Sleep Science

ORIGINAL ARTICLE

Disruptions in 24-hour profile of hemodynamic parameters in severe sepsis and septic shock

Distúrbios no perfil circadianos de paramêtros hemodinâmicos na sepse grave e no choque séptico

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ABSTRACT

Objective: Circadian disruptions in septic patients, and their relation to clinical outcome, have been described by several researchers. **Methods:** In this work we performed an individual analysis of hemodynamic variables (cardiac frequency and mean blood pressure) in three groups of patients: severe sepsis, septic shock and individuals housed in the same intensive care unit by causes other than inflammation or infection, as controls, during the first and the last 24 hours of their permanency in the critical care unit. **Results:** Although the cosinor analysis showed no difference in the proportion of patients that expressed a statistically significant circadian rhythm, during the first 24 hours, the phase of the variations were disrupted in both septic groups, being almost in anti-phase as compared to control individuals. During the last 24 hours, this variation was present only for mean blood pressure. No association of these changes could be related to outcome (surveillance). **Conclusion:** We conclude that disruptions in circadian rhythms in patients during severe stages of sepsis are related to phase better than presence/absence of variation, which could be crucial to time scheduled therapies.

Keywords: Keywords are missing.

RESUMO

Objetivo: Distúrbios circadianos em pacientes sépticos e suas relações com desfechos clínicos têm sido descrito por diversos pesquisadores. **Métodos:** No presente trabalho nós conduzimos uma análise individual das variáveis hemodinâmicas (frequência cardíaca e pressão arterial média) em três grupos de pacientes: sepse grave, choque séptico e indivíduos internados na mesma unidade de tratamento intensivo por outras causas além de inflamação ou infecção, como controles, durante as primeiras e últimas 24 horas de suas permanências na unidade. **Resultados:** Embora a análise por meio do cosinor não tenha apresentando diferença na proporção de pacientes que expressaram um ritmo circadiano estatisticamente significativo, durante as primeiras 24h, a fase das variações estavam alteradas em ambos os grupos sépticos, sendo quase observada anti-fase quando comparados com indivíduos controle. Nas últimas 24h essa variação esteve presente apenas na pressão arterial média. Associações destas alterações não foram relacionadas a outros desfechos. **Conclusão:** Concluímos que alterações nos ritmos circadianos em pacientes durante estágios graves da sepse estão mais bem relacionados a fase do que à presença ou ausência de variações, as quais podem ser cruciais para o agendamento de terapias.

Descritores:

INTRODUCTION

Sepsis is one of the most important causes of mortality in critical care units. Despite advances in monitoring the condition and in related therapeutics, mortality still remains high, rising between 30 and 50 percent[1]. One explanation is the multiorganic failure developed in critical stages (severe sepsis and septic shock), which determines disarrangements in organic physiology[2]. An important part of this complex misalignment is circadian organization. Several works have suggested a blunting of daily variation in several variables, including 6-sulfatoximelatonin (the urinary metabolite of melatonin), leptin, cortisol and adrenocorticotrophin[3,4].

Several of these descriptions, however, have been performed without specific chronobiological methodologies (hourly population means, instead of individual descriptions), thus leaving valuable information out of the evaluation, such as changes in phase or amplitude of the variation. Moreover, these endocrine variables, although representing an important marker of circadian status and/or physiological homeostasis, are not directly related to pathological outcome in critically ill patients as hemodynamic variations, which are indeed crucial to surveillance in septic patients.

In this work we aimed to perform an individual analysis of circadian organization of cardiac frequency and mean blood pressure in patients housed in a critical care unit, during the course of severe sepsis and septic shock, as well as to search for associations of time-dependent changes with survival. Data were compared to patients housed in the same unit with no diagnosis of infectious or inflammatory disease. Since the course of sever sepsis and septic shock changes over time, we performed this analysis during the first and the last 24 hours of hospitalization.

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MATERIALS AND METHODS

Patients

Patients were recruited in the adult intensive care units of Prof. A. Posadas Hospital, Haedo, Bs. As., Argentina (PH), and La Trinidad Hospital (TH), San Isidro, Bs. As., Argentina, diagnosed with sever sepsis and septic shock, according to the American College of Chest Physicians-Society for Critical Care Medicine Consensus Conference Committee and its modifications(5,6). The time elapsed in the unit was less than 3 days, so as to avoid confounding variables related to extended permanence. Exclusion criteria were for patients younger than 16 and older than 60 years old, patients diagnosed with any kind of immunodeficiency, psychiatric or neurological disease, encephalocranial trauma, and also patients under treatment with corticosteroid, immunosuppressant, non-steroid antiinflammatory or psychiatric drugs other than benzodiazepines.

Patients with a previous history of night work were also excluded. Severe sepsis was defined as a systemic inflammatory response syndrome (two or more of these criteria: cardiac frequency > 100/minute, respiratory frequency > 20/minute or pCO_2 < 32mmHg, plasma neutrophils > 12000 or < 4000 cells/mm^3, core temperature > 38.3ºC or < 35.6ºC) due to an infection with failure of at least two organs, while septic shock corresponded to a multiorganic failure due to a systemic inflammatory response syndrome with hemodynamic instability that require inotropic support[5,6].

For the control group, we included patients housed in the same critical care units with no diagnoses of systemic inflammation, sepsis, severe sepsis nor septic shock, with the same exclusion criteria of the study groups.

In total, 11 patients with septic shock, nine with sever sepsis, and 10 controls were included in the study. The inotropic drugs used in shocked patients were dopamine, noradrenaline and dobutamine, in different combinations, as required.

Ethical considerations

This study was approved by the corresponding ethical committees of the involved institutions. Informed consent was given by the patient or a first degree relative, according to patients' consciousness level.

Blood pressure and cardiac frequency data acquisition

In septic patients, data was obtained via an endovascular catheter, with a measurement frequency of 15 minutes, over a multiparametric monitor (Agilent, Philips® or Criticon, Johnson & Johnson®). Data from the control group was obtained non-invasively, automatically every 15 minutes, with the cuff connected to a similar multiparametric monitor.

Statistical analysis

Modeling of 24-hour variation was performed with the Cosinor method. This is a traditional mathematical waveform modeling method, widely used in chronobiology. It expresses the variation in terms of period, phase and amplitude, according to the formula $y = M + A\cos(f+wt)$, were M corresponds to mesor (*m*ean *e*stimated *o*ver *r*hythm), A is the amplitude, which corresponds to half the difference between maximum and minimum values of the adjustment curve, f represents the acrophase (time of peak), t is time, and w represents angular velocity, that in a rhythm with a period of 24 hours is 2p/24 = 0,2618 radians/h; f can be turned in hours dividing it by w. Adjustment curves with $p < 0.05$ were considered as statistically significant, corresponding to the presence of a circadian rhythm. Amplitude and acrophase of the rhythm were analyzed only in individuals with circadian rhythm present.

Comparisons among proportions were done with Fisher's exact test, and differences among numerical data were performed with ANOVA test (according to normality distribution of data, which was analyzed with the combination of Shapiro-Wilk test and visual examination of normality curve and box plot, by at least two entrained researchers, and the comparison of standard deviations with F test), with Bonferroni's post-hoc evaluation. Analysis of the proportion of patients that change their status of being with or without circadian rhythm, between the first and the last 24 hours of the study, was performed with McNemar's test. In all evaluations the alpha value was set at 0.05.

RESULTS

Population characteristics

No statistically significant difference was found among groups regarding age (mean ± SEM, 56.3 ± 6.1 in septic shock, 43.8 ± 12.9 in severe sepsis and 61.7 ± 9.3 in controls) and gender (female/male, 8/3 in septic shock, 6/3 in sever sepsis and 7/3 in controls). In addition, about half of the members of each group were housed in each of the institutions. Etiologies found in septic patients were peritonitis, acute cholecystitis, mediastinitis, miliary tuberculosis or renal abscess, while in the control group patients were diagnosed with unstable angor, severe asthmatic crisis, lung thromboembolism, congestive heart failure and pre-eclampsia.

Presence/absence of circadian variations

The analysis of the first 24 hours spent in the intensive care unit did not reveal statistically significant differences among the three groups concerning the proportion of individuals with circadian variation in cardiac frequency nor in mean blood pressure (Table 1). Moreover, the analysis of the last 24 hours in the ICU did not show any difference among the population under study. Indeed the evaluation of how many patients lost, restored, or sustained circadian rhythmicity did not show statistical differences. However, it is interesting to note that only 50-60% of all patients (regardless of the group) showed significant diurnal rhythms in heart rate and blood pressure, suggesting that the conditions of the ICU are important disruptors for the circadian system, as has been suggested in previous studies[7].

Table 1. Presence, amplitude and acrophase of circadian rhythms in cardiac frequency and mean blood pressure in septic shock, severe sepsis and controls, during the first and the last 24 hours spent in an intensive care unit.

	Septic shock	Severe sepsis	Controls
Cardiac frequency Presence of circadian rhythm			
first day	63.6%	55.6%	60.0%
last day	63.6%	55.6%	50.0%
Amplitude (beats/minute)			
first day	15.16 ± 1.75 (n = 7)	12.30 ± 1.74(n = 5)	15.38 ± 3.43 (n = 6)
last day	13.66 ± 3.45 (n = 7)	13.68 ± 5.74(n = 5)	10.91 ± 2.33 (n = 5)
Acrophase (hours)			
first day	00.90 ± 1.54 (n = 7)*	19.52 ± 3.07(n=5) *	10.50 ± 1.13 (n=6) *
last day	16.31 ± 3.13 (n = 7)	17.38 ± 4.44(n=5)	16.28 ± 3.57 (n=5)
Mean blood pressure Presence of circadian rhythm (%)			
first day	54.6%	55.6%	60.0%
last day	54.6%	44.4%	40.0%
Amplitude (mmHg)			
1st. day	24.34 ± 9.58 (n = 6)	16.86 ± 5.12(n = 5)	19.65 ± 3.92 (n = 6)
last day	8.59 ± 1.00 (n = 6)	14.70 ± 2.00 (n = 4)	11.51 ± 2.89 (n = 4)
Acrophase (hours)			
1st. day	22.10 ± 1.25 (n = 6)*	02.80 ± 1.10(n = 5)*	12.25 ± 1.44 (n = 6)*
last day	00.89 ± 1.70 (n = 6)**	23.60 ± 4.08(n = 4)**	12.87 ± 2.31 (n = 4)**

Data is shown as mean ± SEM. For amplitude and acrophase, each group's n is shown between brackets, and corresponds to the percentage of individuals with significant circadian rhythm shown in this table. * $p < 0.001$ and ** $p < 0.02$ for ANOVA. Post-ANOVA Bonferroni's test for comparisons of cardiac frequency (1st. day) in septic shock vs. controls, $p < 0.001$, and in severe sepsis vs. controls $p < 0.02$. Comparisons of mean arterial pressure the 1st. day, $p < 0.001$ in septic shock vs. controls, and severe sepsis vs. controls; $p < 0.02$ in septic shock vs. controls, and $p < 0.05$ in severe sepsis vs. controls.

Amplitude and phase of circadian variations

We performed an evaluation of the characteristics of the waveform-adjusted variations. Amplitude and acrophase (time of peak) were analyzed in patients with statistically significant circadian rhythmicity.

In the case of amplitude, no difference in any hemodynamic variable was found among the three groups even in the first or the last 24 hours spent in the ICU. On the other hand, the analysis of the acrophases did show important differences. As described in Table 1, during the first 24 hours in the intensive care unit, the time of peak in both sepsis groups was in antiphase (i.e., with a difference close to 12 hours) with respect to the control group, for both cardiac frequency and mean blood pressure. The analysis of the last 24 hours, showed the same difference for mean blood pressure, but not for cardiac frequency. It is important to note that the times of peak found for the control group in all data series analyzed, were similar to that found in normal healthy subjects[8].

Association of disruptions to outcome

In order to know whether the different phases in cardiac frequency and mean blood pressure rhythm found in septic patients were related to differences in survival rates, we performed Fisher's test to compare diagnosis of surveillance or mortality in patients and controls with phase or antiphase oscillation (time of peak between 6 to 18 hs –daily-, and between 18 and 6 hs –nightly-, respectively) during the last 24 hours of recordings. No differences were found.

DISCUSSION

Time dependency in intensive care units has long been studied in medicine, because of the particular dynamics required for the management of critical patients[9]. Indeed, many works have described a significant decrease in both patients and staff health status and quality of life, as well as a tendency to increase errors in clinical decisions and order execution[3,7,10-13].

As suggested in previous works[3,4], we found a long proportion of individuals with absent circadian variation in the severe sepsis or septic shock groups, however, despite those descriptions, the individual mathematical modeling used in this work showed no differences with non-septic subjects: about half of the whole population expressed statistically significant circadian rhythms. This relatively low percentage of individuals with circadian variations in hemodynamic variables might be related to the intrinsic environmental characteristics of the ICU, which include constant illumination, a relatively noisy environment and frequent disruptions because of clinical procedures. Instead, we did find differences in the timing of the rhythms under study (in particular, in the acrophase or time of maximum value). The fact that the values shown in control subject (midday peak) are similar to that described in normal general population supports the validity of the analysis[8].

This different nature of circadian disruption in patients with severe sepsis and septic shock can be explained from the different methodology performed. In previous

works, daily variations were analyzed from population hourly means. The fact that we found shifted times of peak suggests that, for each hour, there could be a co-existence of patients with maximum levels and patients with minimum levels of the variable analyzed, which determines an almost similar hourly mean with a large degree of variability, and a false definition of absence of time-dependent variation. It is also important to note that the population tested in our work differs from others (severe stages of sepsis and sepsis, respectively), as well as the variable analyzed (hemodynamic measurements and endocrine parameters, respectively), which could contribute to the differences between our results and those published elsewhere[3,4].

The methodology of analysis of group means is a good tool for the study of circadian modifications that are expressed simultaneously in the population, when similar changes are expected to be found. Our analysis suggests that this is not the appropriate statistical methodology for septic patients.

It is difficult to find a clear explanation for such a large difference in the times of peak (close to 12 hours). Since the analysis of the first 24 hours does not represent the acute beginning of the pathologic processes, but the first day in the critical care unit, we cannot conclude whether this is the result of a previous phase shift of blood pressure and cardiac frequency rhythms. It was also surprising to find a different evolution of these phase shifts in the two variables. During septic state, physiopathology changes over time[2], so our results could be the consequence of a different sensitivity of the two systems to immune signals, as described in animal models of the pathology[14,15].

In our study, the changes in acrophase of hemodynamic variables were not associated with the natural evolution of the pathology (i.e., survival rates). However, a larger population should be studied in order to draw more definite conclusions. It is important to emphasize that survival analysis was performed during the last day of surveillance. Only patients that stayed up to 3 days in the intensive care unit (both because of good response to treatment or decease) were analyzed, without the cooresponding follow-up after leaving the hospital. In addition, a more profound evaluation of quality of life parameters (including the quality of the sleep-wake cycle) and time for recovery and disappearance of symptoms should be performed.

No statistically significant difference was found among groups regarding age; although a note of caution should be stated, since this may be due (at least in part) to the high variability among subjects; again, sampling of a larger population might yield an age-dependent difference in hemodynamic parameters.

Another important finding is the coincidence of disruptions developed in both sepsis groups (i.e., severe sepsis and septic shock). We hypothesized that the septic shock group would develop more profound alterations than the severe sepsis group, because although in both stages there is a multiorganic damage, septic shock includes by definition a hemodynamic failure; moreover, this pathological stage determines the requirement of inotropic treatment which could also affect measurements. Notwithstanding, the similarity between the two groups suggests a strong compromise of immune signals in the generation of phase disruption, rather than a pharmacologically-related failure.

The timing of circadian rhythms (including phase-shifting) constitutes a very important aspect of health care in patients, because it could represent that "external time" (i.e., environmental hours) does not coincide to "internal time" (i.e., endogenous timing related to the circadian clock). In such a case, the timing of drug is not preserved, which, in some cases is crucial to its mechanism of action[16,17]. It is important to note that there have been many efforts to control environmental timing in patients housed in critical care units, with scheduling of switching lights on and off, isolation of patients and training of health practitioners[7,11,12,18,19]. More descriptions of circadian rhythms in septic patients are definitively needed to better understand what happens in time-dependent physiopathology and to define the steps to be taken according to individual differences in the chronobiology of the patients.

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