.

III. RESULTS

A. Statistical analysis

Table I shows median and interquartile ranges of the considered features for both septic and control population. It is worth mentioning the higher median values of AVSAP, SDSAP and SDDAP for septic subjects (133.3mmHg, 9.2mmHg and 5.59mmHg) with respect to control ones (125.6mmHg, 7.5mmHg, 4.7mmHg) as well as the sensibly lower median values of the following measures of entropy SAP_SampEn (S: 0.167, C: 0.262) and DAP_SampEn (S: 0.281, C: 0.493) and XEn_RR-SAP (S: 0.817, C: 1.048). The comparison of some generic features describing the patients' cardiovascular state and the non-linear features extracted between septic and control populations is presented in Table II. Average RR interval (*AVNN*) and its variability (*SDNN*) did not show statistically significant difference, however, average systolic pressure (*AVSAP*) and *SDSAP* show significant (respectively, $p<0.05$ and $p<0.01$) changes with respect to the control

Feature Distributions		
Feature	Sepsis	Control
AVNN [ms]	702.5 618.8-804.6	744.1 633.4-875.0
SDNN [ms]	35.0 18.7-61.8	30.9 16.9-61.5
AVSAP [mmHg]	133.3 112.6-144.87	125.6 114.17-135.69
SDSAP [mmHg]	9.2 6.9-13.3	7.5 5.7-9.9
AVDAP [mmHg]	70.7 60.7-81.2	70.9 63.0-78.8
SDDAP [mmHg]	5.6 4.3-7.8	4.7 3.7-6.2
AVPAT [s]	0.285 0.263-0.316	0.273 0.235-0.291
SDPAT [s]	0.017 0.011-0.031	0.012 0.008-0.019
RR_SampEn	1.062 0.878-1.514	1.199 0.856-1.815
XEn_RR-SAP	0.817 0.516-1.174	1.048 0.858-1.678
SAP_SampEn	0.167 0.12-0.279	0.262 0.177-0.422
DAP_SampEn	0.281 0.177-0.579	0.493 0.283-0.832
PAT_SampEn	0.812 0.708-1.066	0.889 0.745-1.096

TABLE I

MEDIAN AND INTERQUARTILE RANGES FOR SEPISIS AND CONTROL.

Sepsis-Control			
Feature	Coefficient	pValue	Odds (Increase)
AVNN [ms]	-0.001±0.001	0.4880	0.914 (+100)
SDNN [ms]	0.009±0.006	0.1562	1.092 (+10)
AVSAP [mmHg]	0.020±0.010	0.0422*	1.221 (+10)
SDSAP [mmHg]	0.142±0.052	0.0066†	4.14 (+10)
AVDAP [mmHg]	0.009±0.015	0.5344	1.096 (+10)
SDDAP [mmHg]	0.162±0.078	0.0364*	5.069 (+10)
AVPAT [s]	14.1±4.27	0.0009‡	4.122 (+0.1)
SDPAT [s]	46.7±16.7	0.0054†	1.595 (+0.01)
RR_SampEn	0.137±0.367	0.7094	1.146 (+1)
XEn_RR-SAP	-1.394±0.404	0.0006‡	0.248 (+1)
SAP_SampEn	-3.28±1.20	0.0063†	0.038 (+1)
DAP_SampEn	-1.33±0.555	0.0165*	0.264 (+1)
PAT_SampEn	-1.34±0.748	0.0735	0.262 (+1)

TABLE II

ESTIMATED COEFFICIENTS (± STANDARD ERROR), P-VALUES (*P<0.05, †P<0.01, ‡P<0.001) AND ODDS RATIOS FOR EACH OF THE EXTRACTED FEATURES.

population, with respectively 1.2 and 4.1 times increase in probability of being septic when an increase of 10 mmHg is observed. Similarly, diastolic series variability shows a significant ($p<0.05$) difference with odds>1 whereas *AVDAP* does not. Pulse arrival time linear features *AVPAT* and its variability *SDPAT* result to be significantly ($p<0.001$ and $p<0.01$, respectively) different between septic and control subjects, with odds respectively equal to 4.1 and 1.6 for corresponding increases of 0.1 and 0.01 seconds.

Sample entropy measures computed on pressure time series (*SAP_SampEn* and *DAP_SampEn*) result statistically significant ($p<0.01$ and $p<0.05$) when comparing the two populations, showing both odds<1 for unitary increase as well as cross-sample entropy from RR and SAP series (*XEn_RR-SAP*) which shows odds=0.248 ($p<0.001$).

Fig.1 shows ECG and ABP traces from two distinct subjects: a septic (upper) and a control (lower) subject with XEn_RR-SS equal to 0.1698 and 7.272, respectively. The high overall blood pressure variability, please note the difference in the two scales, and the stronger synchronization between RR and SAP time series can be appreciated in the septic traces with respect to the control ones.

B. Identification Model Results

Results obtained for sepsis identification showed an increase in discriminating ability when comparing the new updated model, including the information of the pressure related entropy and cross-entropy measures, with the best performing logistic regression model previously developed. Specifically, the new model achieves an area under receiving operating curve (AUROC=0.95) and an area under precision recall curve (AUPRC=0.95) significantly higher than the values obtained with the previous model (AUROC=0.91 and AUPRC=0.90, respectively).

IV. DISCUSSIONS

A. Statistical Analysis

Statistical results indicate that pressure signals are strongly informative about the presence of sepsis. Indeed, this study confirms the importance of pressure time series and pressure variability, showing that an increase in blood pressure variability is associated with sepsis. Similar results were also found by previous studies [12], [13] that associated a higher pressure variability with illness severity. Of note, septic subjects overall show higher heart rate (lower AVNN, not significant) and, differently from clinical expectations [1], a significantly higher average systolic pressure, possibly due to the differences in sepsis evolution between patients in the early stage of ICU admission. A significantly higher average pulse arrival time is also observed, suggesting a general state of vasodilation, a condition known to be present in sepsis [19]. The significant differences in systolic, diastolic and pulse arrival time variabilities further suggest an impaired autonomic regulation that does not properly reflect onto vessels regulation. This is in line with recent literature finding [20] showing a reduced reactive hyperaemia and peak hyperaemic blood flow.

The relevance of our results is further motivated by the entropy features which, differently from previous studies show that RR interval entropy is not significantly influenced in septic patients when compared with other ill patients in the ICU, whereas systolic and diastolic entropy are significantly reduced in sepsis. This possibly indicates a loss of complex non-linear interactions between the cardiovascular and the autonomic nervous systems that may be attributed to the hypothesized impairment in vasculature regulation. This observation is further emphasized by the observed significant loss of cross-entropy in septic patients between RR and

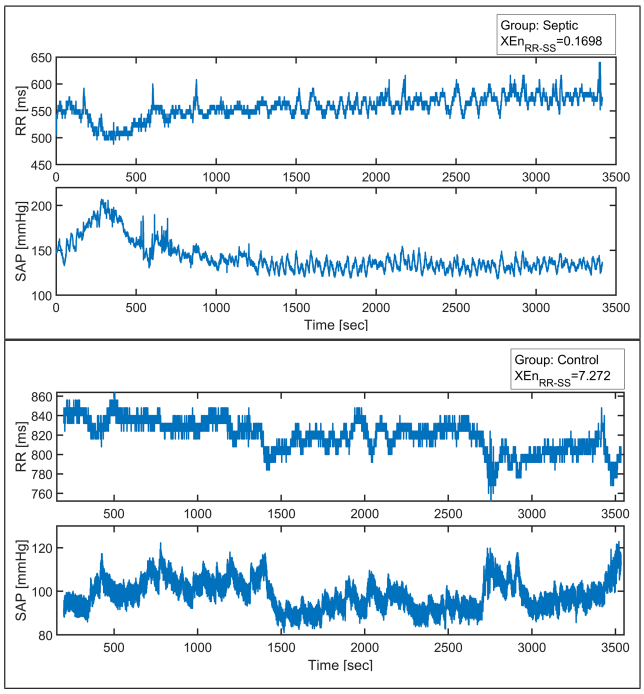

Fig. 1. RR and SAP traces for septic (top) and control (bottom) subjects with respectively low (0.1698) and high (7.272) values of Cross-SampEn.

SAP, which points at a higher synchronization between the two series, thus suggesting that blood pressure is reflecting more the heart activity with a loss in the non-linear control of the autonomic nervous system of blood pressure. It has to be mentioned that, despite the analysis were adjusted also for the presence of mechanical ventilation, patients' respiration, highly influenced by sepsis [22], might play a key role influencing both RR and SAP, indeed previous studies already assessed a reduction in cross-entropy between RR and respiration [18], and this effect might be reflected on blood pressure as well [21].

Finally, the obtained increase in discriminating ability of the developed machine learning model strengthens the importance of features coming from the complex domain both for blood pressure time-series (their high predictive power was indeed previously observed in [11]), and for describing the complex interaction between heart and blood pressure as well as their potential clinical role in ICU.

V. CONCLUSIONS

The study highlights the importance of monitoring complex cardiovascular dynamics in the ICU, demonstrating how differences in these indices provide relevant insights into the underlying pathophysiology of septic patients when compared with other ICU patients. We also show that complex indices derived by blood pressure dynamics are able to boost up performances of machine learning models in order to identify sepsis as early as possible after patients' admission.

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