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Heart rate time series characteristics for early detection of infections in critically ill patients

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ABSTRACT

It is difficult to make a distinction between inflammation and infection. Therefore, new strategies are required to allow accurate detection of infection. Here, we hypothesize that we can distinguish infected from non-infected ICU patients based on dynamic features of serum cytokine concentrations and heart rate time series. Serum cytokine profiles and heart rate time series of 39 patients were available for this study. The serum concentration of 10 cytokines were measured using blood sampled every 10 minutes between 2100 and 0600 hours. Heart rate was recorded every minute. Ten metrics were used to extract features from these time series to obtain an accurate classification of infected patients. The predictive power of the metrics derived from the heart rate time series was investigated using decision tree analysis. Finally, logistic regression methods were used to examine whether classification performance improved with inclusion of features derived from the cytokine time series. The AUC of a decision tree based on two heart rate features was 0.88. The model had good calibration with 0.09 Hosmer-Lemeshow *p* value. There was no significant additional value of adding static cytokine levels or cytokine time series information to the generated decision tree model. The results suggest that heart rate is a better marker for infection than information captured by cytokine time series when the exact stage of infection is not known. The predictive value of (expensive) biomarkers should always be weighed against the routinely monitored data, and such biomarkers have to demonstrate added value.

Keywords: Infection monitoring, Cytokines, Heart rate, ICU

INTRODUCTION

The risk for a hospital acquired infection for patients admitted to the Intensive Care Unit (ICU) is 5-10 times higher than for other hospital patients [1]. At the ICU, infection is a common cause of morbidity and mortality [2]. Infection leads to the release of both inflammatory and anti-inflammatory cytokines [3]. An imbalance between both responses can contribute to a potentially lethal course of this condition in critically ill patients [3, 4]. Early detection of infection could have a major impact on infection management and disease outcome in acute care settings [5]. It is often difficult to differentiate between infection and inflammation as symptoms overlap [6]. In addition, it is a challenge to diagnose a new infection in a patient with ongoing inflammation (e.g. due to surgery or an earlier infection).

The clinical suspicion of an infection is based on sensitive but non-specific vital signs such as tachycardia, or fever. In addition to tachycardia, several studies proposed that other heart rate characteristics such as signal complexity, signal variability and signal asymmetry could also be used as early markers for infection [7-10]. Most of these studies found a satisfactory sensitivity, but a rather low specificity [8].

During the last decade many studies focused on the search for accurate laboratory markers of infection. Two potential markers that received much attention are C reactive protein (CRP) and procalcitonin (PCT) [11, 12]. However, several studies indicate that both parameters can also be increased in non-infectious conditions suggesting the need for other markers which are more specific or for tests which could be used in combination with these parameters.

In this study, we hypothesized that we can differentiate between infected patients and non-infected subjects (patients with inflammation and healthy subjects) based on dynamic features of heart rate and serum cytokine time series. The main objective was to use simple metrics to quantify these time series to obtain an accurate classification of infected patients. First we studied the predictive power of the metrics derived from the heart rate time series, and second whether classification performance improved with inclusion of information derived from static cytokine values or cytokine time series.

MATERIALS AND METHODS

Patients and healthy subjects

A prospective observational study was performed at the surgical and medical intensive care units (ICU) of the

University Hospitals Leuven, Belgium. The study was approved by the Institutional Ethical Review Board of the University Hospitals Leuven (ML6625). The clinical trial was registered at the International Standard Randomized Controlled Trial Number Register (ISRCTN49306926). Written informed consent was obtained from the patients' next of kin and from the healthy volunteers.

Consecutive mechanically ventilated adult (age ≥ 18 years) patients, who had an arterial line in place, were eligible for inclusion in the study. In addition, age, gender, and BMI matched healthy volunteers were selected, and were admitted in a room adjacent to the ICU for 1 night, where an arterial line in the left or right radial artery was inserted.

In all subjects, night-time serial blood sampling, over 9 hours, from 9 p.m. until 6 a.m. on the next morning, was performed. Undiluted 2 ml arterial blood samples were drawn every 10 minutes. A blood management protection system (Edwards Lifesciences, Irvine, CA) was used to minimize unnecessary blood waste. Total blood loss per subject did not exceed 110 ml.

Blood was collected in prechilled EDTA tubes that were placed immediately on ice. They were cold-centrifuged, frozen at -20°C , before they were stored at -80°C . In the serum of each sample, the concentration of the following 10 cytokines were determined with an immunoassay (Bio-Plex Precision ProTM, BioRad Laboratories, CA, USA): interleukin-1 beta (IL-1 β), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-13 (IL-13), interferon gamma (IFN γ) and tumor necrosis factor-alpha (TNF α). This immunoassay has a reliable performance as supported by independent studies (e.g. [13]).

During the same period of 9 h, also heart rate measurements were recorded from the patients via surface electrodes and a patient monitor (IntelliVue[®] MX800; Philips[®], Eindhoven, The Netherlands) and stored with a sampling rate of 1 sample/ 1 min using a patient data management system (MetaVision[®]; iMD-Soft[®], Needham, MA, USA). For the healthy volunteers (N=5), no heart rate measurements were available.

All patients were scored for infection, by retrospective review of their computerized medical charts, by two independent clinicians (P.M., G.M.). The CDC criteria for infections in the ICU setting were used [14]. Infection scoring was done in an electronic CRF, in Filemaker Pro (Filemaker, Inc, Santa Clara, CA, USA). Patients were categorized as not-infected when no signs of infection were present, active infection when there were signs of infection, and non-active infection when patients were still treated with antibiotics for an earlier infection, but had no active signs of infection any longer. The volunteers were examined by a medical doctor to confirm that they were healthy and not suffering from infection, at the time of sampling.

Pre-processing and feature extraction

The hypothesis of this study was that infected patients can be distinguished from non-infected patients based on features of the heart rate and cytokine time series. Therefore, ten different methods were used to derive descriptive features from these time series: mean, variance, minimum, maximum, maximum–minimum, autoregressive coefficient of a first order autoregressive [AR(1)] model, skewness, kurtosis, sample entropy and the cumulative sum (for details on the calculation of the cumulative sum: see [15]). The selection of these features is supported by other studies, which indicate that such generic features may be used for a detailed quantification of time series in a wide range of fields (e.g. [16-17]). Most of these metrics are measures for signal complexity (sample entropy), signal variability (variance, kurtosis, cumulative sum, autoregressive coefficient of AR(1) model) or signal asymmetry (skewness, mean of detrended time series) [16-19]. The same ten features were calculated for the detrended time series. Each time series was first standardised (subtraction of mean and divided by standard deviation) and afterwards detrended using an integrated random walk model (IRW) with noise variance ratio (NVR) of 0.001 for the heart rate time series and a NVR of 0.01 for the cytokine time series (CAPTAIN toolbox in Matlab) [20]. In this study, these detrended time series are also called the fast dynamics of the time series, because by subtracting the IRW model from the original data, the slow trend was removed.

Feature selection and classification models

Decision tree analysis was applied to determine appropriate classification models for infection based on these features (Statistics Toolbox in Matlab). First, a decision tree model was developed based only on the features of the heart rate time series (i.e. heart rate model or HR model). To obtain a robust HR model, a bootstrapping procedure ($n = 1000$ bootstrap samples) was used for the selection of the heart rate based features [21]. For each bootstrap sample, a new pruned decision tree was calculated resulting in a total of 1000 decision trees. Afterwards, the frequency of features selected as tree nodes across bootstrap replicas was used to rank them for predictive performance. Features with the highest count were selected for the final decision tree model. Afterwards, receiver operating characteristic (ROC) analysis was used to evaluate the performance of a diagnostic test based on this final decision tree model. The area under the ROC curve (AUC) was calculated to quantify the discriminatory power of the HR model [22]. Since bootstrapping provides accurate and unbiased estimates of model performance in small datasets, bootstrapping (based on 1000 bootstrap samples) was used to

calculate confidence intervals for the used performance metrics (sensitivity, specificity, AUC) [21]. Hosmer-Lemeshow p value was used to evaluate the model calibration.

After development of the HR model, the discriminatory power of single blood cytokine levels was investigated. Therefore, the AUC values were calculated for four different time points per cytokine: 9:00 p.m., 0:00, 3:00 a.m. and 6:00 a.m. Afterwards, logistic regression (Statistics toolbox in Matlab) was used to investigate whether the HR model could be improved by adding values of single blood cytokine levels or in more practical terms it was tested whether it is clinically relevant to measure blood cytokine levels in addition to available heart rate recordings for obtaining a more accurate classification of infected patients. The HR model was extended with the most significant cytokines ($p < 0.1$). Finally, the added value of features based on the blood cytokine time series was examined. First, the most predictive features of the cytokine time series were selected based on a bootstrap procedure (see bootstrapping procedure described above for feature selection of heart rate based features). Afterwards, again logistic regression (Statistics toolbox in Matlab) was used to investigate whether the HR model could be ameliorated by adding features of the blood cytokine time series.

RESULTS

Patients

39 subjects, of whom serum from the night-time serial blood sampling was available for cytokine quantification, were included in this study [age (mean $\pm$ SD): 59 ± 17 ; BMI (mean $\pm$ SD): 26 ± 5 ; sex: 26 M and 13 F]. According to the CDC criteria, 16 patients were defined as infected and the other 23 subjects were defined as non-infected (see Table 1). Five of the non-infected subjects were healthy volunteers.

Classification of infected patients based on heart rate time series

As described in the methods section, decision trees were calculated based on all the heart rate based features for each of the 1000 bootstrap samples. Two parameters were present in more than 40% of the calculated trees: the mean of the fast dynamics of the heart rate and the mean of the raw heart rate time series. Therefore, a decision tree was determined for a combination of these two parameters (i.e. the HR model). Figure 1 shows the scatter plot of the HR model. The sensitivity and specificity of the HR model were 88% (95% confidence interval of bootstrap samples: [0.69-1.00]) and 88% (95% confidence interval based on bootstrap samples: [0.68-1.00]),

respectively. The corresponding AUC was 0.88 (95% confidence interval based on bootstrap samples: [0.77-1.00]). The model had good calibration with 0.09 Hosmer-Lemeshow p value.

Added value of static blood cytokine levels

First, the discriminatory power of single blood cytokine levels was assessed. Therefore, the AUC values were calculated for four different time points per cytokine: 9:00 p.m., 0:00, 3:00 a.m. and 6:00 a.m. All the AUC values are listed in Table 2. None of the cytokines has an AUC value, which is significantly higher than 0.5 showing very weak discriminatory power for classification of infected patients based on single cytokines. Afterwards, we tested whether the accuracy of the decision tree based on the two heart rate parameters could be improved by adding single cytokine blood level values. In a multivariate logistic regression model for infection, in addition to the 2 selected heart rate features, four cytokines had a p value below 0.1: IL-1b, IL-4, IL-10 and IL-12. Bootstrapping was applied to quantify the added value of a decision tree based on all these features (four cytokines + two heart rate features) compared with the HR model (the tree based on only the two heart rate parameters). Therefore, we calculated for each bootstrap sample, the AUC value of a tree based on only the two heart rate measures (AUC_{HR}) and the AUC value of a tree based on the two heart rate measures with the four selected cytokines ($AUC_{HR+cyto}$). The difference between both AUC values ($AUC_{HR} - AUC_{HR+cyto}$) was calculated for all bootstrap samples. The 95% confidence interval based on the differences for all bootstrap samples is [-0.0881 to 0.0883]. Zero is part of this interval showing that there is no significant additional value of adding the cytokines to the generated decision tree model.

Added value of blood cytokine time series

In comparison with the single blood cytokine levels, more detailed information can be obtained by quantification of the complete blood cytokine time series. Figures showing the median time series of all subjects for each cytokine with the corresponding lower detection limit of the used immunoassay are given in Online Resource 1. To investigate the added value of using blood cytokine time series, all the metrics as described in the methods section were calculated based on these time series. Again bootstrapping was used to find the most predictive features. Five parameters were present in more than 10% of the 1000 calculated trees: the minimum of IL-1B of the raw time series, the sample entropy of IL-2 of the raw time series, the cumulative sum of IL-2 of the detrended time series, the cumulative sum of IL-10 of the detrended time series and the cumulative sum of IL-12 of the detrended time series. The AUC values of these features are summarized in Table 3. The cumulative sum

of the detrended time series was the marker with the highest discriminatory power ($AUC > 0.70$ for IL-10, IL-2 and IL-12). This is a marker for amplitude increases in time series fluctuations [15]. However, logistic regression showed that none of these five markers had a significant added value, when they were added to the heart rate model ($p > 0.1$ for all five features). This result confirmed that the decision tree based on the heart rate time series could not be improved by information of the cytokine time series.

DISCUSSION

In this study we investigated the discriminatory power of information captured by cytokine and heart rate time series to distinguish infected ICU patients from non-infected ICU patients and/or healthy control subjects. We found that among the ICU patients, heart rate was a better marker for infection than information captured by the cytokine time series. Heart rate characteristics appeared to be non-specific but sensitive markers for infection. Based on the bootstrap procedure, two features were selected for the decision tree model: the mean of the raw heart rate signal and the mean of the fast dynamics of the heart rate time series. Infected patients revealed higher values for both parameters (Fig. 2). The mean of the detrended heart rate time series (or fast dynamics) can be seen as a measure for signal asymmetry. When the fast fluctuations of the time series are symmetrical, this marker is expected to be zero. When this marker is higher than zero, the fast fluctuations tend to higher heart rate values. Figure 2 shows an example of standardised time series for an infected and a non-infected patient. These plots illustrate that the fast fluctuations are more symmetrical distributed for the non-infected patients. So far, only a limited number of studies quantified asymmetry in physiological signals [23]. This study indicates that this feature deserves more attention in future studies. Interestingly, this decision tree model could not be improved by including information of single cytokine blood levels nor cytokine time series. These results suggest that the determination of cytokine blood levels with a high sample frequency will not lead to a more accurate detection of infection in the ICU setting. This result is unexpected since cytokines are key players in the regulation of the body's response to infection [24]. However, it is known that cytokine blood levels can also be induced by non-infectious conditions [25-28], which complicates the use of cytokines for infection monitoring purposes. Moreover, depending on the kind of pathogen, the stage of infection and the site of infection the individual responses can be very different [29]. The results of this study suggest that the predictive value of (expensive) biomarkers should always be weighed against the routinely monitored data, and such biomarkers have to demonstrate added value.

Several limitations of this study should be noticed. First, a small dataset was used and therefore the obtained results should be confirmed by larger studies. Secondly, short time series were used for which the stage of the infection was not known. This is an inherent limitation of this clinical setting in practice, since the exact onset of infection cannot be measured. Therefore, it was impossible to identify markers related with the start of infection. Longer time series with samples before and after the infection would allow to analyse the initial phase and the different stages of the infection. A third remark is that heart rate can never be a very specific marker, since it is known that heart rate increases in response to a wide range of other stimuli of the body.

Several studies advocate the use of a dynamic system approach, which focuses on the simultaneous dynamic analysis of many parameters and their interactions [30, 31]. In this study, we found no added value in the combination of heart rate characteristics and cytokine time series characteristics. In future studies, these parameters should be investigated in combination with dynamic analyses of other markers such as blood temperature, white blood cells, PCT, CRP, etc. Such a dynamic system approach would potentially allow determining the individual dynamic infection state in a more detailed way and could be used to guide interventions for early treatment of infection (e.g. administering antibiotics).

AUTHORS' CONTRIBUTIONS

TT, GVdB and GM designed the study and interpreted the results. EB and HV performed the blood sampling in patients and healthy volunteers. TH and MB quantified the serum cytokine concentrations. PM and GM performed the infection scoring, and obtained the informed consents from the patients. FG and GM supervised the machine learning analyses. JMA and DB supervised the time series analyses. TT did the data analyses. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

ETHICAL STANDARDS

The study was approved by the Institutional Ethical Review Board of the University Hospitals Leuven (ML6625).

INFORMED CONSENT

Written informed consent was obtained from the patients' next of kin and from the healthy volunteers.

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Table 1 Detailed overview of patient information

Subject n°	Age	Sex	BMI	ICU Survival?	Hospital Survival?	Length of stay at ICU (days)	Length of stay at hospital (days)	Day of stay at the ICU at the time of blood profile	Infection at admission ICU?	Infection at day of blood profile?	APACHE II score	Type of infection at the time of blood profile ^b
1	30,0	V	24,2	Yes	Yes	9	9	4	Yes	Yes	42	PL
2 ^a	61,4	M	21,8	Yes	Yes	/	/	/	No	No	/	/
3 ^a	57,7	M	24,7	Yes	Yes	/	/	/	No	No	/	/
4 ^a	55,2	M	22,9	Yes	Yes	/	/	/	No	No	/	/
5	72,6	M	18,7	Yes	Yes	16	32	9	No	Yes	38	PL
6	52,8	V	27,6	Yes	Yes	12	25	7	Yes	Yes	34	BS, PL, GI
7	27,1	M	24,2	Yes	Yes	7	32	4	Yes	Yes	29	SS, BS, PL, GI
8	52,4	M	19,6	No	No	10	10	6	Yes	No	46	/
9	85,9	M	23,4	Yes	No	15	60	5	Yes	No	45	/
10	52,7	M	24,9	Yes	Yes	396	424	5	Yes	No	35	/
11	45,8	M	25,7	Yes	Yes	21	33	3	Yes	Yes	32	SS
12	84,4	M	24,1	Yes	Yes	31	53	3	No	No	40	/
13	46,4	M	31,0	Yes	Yes	15	26	4	No	No	32	/
14	48,4	V	27,6	Yes	Yes	12	43	5	No	Yes	39	BS
15	69,1	M	22,9	Yes	No	12	32	3	Yes	No	39	/
16	44,4	V	20,8	Yes	Yes	8	33	2	Yes	No	38	/
17	29,6	V	19,6	Yes	Yes	22	34	2	Yes	Yes	37	GI
18	30,6	M	23,1	Yes	Yes	10	64	2	Yes	Yes	33	BS, CV
19	58,6	M	23,4	Yes	Yes	17	45	5	Yes	No	36	/
20	67,7	M	29,0	Yes	Yes	14	60	3	No	Yes	43	BS
21 ^a	53,8	V	26,4	Yes	Yes	/	/	/	No	No	/	/
22 ^a	59,0	V	21,8	Yes	Yes	/	/	/	No	No	/	/
23	60,1	V	35,2	Yes	Yes	59	59	4	Yes	No	34	/
24	85,5	M	24,7	Yes	Yes	7	67	3	Yes	No	44	/
25	54,1	M	20,8	Yes	Yes	6	6	1	No	No	34	/
26	79,8	V	31,6	Yes	Yes	17	73	2	Yes	Yes	37	GI
27	78,4	V	25,0	Yes	Yes	8	35	3	Yes	Yes	32	CV
28	35,3	V	30,5	Yes	Yes	10	19	5	No	No	31	/
29	56,4	M	27,8	Yes	Yes	19	27	8	No	No	35	/
30	60,9	M	37,0	Yes	Yes	32	54	7	Yes	Yes	33	PL, GI
31	73,5	M	24,8	Yes	Yes	9	27	1	No	No	36	/
32	78,1	M	27,8	Yes	No	11	30	5	Yes	No	39	/
33	64,6	M	21,0	Yes	Yes	23	131	3	No	No	37	/
34	59,3	M	18,0	Yes	Yes	3	22	1	Yes	Yes	36	PL
35	36,5	V	30,4	Yes	Yes	11	44	2	Yes	Yes	29	PL
36	79,8	V	40,0	Yes	Yes	8	37	1	Yes	Yes	41	PL
37	88,3	M	34,4	Yes	Yes	26	50	4	No	Yes	37	PL
38	60,5	M	24,9	No	No	17	17	2	No	No	32	/
39	54,9	M	25,1	No	No	16	16	5	Yes	No	38	/

^a Subject of healthy control group;^b PL= Pneumonia or lower respiratory tract infection other than pneumonia; GI = Gastrointestinal infection; CV= Cardiovascular system infection; BS = Bloodstream infection; SS = Surgical site infection.

Table 2 Overview of AUC values with bootstrapped confidence intervals (CI) for all cytokines at four different time points: 9:00 p.m., 0:00, 3:00 a.m. and 6:00 a.m.

Time	9:00 p.m.		0:00		3:00 a.m.		6:00 a.m.	
	AUC	CI	AUC	CI	AUC	CI	AUC	CI
IL-1b	0,54	[0,35-0,72]	0,57	[0,33-0,70]	0,52	[0,32-0,71]	0,49	[0,31-0,70]
IL-2	0,52	[0,34-0,72]	0,54	[0,35-0,74]	0,48	[0,30-0,67]	0,58	[0,32-0,72]
IL-4	0,64	[0,40-0,77]	0,58	[0,40-0,77]	0,49	[0,31-0,69]	0,55	[0,32-0,70]
IL-5	0,52	[0,33-0,71]	0,52	[0,32-0,73]	0,54	[0,34-0,73]	0,59	[0,40-0,78]
IL-6	0,49	[0,30-0,70]	0,47	[0,28-0,67]	0,44	[0,26-0,64]	0,44	[0,25-0,64]
IL-10	0,48	[0,29-0,67]	0,48	[0,27-0,69]	0,51	[0,31-0,69]	0,61	[0,35-0,74]
IL-12	0,58	[0,40-0,77]	0,58	[0,40-0,76]	0,50	[0,31-0,70]	0,54	[0,33-0,72]
IL-13	0,58	[0,33-0,70]	0,53	[0,35-0,73]	0,58	[0,39-0,78]	0,51	[0,32-0,71]
IFNg	0,52	[0,32-0,71]	0,55	[0,37-0,74]	0,49	[0,30-0,69]	0,52	[0,33-0,70]
TNFa	0,54	[0,36-0,74]	0,64	[0,41-0,78]	0,54	[0,32-0,70]	0,59	[0,33-0,72]

Table 3 Overview of AUC values with bootstrapped confidence intervals (CI) for the selected feature based on the cytokine time series

Feature of the cytokine time series	AUC	CI
The minimum of IL-1B of the raw time series	0.63	[0.44 0.82]
The sample entropy of IL-2 of the raw time series	0.59	[0.39 0.79]
The cumulative sum of IL-2 of the detrended time series	0.76	[0.60 0.93]
The cumulative sum of IL-10 of the detrended time series	0.72	[0.53 0.90]
The cumulative sum of IL-12 of the detrended time series	0.71	[0.52 0.91]

Fig. 1 Scatter plot of results for the HR model (a decision tree based on mean of the raw heart rate and the mean of the high frequent heart rate component). Circles represent the infected patients, whereas stars indicate non-infected patients. All stars/circles within the white area will be classified by the decision tree model as infected. Stars/circles within the grey area will be classified as non-infected.

Fig. 2 Raw heart rate signal, standardised heart rate signal and fast dynamics of heart rate signal (i.e. standardized and detrended time series) for an infected (*left*) and an non-infected (*right*) patient. In the *middle plots*, the trend model is represented by a *black line*

Online Resource 1 *This pdf contains figures showing the median time series of all subjects ($n = 39$) for each cytokine with the corresponding lower detection limit of the used immunoassay.*