Circadian rhythm in critically ill patients: Insights from the eICU Database

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OBJECTIVE To investigate the circadian variation among critically ill patients and its association with clinical characteristics and survival to hospital discharge in a large population of patients in the intensive care unit (ICU).

METHODS Circadian variation was analyzed by fitting cosinor models to hourly blood pressure (BP) measurements in patients of the eICU Collaborative Research Database with an ICU length of stay of at least 3 days. We calculated the amplitude of the 24-hour circadian rhythm and time of the day when BP peaked. We determined the association between amplitude and time of peak BP and severity of illness, medications, mechanical intubation, and survival to hospital discharge.

RESULTS Among 23,355 patients (mean age 65 years, 55% male), the mean amplitude of the 24-hour rhythm was 4.5 ± 3.1 mm Hg. Higher APACHE-IV scores, sepsis, organ dysfunction, and mechanical ventilation were associated with a lower amplitude and a shifted circadian rhythm ($P < .05$ for all). The timing of the BP peak was associated with in-hospital mortality ($P < .001$). Higher BP amplitude was associated with shorter ICU (2 mm Hg amplitude: 7.0 days, 8 mm Hg amplitude: 6.7 days) and hospital (2 mm Hg amplitude: 11.8 days, 8 mm Hg amplitude: 11.3 days) lengths of stay and lower in-hospital mortality (2 mm Hg amplitude: 18.2%, 8 mm Hg amplitude: 15.2%) ($P < .001$ for all).

CONCLUSION The 24-hour rhythm is dampened and phase-shifted in sicker patients and those on mechanical ventilation, vasopressors, or inotropes. Dampening and phase shifting are associated with a longer length of stay and higher in-hospital mortality.

KEYWORDS Circadian variation; Circadian rhythm; Chronobiology; Critical illness; Cosinor analysis

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Introduction

Many physiological variables fluctuate over time according to circadian rhythms. Under normal conditions, this is thought to facilitate synchronization[1] and optimal preparation for recurring tasks, thereby conveying a survival advantage.[2] In critically ill patients, however, the circadian variation of many variables is altered[3,4] owing to various interventions, including ventilation and medication administration, environmental factors such as light and noise, and critical illness itself.[5,6] The degree of alteration may be correlated with the severity[1] and outcome[7] of the disease.

Different surrogate markers have been used in limited, small study populations to assess the circadian rhythm in critically ill patients, including melatonin secretion[8,9] and core body temperature.[1] While many of these parameters are often only intermittently obtained in routine clinical settings, the widespread use of the electronic health record has made high-resolution clinical data available through a variety of sources.[10] Variables such as blood pressure (BP) are well known to exhibit circadian variation in healthy individuals,[11] but data on their prognostic value in critically ill patients are limited.

Recently, decreased fluctuations between day and night BP have been associated with increased mortality in critically ill patients.[7] While important, a simple estimate of BP difference between predetermined day and nighttime intervals might fail to take into account more complex changes in the circadian rhythm. These limitations might be overcome by using cosinor analyses to fit sine waves to the time series of parameters of interest.[12] In addition to the magnitude of the daily variations (amplitude), cosinor analysis techniques also

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KEY FINDINGS

- Circadian variation can be studied using high-resolution clinical data such as blood pressure values. Cosinor models can be used to characterize the 24-hour circadian rhythm by identifying the 24-hour blood pressure amplitude and the time to 24-hour peak blood pressure.
- A variety of parameters, including the illness characteristics such the APACHE-IV score, sepsis, and organ dysfunction and interventions such as mechanical ventilation or treatment with vasopressors and inotropes, affect the circadian rhythm. However, the contribution of each individual parameter is very small.
- Changes in the circadian rhythm are associated with adverse clinical outcomes including longer length of stay and higher in-hospital mortality even after adjustment for other markers of severity of illness. Characterization of the circadian rhythm might help to risk-stratify patients. Future studies are needed to determine whether incorporating predictive models based on high-resolution clinical data in clinical care can improve patient outcome.

allow to estimate the time of the day when peaks and troughs occur.[13,14] The prognostic value of these parameters in critically ill patients is unknown.

The goals of this study were to (1) characterize the circadian variation in critically ill patients by applying cosinor analysis techniques to noninvasive BP time series and (2) to investigate the association of the circadian variation with intensive care unit (ICU) length of stay, hospital length of stay, and in-hospital mortality.

Methods

eICU Collaborative Research Database

The present study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.[15] Data for this study were obtained from the eICU Collaborative Research Database v2.0, a large multicenter critical care database made available by Philips Healthcare in partnership with the MIT Laboratory for Computational Physiology.[16,17] The database is populated with clinical information from many critical care units throughout the continental United States, covering patients who were admitted to ICUs in 2014 and 2015.

Ethical approval

The research reported in this paper adhered to the Helsinki Declaration as revised in 2013. This study was exempt from institutional review board approval owing to the retrospective design, lack of direct patient intervention, and the security schema for which the reidentification risk was certified as meeting Safe Harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2). The data extraction queries and code are available online at https://github.com/cmsalgado/circadian.

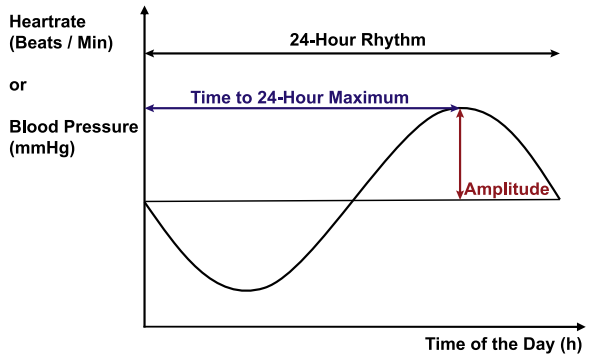

Figure 1 Circadian rhythm. The figure shows the assessment of the time to the 24-hour maximum and the amplitude. The amplitude is the difference between the maximum and the average.

Inclusion and exclusion criteria

We included all patients with an ICU length of stay of at least 72 hours and with at least 6 recorded BP values per day to improve detection of a circadian rhythm. We excluded patients with multiple hospital admissions, as there is no systematic method to determine the order of each patient's admissions in the eICU database. We also excluded patients with missing covariates. If patients were admitted to the ICU more than once, only the last ICU stay was included in order to preserve independence of the outcomes.

Data preprocessing

Both the length of available data and the sampling rate of noninvasive BP varied across patients. To allow comparison, data across all patients were condensed into hourly measurements by selecting the median value of the available measurements within each hour. This was performed for every hour after ICU admission. BP measurements 3 standard deviations from the mean of the individual's corresponding signal were considered as artifact and excluded from the analysis (0.96% observations excluded).[18]

Cosinor analysis

Details of the cosinor method have been previously described.[12] In brief, cosinor analysis is used to fit a sine wave to the time series with the model specified as $Y = M + A * \cos [2\pi(T-\phi/)/24]$, where Y was the marker value (heart rate or BP), M represented the MESOR (midline estimating statistic of rhythm), A the amplitude, T the time of day in hours, and ϕ the acrophase of the circadian rhythm (Figure 1). Using the Law of Cosines, the model can be reparametrized as follows: $Y = M + A * \cos [2\pi(T-\phi/)/24] = M + A [\cos (2\pi T/24) \times \cos (2\pi\phi/24) + \sin (2\pi T/24) * \sin (2\pi\phi)/24)] = M + \beta_1 * \cos(2\pi T/24) + \beta_2 * \sin(2\pi T/24)$, where $\beta_1 = \text{amp} * \cos(2\pi\phi/24)$ and $\beta_2 = \text{amp} * \sin(2\pi\phi)/24)$. According to the cosinor model, the 3 parameters

MESOR, amplitude, and acrophase characterize the circadian rhythm of BP.

Statistical analysis

Single cosinor models with a 24-hour period were fitted to the BP time series. Single cosinor analysis represents the circadian rhythm of each subject and allows determination of the amplitude of the 24-hour rhythm and the time of day when peaks and troughs occur. We excluded the first 24 hours after ICU admission from the analysis, as the initial stabilization of the patient is expected to lead to considerable changes in BP independent of a possible underlying 24-hour rhythm. For the primary analysis, we determined the circadian rhythm between hours 24 and 72 (ICU days 2 and 3) after ICU admission to allow for enough time to detect a possible 24-hour rhythm. Secondary analyses included the assessment of the circadian rhythm of BP on (1) ICU days 2–4, (2) ICU days 2–5, and (3) ICU days 2–6 to investigate whether longer time intervals improve the detection of a possible 24-hour rhythm. We only included patients with an ICU length of stay that exceeded the time period used to fit the cosinor models in the secondary analyses.

We evaluated the association between clinical characteristics (sex, age, APACHE [Acute Physiology and Chronic Health Evaluation] version IV score as a marker of disease severity [categorized into quartiles], sepsis, organ dysfunction, mechanical ventilation [all assessed at the time of ICU admission], and medications received during the first 24 hours of ICU admission [vasodilators, vasopressors/inotropes, sedatives, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors / angiotensin receptor blocker, diuretics]) and the 24-hour BP rhythm. Differences between groups were tested using linear regression models. We then evaluated the association between 24-hour BP amplitude and time to 24-hour BP peak and (1) in-hospital mortality, (2) ICU length of stay, and (3) hospital length of stay using logistic and linear regression models, respectively. Analyses with ICU and hospital length of stay as outcomes were restricted to patients who survived to hospital discharge. We investigated the relationships between BP rhythm and each outcome by including polynomial terms and defined nonlinearity as a P value of $<.05$ of a likelihood-ratio test comparing the model with the polynomial term to the model including only the linear term. Results are displayed graphically, as there was evidence that most relationships were best modeled using quadratic regression. All analyses were adjusted for all clinical characteristics as detailed above. Covariates were selected *a priori*.

Sensitivity analyses

We compared patients included in the study to those excluded because of an ICU length of stay of less than 3 days. Further, we repeated the primary analysis in patients with a significant 24-hour BP rhythm. Patients with nonsignificant 24-hour rhythms may have poor estimates of the 24-hour amplitude and time to peak and were excluded in the sensitivity analysis. The significance of the circadian rhythm was tested by a zero-amplitude test.[14] We also repeated the analysis in patients with and without missing data to determine the effect of excluding patients with missing data. We used multiple imputation by chained equations to generate 5 complete datasets.[19] We used predictive mean matching with 3 nearest neighbors for continuous variables and logistic regression for binary variables. Rubin's rule was used to pool estimates and standard errors of the beta coefficients as well as predictions.[19] Finally, we repeated the analysis after adjustment for the mean arterial BP during ICU days 2 and 3 to determine the independent effect of the 24-hour rhythm.

We used Python v.2.7 (Python Software Foundation, Wilmington, DE) and STATA v.16 (StataCorp, College Station, TX) for all statistical analyses.

Results

Sample characteristics

Among the cohort of 139,185 adult ICU patients, 28,790 adult patients with 1 hospitalization were admitted to the ICU for at least 3 days. Of these, we excluded 5535 patients because of missing data. The remaining 23,355 patients constituted the study cohort (Figure 2). The mean age was 64.5 years, 55.4% were male. The mean amplitude of the 24-hour BP rhythm was 4.46 ± 3.08 mm Hg. The mean APACHE-IV score was 66.6 ± 27.3. Sepsis was diagnosed in 2507 (10.7%) patients. Organ dysfunction was present in 7581 (32.5%) patients, 10,784 (46.2%) patients were mechanically ventilated, 5631 (24.1%) patients received sedatives, and 4976 (21.3%) patients were treated with vasopressors or inotropes. Overall, 3956 (16.9%) patients died prior to hospital discharge (Table 1).

Association between clinical characteristics and 24-hour BP amplitude

The amplitude of the 24-hour BP rhythm was lower in patients with a higher APACHE score (highest quartile vs lowest quartile: 4.39 mm Hg vs 4.54 mm Hg, $P = .009$), sepsis (4.22 mm Hg vs 4.49 mm Hg, $P < .001$), organ dysfunction (4.34 mm Hg vs 4.51 mm Hg, $P < .001$), patients on mechanical ventilation (4.41 mm Hg vs 4.50 mm Hg, $P = .037$), patients on vasopressors or inotropes (4.09 mm Hg vs 4.56 mm Hg, $P < .001$), patients who did not receive a beta-blocker (4.42 mm Hg vs 4.61 mm Hg, $P < .001$), patients who did not receive an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (4.43 mm Hg vs 4.94 mm Hg, $P < .001$), and patients who did not receive diuretics during the first 24 hours after ICU admission (4.45 mm Hg vs 4.96 mm Hg, $P < .001$) (Table 1).

Association between clinical characteristics and time of peak 24-hour BP

A higher APACHE score was associated with an earlier peak in 24-hour BP (peak at 12.90 hours after midnight in patients in the highest quartile vs 13.63 hours after midnight in

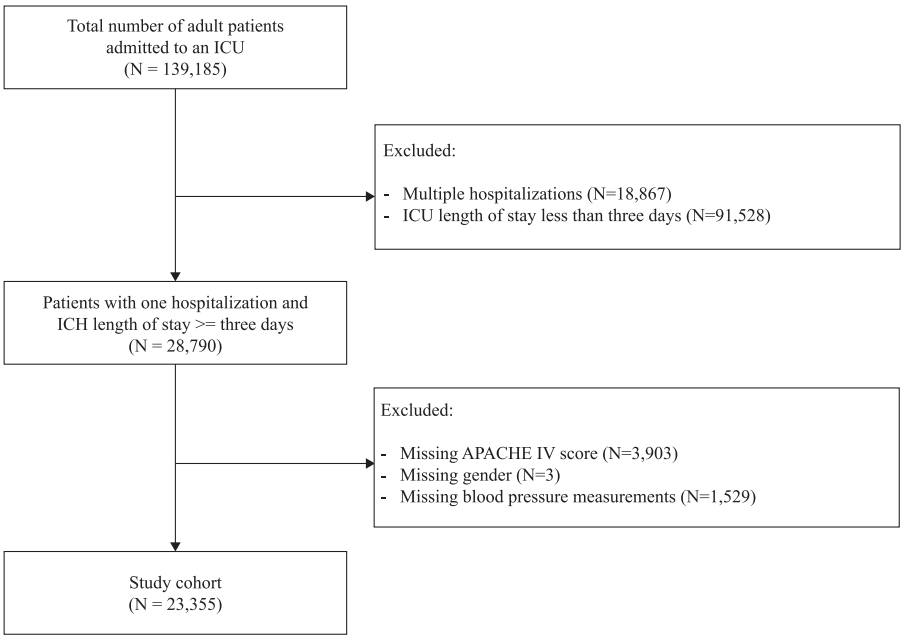

Figure 2 Study cohort. ICU = intensive care unit.

patients in the lowest quartile, $P < .001$). Similarly, sepsis (peak at 12.98 hours vs 13.32 hours, $P = .015$), organ dysfunction (peak at 13.14 hours vs 13.35 hours, $P = .021$), mechanical ventilation (peak at 13.19 hours vs 13.36 hours, $P = .043$), use of vasopressors or inotropes (peak at 12.81 hours vs 13.41 hours, $P < .001$), and no use of diuretics (peak at 13.27 hours vs 14.41 hours, $P = .031$) were also associated with an earlier peak in 24-hour BP (Table 1). The association between clinical characteristics and the 24-hour BP rhythm on ICU days 2–4, 2–5, and 2–6 are shown in Supplemental Tables 1–3.

Association between 24-hour BP rhythm and mortality and length of stay

After adjustment, higher BP amplitude on ICU days 2 and 3 was associated with a shorter ICU length of stay (2 mm Hg amplitude: 7.0 ± 0.05 days, 8 mm Hg amplitude: 6.7 ± 0.06 days), shorter hospital length of stay (2 mm Hg amplitude: 11.8 ± 0.09 days, 8 mm Hg amplitude: 11.3 ± 0.1 days), and lower probability of in-hospital mortality (2 mm Hg amplitude: 18.2% ± 0.03%, 8 mm Hg amplitude: 15.2% ± 0.004%) ($P < .001$ for all) (Figure 3). Higher BP amplitudes on ICU days 2–4 (Supplemental Figure 1), ICU days 2–5 (Supplemental Figure 2), and ICU days 2–6 (Supplemental Figure 3) were similarly associated with a shorter length of stay and lower in-hospital mortality.

The timing of the BP peak was associated with in-hospital mortality ($P < .001$), but not with ICU length of stay ($P = .077$) or hospital length of stay ($P = .465$). In-hospital mortality was lowest in patients with a peak between the times of 16:00 and 20:00 (Figure 3). Results were similar for 24-hour BP rhythm on ICU days 2–4 (Supplemental Figure 1), 2–5 (Supplemental Figure 2), and 2–6 (Supplemental Figure 3).

Sensitivity analyses

Compared to patients with an ICU length of stay less than 3 days, patients included in this study had a higher APACHE score (66.6 ± 27.3 vs 50.1 ± 25.2) and were more often found to have sepsis (10.7% vs 3.8%) and organ dysfunction (32.5% vs 14.5%). Further, patients with an ICU length of stay of at least 3 days were more commonly treated with mechanical ventilation (46.2% vs 14.2%) and vasopressors or inotropes (21.3% vs 7.4%). In-hospital mortality was higher in patients with an ICU length of stay of at least 3 days (16.9% vs 3.1%) (Supplemental Table 4). Results were similar in the subset of patients with a statistically significant 24-hour BP amplitude on ICU days 2 and 3 (Supplemental Table 5 and Supplemental Figure 4) and in the cohort combining patients with and without missing data following multiple imputation of missing variables (Supplemental Table 6 and Supplemental Figure 5). Higher mean arterial BP was associated with a higher 24-hour BP amplitude ($P < .001$), but not with the timing of BP peak ($P = .234$). Results after adjustment for mean arterial BP were similar to the primary analysis. Higher 24-hour BP amplitude during ICU days 2 and 3 was still associated with shorter ICU and hospital length of stay ($P = .015$, $P = .002$, and $P = .019$, respectively). Time to peak 24-hour BP was associated with in-hospital mortality ($P < .001$) but not with ICU length of stay ($P = .055$) or hospital length of stay ($P = .457$).

Discussion

In this analysis of a large multicenter critical care database, we demonstrate that the 24-hour BP rhythm is altered in critically ill patients. The 24-hour BP rhythm was dampened and phase shifted in sicker patients, patients with sepsis and organ dysfunction, and those on mechanical ventilation,

Table 1 Association of baseline parameters with 24-hour blood pressure rhythm on ICU days 2 and 3

Parameter	N (%)	Amplitude (95% confidence interval)	*P* value	Time of peak blood pressure (95% confidence interval)	*P* value
Sex					
Female	10,415 (44.6)	4.52 (4.46–4.58)	.004	13.33 (13.20–13.46)	.333
Male	12,940 (55.4)	4.41 (4.35–4.46)		13.24 (13.13–13.36)	
Age					
40 years	–	4.54 (4.44–4.64)	0.094	13.59 (13.36–13.82)	.004
50 years	-	4.52 (4.44–4.60)		13.51 (13.33–13.69)	
60 years	-	4.50 (4.44–4.56)		13.44 (13.30–13.57)	
70 years	-	4.48 (4.43–4.52)		13.36 (13.26–13.46)	
80 years	-	4.46 (4.42–4.50)		13.28 (13.20–13.37)	
APACHE score					
First quartile	6,093 (26.1)	4.54 (4.46–4.61)	Reference	13.63 (13.46–13.80)	Reference
Second quartile	5,862 (25.1)	4.49 (4.41–4.57)	.415	13.40 (13.23–13.57)	.058
Third quartile	5,574 (23.9)	4.40 (4.32–4.49)	.021	13.18 (13.00–13.35)	<.001
Fourth quartile	5,826 (25.0)	4.39 (4.31–4.47)	.009	12.90 (12.73–13.07)	<.001
Explicit sepsis					
No	20,848 (89.3)	4.49 (4.44–4.53)	<.001	13.32 (13.23–13.41)	.015
Yes	2,507 (10.7)	4.22 (4.10–4.34)		12.98 (12.71–13.24)	
Organ dysfunction					
No	15,774 (67.5)	4.51 (4.46–4.56)	<.001	13.35 (13.25–13.46)	.021
Yes	7,581 (32.5)	4.34 (4.27–4.41)		13.14 (12.98–13.29)	
Mechanical ventilation					
No	12,571 (53.8)	4.50 (4.44–4.55)	.037	13.36 (13.25–13.48)	.043
Yes	10,784 (46.2)	4.41 (4.35–4.47)		13.19 (13.06–13.31)	
Medications received					
Vasodilators					
No	22,568 (96.6)	4.45 (4.41–4.49)	.144	13.28 (13.19–13.37)	.856
Yes	787 (3.4)	4.62 (4.40–4.83)		13.33 (12.86–13.79)	
Vasopressors / Inotropes					
No	18,379 (78.7)	4.56 (4.51–4.60)	<.001	13.41 (13.31–13.51)	<.001
Yes	4,976 (21.3)	4.09 (4.01–4.18)		12.81 (12.62–12.99)	
Sedatives					
No	17,724 (75.9)	4.46 (4.42–4.51)	.570	13.31 (13.22–13.41)	.194
Yes	5,631 (24.1)	4.44 (4.36–4.52)		13.18 (13.01–13.36)	
Beta-blockers					
No	19,079 (81.7)	4.42 (4.38–4.47)	<.001	13.27 (13.17–13.37)	.557
Yes	4,276 (18.3)	4.61 (4.52–4.71)		13.34 (13.14–13.54)	
Calcium channel blocker					
No	22,053 (94.4)	4.46 (4.42–4.50)	.830	13.29 (13.20–13.38)	.338
Yes	1,302 (5.6)	4.44 (4.27–4.61)		13.11 (12.75–13.47)	
ACE inhibitors / ARBs					
No	22,030 (94.3)	4.43 (4.39–4.47)	<.001	13.28 (13.19–13.37)	.859
Yes	1,325 (5.7)	4.94 (4.78–5.11)		13.31 (12.95–13.67)	
Diuretics					
No	23,191 (99.3)	4.45 (4.41–4.49)	.035	13.27 (13.19–13.36)	.031
Yes	164 (0.7)	4.96 (4.49–5.43)		14.41 (13.39–15.43)	

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers.

vasopressors, or inotropes. Both dampening and phase shifting were associated with longer length of stay and higher inpatient mortality.

Prior reports have shown that critical illness is associated with dampening[9,20,21] and phase shifting[1,22] of the circadian rhythm. While important, most of these studies are limited by small sample sizes and the use of markers such as melatonin that are not routinely measured in the ICU. Less is known about the circadian rhythm of more readily available parameters such as noninvasive BP. Gao and colleagues[7] looked at mean arterial BP fluctuation using MIMIC-II, a large dataset of critically ill patients, and found a possible association of lower fluctuations with higher ICU and hospital mortality. This study determined the difference between the mean nighttime (11 PM –7 AM) and mean daytime BP. While this confirms the abnormality of the circadian rhythm in critically ill patients, it is limited, as sleep in the ICU is known to be fragmented and distributed across the entire 24-hour day.[5] Further, this approach does not allow to differentiate between changes in the amplitude and phase shifting of the circadian rhythm. Our investigation adds to these reports by demonstrating the feasibility of modeling the circadian rhythm of BP in critically ill patients using cosinor analyses and by correlating the findings with baseline parameters as well as clinical outcomes.

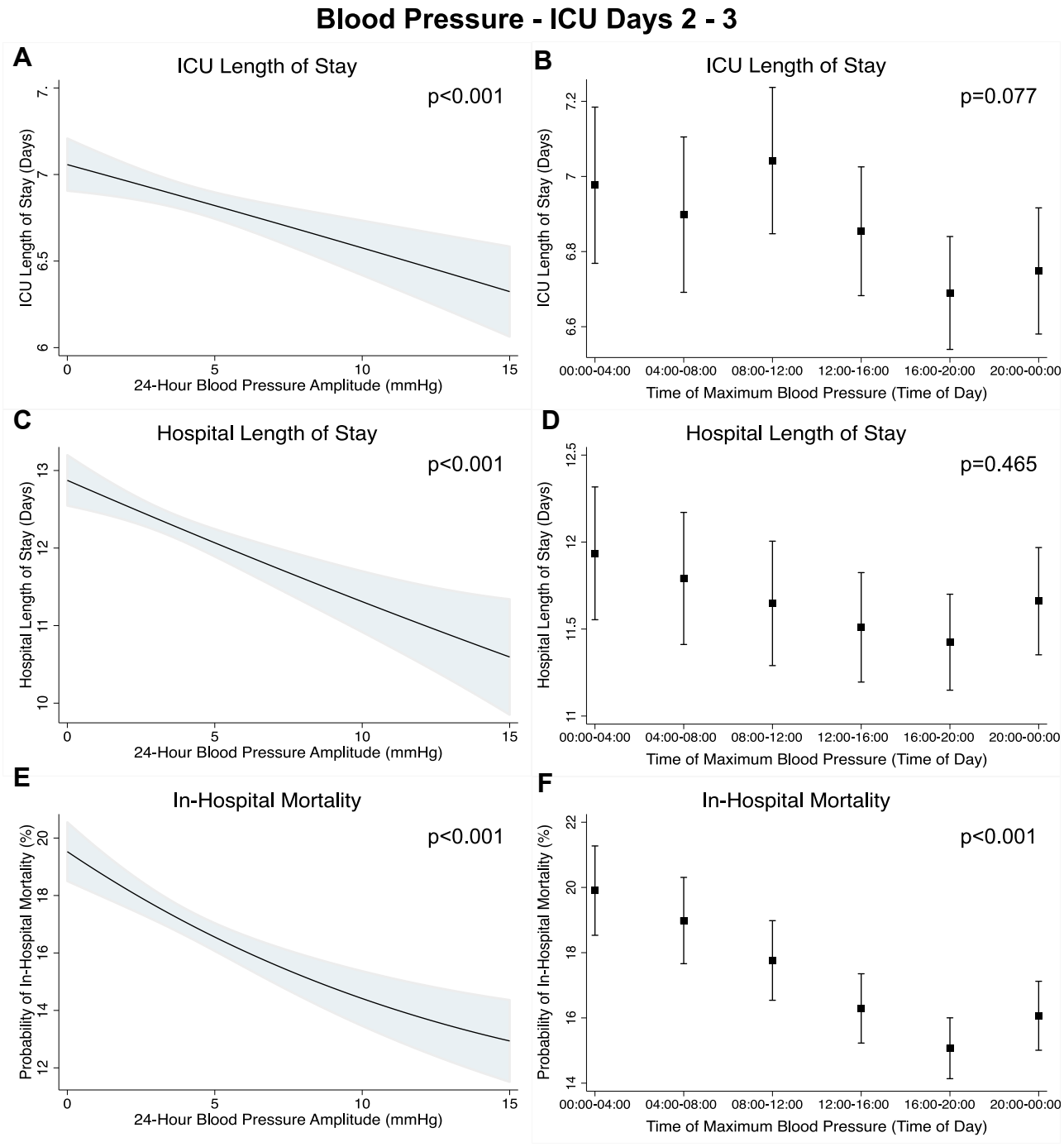

Figure 3 Association between 24-hour blood pressure rhythm on intensive care unit (ICU) days 2 and 3 and length of stay and in-hospital mortality. Higher levels of 24-hour blood pressure amplitude are associated with shorter ICU length of stay (**A**), shorter hospital length of stay (**B**), and lower in-hospital mortality (**C**). While the time of the day when the blood pressure is highest is not associated with ICU length of stay (**D**) and hospital length of stay (**E**), it is associated with in-hospital mortality (**F**). Results are adjusted for sex, age, APACHE (Acute Physiology and Chronic Health Evaluation) version IV score as a marker of disease severity (categorized into quartiles), sepsis, organ dysfunction, mechanical ventilation, and medications received (vasodilators, vasopressors/inotropes, sedatives, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors / angiotensin receptor blockers, diuretics).

In our study we found that the 24-hour BP rhythm was dampened in patients with higher APACHE scores, sepsis, and organ dysfunction. Dampening of the BP rhythm in this patient population was likely at least partly mediated by the use of vasopressors, inotropes, and mechanical ventilation. While statistically significant, many of these differences are very small. It is therefore likely that many different parameters in addition to critical illness itself affect circadian variation in critical illness. Together, this might lead to the more profound change in the circadian rhythm in critically ill patients compared to healthy subjects.[3] While the small differences associated with each parameter are

likely not clinically meaningful, they may allow further insight into the underlying pathophysiology.

Notably, our results indicate that association between the circadian rhythm and the clinical outcomes length of stay and mortality may, on the other hand, be clinically meaningful. Higher levels of 24-hour BP amplitude are, for example, associated with a 2-day decrease in the expected hospital length of stay. Even after adjustment for markers of illness severity and medications used, dampening of the 24-hour BP rhythm was still associated with longer length of stay and higher in-hospital mortality. Those findings are in line with prior reports suggesting that the efficacy and toxicity of medications[23] as well as the recovery from sepsis[24] may be affected and/or reflected by the absence of a circadian rhythm. The 24-hour BP rhythm might therefore provide important prognostic information beyond the variables that are included in commonly used predictive scores such as APACHE[25] or SOFA.[26] Notably, the findings were similar even after adjustment for mean arterial BP, indicating that the 24-hour BP rhythm may allow to further stratify patients and identify patients at high risk for adverse clinical outcomes.

The 24-hour BP rhythm was also phase shifted, which increased with level of severity. Abnormal timing of the circadian rhythm in critically ill patients has previously been described for other markers of circadian variation, such as core body temperature.[1,22,27] Our findings extend those reports by adjusting for ICU interventions such as mechanical ventilation and administration of medications, including vasodilators, vasopressors/inotropes, and sedatives. In addition to the various treatments administered to ICU patients, abnormal timing may also result from abnormal zeitgebers such as light and noise.[28] The association of abnormal timing with length of stay and mortality might imply a potential benefit of interventions aimed at normalizing the circadian rhythm.

Notably, a phase shift of the BP rhythm was associated with mortality but not length of stay. While length of stay and mortality are often well correlated,[29] some parameters obtained early in the hospital course may be more predictive of mortality than length of stay.[30] Earlier reports found that early markers of severity of illness such as the Shock Index predict mortality, but not length of stay.[31] Similarly, early intervention such as fluid resuscitation in severe sepsis and septic shock reduce mortality, but may not affect length of stay to the same degree.[32] Part of these differences may occur because length of stay can only be assessed in patients who survive to hospital discharge. In addition, length of stay (and in particular hospital length of stay) is related not only to the severity of illness at presentation, but also to complications that occur at a later point during the hospitalization, as well as to institutional differences. This may be reflected by the trend toward a significant association between the phase shift of the BP rhythm and ICU length of stay, but not with hospital length of stay.

Our results have to be interpreted in the setting of the study design. Since we only modeled the 24-hour rhythm, no conclusions can be drawn about the relevance of potential changes in the duration of circadian rhythm. Further, there is a potential for selection bias because of the exclusion of patients with an ICU stay shorter than 3 days. A comparison of patients included in this study and those with a shorter ICU length of stay indicated that the findings of our study primarily apply to sicker ICU patients, such as those with a higher APACHE score, sepsis, or organ dysfunction and patients on mechanical ventilation or medications for hemodynamic support. Finally, even though we adjusted for many covariates, residual confounding of the associations between the circadian rhythm and the clinical outcomes cannot be excluded.

In conclusion, we found that the 24-hour BP rhythm is altered in critically ill patients. Both illness characteristics and interventions such as the administration of vasoactive medications contribute to alterations. Blunting and phase shifting of the circadian rhythm are associated with adverse clinical outcomes. Future research should determine if interventions aimed at reducing nighttime disruptions and preserving the circadian rhythm will improve patient outcome.

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Disclosures

The authors have no conflicts to disclose.

Ethics Statement

The research reported in this paper adhered to the Helsinki Declaration as revised in 2013. This study was exempt from institutional review board approval owing to the retrospective design, lack of direct patient intervention, and the security schema for which the reidentification risk was certified as meeting Safe Harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2).

Patient Consent

Because this study was a secondary analysis of fully anonymized data, individual patient consent was not required.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.cvdhj.2021.01.004.

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