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ACCURACY OF THE ESTIMATED CORE TEMPERATURE (ECTEMP™) ALGORITHM IN ESTIMATING CIRCADIAN RHYTHM INDICATORS

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United States Army
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USARIEM TECHNICAL REPORT T17-08

ACCURACY OF THE ESTIMATED CORE TEMPERATURE (ECTEMP™) ALGORITHM IN ESTIMATING CIRCADIAN RHYTHM INDICATORS (April 2017)

David P. Looney[1]
Mark J. Buller[1]
Alexander P. Welles[1]
Jayme L. Leger[2]
Michelle Stevens[2]
Andrei Gribok[2]
William V. Rumpler[2]
Reed W. Hoyt[1]

[1] Biophysics and Biomedical Modeling Division, US Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760-5007

[2] Food Components and Health Laboratory, Beltsville Human Nutrition Research Center, Agricultural Research Service, United States Department of Agriculture, Beltsville, Maryland 20705

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Natick, MA 01760-5007

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David P. Looney, Mark J. Buller, Alexander P. Welles, Jayme L. Leger, Michelle Stevens, Andrei Gribok, William V. Rumpler, and Reed W. Hoyt

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14. ABSTRACT

While circadian rhythm analysis provides information critical to physiological status monitoring, there are considerable challenges to core body temperature (CT) measurement outside of stringent laboratory environments. This study evaluated ECTemp, a heart rate-based CT estimation algorithm, in the assessment of circadian rhythm indicators. Eleven participants (age, 23±3 years; height, 173.8±7.7 cm; body mass, 70.12±8.94 kg) were assessed on two occasions in which they were confined to a calorimeter chamber for a 22.5-hr period. Circadian rhythm indicators (MESOR, amplitude, and acrophase) were determined using a mixed effects cosinor regression models. ECTemp provided reasonable estimates of MESOR (RMSE, 0.17) and amplitude (RMSE, 0.10). While ECTemp estimates of circadian rhythm indicators were lower than observed CT, the differences were smaller than heart-rate based models analyzed in previous studies. As such, ECTemp demonstrates strong potential for estimating circadian CT rhythm indicators, particularly if the algorithm is updated to fit additional data from periods of low CT and heart rate.

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EXECUTIVE SUMMARY

Core body temperature (CT) fluctuates to a circadian rhythm; a cyclical pattern of oscillation that occurs over a period of approximately 24 hours. While the analysis of circadian rhythms provides information critical to physiological status monitoring, current technology presents considerable challenges to the measurement of CT outside of stringent laboratory environments. This study evaluated ECTemp™, a heart rate-based extended Kalman Filter CT estimation algorithm, in the assessment of circadian rhythm indicators.

Eleven participants (age, 23 ± 3 years; height, 173.8 ± 7.7 cm; body mass, 70.12 ± 8.94 kg) were assessed on two occasions in which they were confined to a calorimeter chamber for a 22.5-hr period. Heart rate data were monitored continuously using an FDA 510(k) certified (K113054) physiological status monitoring device (Equivital™ EQ-02, Hidalgo, Cambridge, UK) that received CT data from an ingestible thermometer pill (Jonah Pill, Mini Mitter Inc., Bend, OR). Circadian rhythm indicators (MESOR, amplitude, and acrophase) were determined using a mixed effect modeling approach to cosinor regression. Root mean square error (RMSE), bias, and Pearson's correlation coefficients were assessed between ECTemp™ and observed CT.

The results of this investigation showed that ECTemp™ provided reasonable estimates of MESOR (RMSE, 0.17) and amplitude (RMSE, 0.10). While ECTemp™ estimates of circadian rhythm indicators were lower than observed CT, the differences were lower than heart-rate based models analyzed in previous studies. As such, ECTemp™ demonstrates strong potential for estimating circadian CT rhythm indicators, particularly if the algorithm is updated to fit additional data from periods of low CT and heart rate.

INTRODUCTION

Nearly all human biological processes fluctuate to a circadian rhythm; a cyclical pattern of oscillation that occurs over a period of approximately 24 hours. Circadian rhythms have become an increasingly popular research topic for investigators across a wide array of disciplines due to their impact on biological systems [1]. The current phase of a biomarker within its circadian rhythm has physiological consequences that can alter behavioral, cognitive, perceptual, and physical functions [2]. Moreover, circadian rhythm profiles can be used by clinicians in the diagnosis, prognosis, and treatment of serious medical conditions such as cancer [3], sleep disturbances [4] and cardiovascular disorders [5]. As the importance of circadian rhythms becomes increasingly evident, there is a growing need to for physiological models capable of easily capturing the circadian rhythms of key biological signals using wearable sensors.

While many biological parameters have been investigated, a considerable amount of research has focused on characterizing the circadian rhythms of core body temperature (CT) [6-8]. Monitoring CT is especially important to soldier performance optimization and heat illness prevention when training or in combat in stressful environments [9]. However, most methods of measuring CT are invasive, impractical outside of laboratory settings, and/or shown to be largely unreliable [10]. As such, there is a substantial value in identifying a method to characterize CT circadian rhythms outside of the scope of traditional laboratory techniques.

Homeostatic thermoregulation is contingent on the control of heat transfer from the core to the extremities [11]. As such, heart rate plays a pivotal role in thermoregulation as a primary determinant of the rate of blood flow to the skin. Additionally, the relationship between heart rate and metabolic rate has been long recognized, dating back to the principles established in Fick's Principle [12]. In addition to its deep physiological connections with CT, heart rate is advantageous in that it is a non-invasive measure that can be readily assessed.

For these reasons, recent investigations have examined the viability of heart rate-based CT-estimation algorithms [7, 13, 14]. One notable example is ECTemp^{TM}, which utilizes an extended Kalman Filter to estimate CT from successive heart rate measurements[14]. ECTemp^{TM} was developed as a real-time estimator of CT for assessing thermal-work strain (TWS) in the heat, particularly for warfighters. Accordingly, ECTempTM is optimized for estimating CT when elevated above typical resting temperatures and not the lower temperatures associated with sleep and rest. Therefore, the accuracy of the ECTemp^{TM} algorithm in characterizing the circadian rhythm of CT has yet to be investigated. Subsequently, this investigation sought to examine the performance of ECTemp^{TM} in estimating CT circadian rhythm indicators.

METHODS

PARTICIPANTS

Circadian rhythms were retrospectively analyzed from data collected during a previous investigation [15]. Prior to data collection, participants were briefed on the procedures, benefits, and risks of the study and each participant gave their informed consent. The investigators adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25. In order to be included in this investigation, participants must have attended both experimental visits and have a minimum of twelve hours of both heart rate and core temperature data per visit. Consequently, a total of eleven participants (age, 23 ± 3 years; height, 173.8 ± 7.7 cm; body mass, 70.12 ± 8.94 kg) including nine men (age, 23 ± 3 years; height, 175.6 ± 7.1 cm; body mass, 72.16 ± 8.60 kg) and two women (age, 25 ± 6 years; height, 165.6 ± 4.0 cm; body mass, 60.92 ± 0.91 kg) were included in this investigation.

PROCEDURES

Participants attended two experimental visits ($Visit_1$ and $Visit_2$) in which they were enclosed in a calorimeter chamber for an approximately 22.5-hr period (Table 1). Prior to entering the calorimeter chamber on the day of each visit, participants were provided a standardized breakfast and lunch. Upon arrival at the laboratory, participants were immediately outfitted with an FDA 510(k) certified (K113054) physiological status monitoring device (Equivital™ EQ-02, Hidalgo, Cambridge, UK) which was subsequently used to monitor changes in heart rate and CT at 15-sec intervals. The device recorded CT by receiving transmissions from a thermometer pill (Jonah Pill, Mini Mitter Inc., Bend, OR) which had been ingested orally prior to the start of data collection. The pill was constructed from food grade polycarbonate and conforms to U.S. Food and Drug, Cosmetic Act and Food Additive Regulations 21 CFR 177.1580.

Table 1. Overview of the first ($Visit_1$) and second ($Visit_2$) experimental visit protocols.

Time	Event
1700	Issued EQ-02 Sensor and Pill
1730	Enter Chamber
1800-1830	Dinner
1830-2300	Leisure
2300-0630	Sleep
0700-0730	Breakfast
0730-0930	Leisure
0930-1000	Warm-up*
1000-1100	Exercise Protocol*
1100-1200	Post-Exercise Recovery*
1200-1230	Lunch*
1230-1600	Leisure
1600	Dismissal

* = Exercise and post-exercise exercise excluded from data analysis.

After being equipped with the physiological status monitoring device, the experimental procedures were reviewed before the participant was enclosed within the calorimeter chamber at 1730 hr for the remainder of the visit. During resting conditions, room environmental conditions were set to the temperature and relatively humidity of the participant's preferences. During the exercise protocol, temperature was set to 22°C with a relative humidity of 50%. Once inside the calorimeter chamber, participants were allowed to consume water ad libitum. However, food intake was restricted to three standardized meals; dinner at 1800 hr, breakfast at 0700 hr, and lunch at 1200 hr. All participants were instructed to finish consuming each standardized meal within 30 min.

During designated leisure periods, participants were required to restrict physical activity to sedentary tasks (e.g., computer work, watching television). At 2300 hr, calorimeter lights were extinguished and participants were instructed to lie quietly in bed until awoken at 0630 hr the following morning. At 0930 hr, participants began a series of warmup procedures before performing an exercise protocol (5 mph pace for 60-min at 0% grade incline) on a standard powered treadmill (Smooth Fitness 7.11.HR) from 1000-1100 hr. The protocols differed in whether the participants exercised using their own pacing strategy ($Visit_1$) or a computationally derived policy based upon their thermal-work strain state, distance completed, and the time remaining ($Visit_2$). To minimize the influence of the exercise and any effects related to the differences in pacing strategies, data between 0930 and 1230 hr were excluded from circadian rhythm analysis.

ECTEMP™ ALGORITHM

One-minute average CT and heart rate data were downloaded from the EQ-02 before analysis by the ECTemp™ algorithm [14]. Data were visually inspected for outliers and for water consumption signatures. For the first time point (t=1) of each trial, the estimated CT ($Est.CT_{t=1}$) was set as the corresponding observed CT value with estimated variance set equal to 0 ($Est.Var_{t=1}$). Subsequently, the following six equations were applied iteratively with each additional time point:

1. A preliminary estimate of CT for the current time point ($Pre.CT_t$) was made using the estimated CT from the previous time point ($Est.CT_{t-1}$).

$$Pre.CT_t = Est.CT_{t-1}$$

2. A preliminary estimate of the variance of the estimate of CT for the current time point ($Pre.Var_t$) was made by incorporating the estimated variance from the previous time point ($Est.Var_{t-1}$) into the following equation:

$$Pre.Var_t = Est.Var_{t-1} + 0.000484$$

3. The extended Kalman filter mapping function variance coefficient (C_t) was computed using the following equation:

$$C_t = -9.1428 \times Pre.CT_t + 384.4286$$

4. The Kalman gain weighting factor for the current time (K_t) was computed using the following equation:

$$K_t = \frac{Pre.Var_t \times C_t}{Pre.Var_t \times {C_t}^2 + 356.5654}$$

5. A final estimate of CT for the current time point ($Est.CT_t$) was made by incorporating the heart rate observed at the current time (HR_t) the following equation:

$$Est.CT_t = Pre.CT_t + K_t \times \left(HR_t - \left[-4.5714 \times Pre.{CT_t}^2 + 384.4286 \times Pre.CT_t - 7887.1\right]\right)$$

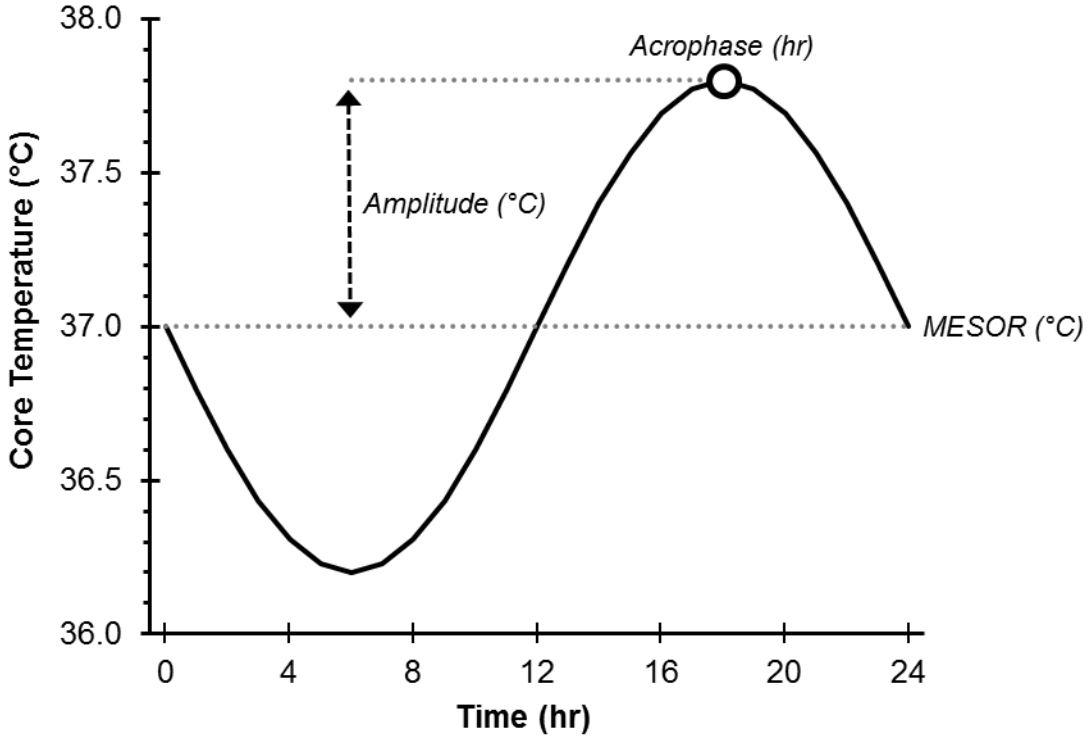
6. The variance of the final estimate of CT for the current time point ($Est.Var_t$) was calculated using the following equation:

$$Est.Var_t = Pre.Var_t \times (1 - C_t \times K_t)$$

CIRCADIAN RHYTHM INDICATORS

As the period was assumed to be 24-hr for all trials, three circadian rhythm indicators were computed (see Figure 1). The first circadian indicator compared was the Midline Estimating Statistic Of Rhythm (MESOR); a rhythm-adjusted mean value around which the biological signal oscillates [1]. The second indicator was the amplitude; the maximal predictable variation that the biological signal oscillates from the MESOR[16]. The last circadian indicator compared was the acrophase; the time point within the period at which the circadian rhythm reaches its apex [7].

Figure 1. Overview of circadian rhythm indicators analyzed.



MESOR, Midline Estimating Statistic Of Rhythm.

STATISTICAL ANALYSES

Heart rate and CT time series were visually inspected for outliers and drink artifacts. Core temperatures from CT and ECTemp™ were subsequently averaged over 5-min time intervals (T) across the period which was assumed to be 24-hr across all trials. Once the estimated values of CT were obtained from ECTemp™, circadian rhythms were determined using cosinor regression [16] and incorporating a mixed effect model approach. Mixed effect models are similar to conventional regression models in that they describe the population-mean (fixed) effects of independent variables on the outcome variable. However, mixed models also describe random effects, which are effects on the outcome variable specific to one or more grouping variables (e.g. participant, visit) within the dataset. The mixed model approach was selected since it provides a better description of fixed effects by accounting for the influence of each participant and visit on their repeated measures [17]. Furthermore, the random effects coefficients determined could be used to calculate circadian rhythm indicators for each participant at each visit.

The single component cosinor regression model for a biological signal can be written as:

$$Y(t) = \beta_0 + \beta_1 \cos(2\pi t/\tau) + \beta_2 \sin(2\pi t/\tau)$$

where Y = biological signal analyzed for circadian rhythmicity; t = time during the phase, β_0 = MESOR; β_1 = coefficient for the cosine term;; τ = period (length of one complete circadian rhythm cycle); and β_2 = coefficient for the sine term.

In order to determine circadian rhythm indicators for each participant at each visit, the cosinor regression model can be modified to the following mixed effects model:

$$Y(t) = \beta_0 + \beta_1\cos(2\pi t/\tau) + \beta_2\sin(2\pi t/\tau) + (\beta_0 + \beta_1 + \beta_2 \mid ID / Visit)$$

Where ID = participant; $Visit$ = experimental visit ($Visit_1$ or $Visit_2$); ($\beta_0 + \beta_1 + \beta_2$ | ID / Visit) = random effects of participant and visit within participant on β_0, β_1, and β_2.

Consequently, the models for CT and ECTemp™ were specified as:

$$CT(t) = \beta_0 + \beta_1\cos(2\pi t/\tau) + \beta_2\sin(2\pi t/\tau) + (\beta_0 + \beta_1 + \beta_2 \mid ID / Visit)$$

$$ECTemp^{TM}(t) = \beta_0 + \beta_1\cos(2\pi t/\tau) + \beta_2\sin(2\pi t/\tau) + (\beta_0 + \beta_1 + \beta_2 \mid ID / Visit)$$

The circadian rhythm indicators for each trial were subsequently determined based on the random effects coefficient estimates produced by each model. Firstly, the MESOR of each trial was considered as the intercept. Secondly, the amplitude of each trial was estimated using the following equation:

$$Amplitude = \sqrt{(\beta_1 + \beta_2)}$$

Thirdly, the acrophase of each trial was estimated using the following equation:

$$Acrophase = \tan^{-1}(-\beta_2/\beta_1) + K\pi$$

where K =
0 if $\beta_1 > 0$ and $\beta_2 > 0$
1 if $\beta_1 < 0$
2 if $\beta_1 > 0$ and $\beta_2 < 0$

All statistical analyses were performed using RStudio (Version 0.98.1056 , RStudio, Inc). Mixed effects models were conducted using the “lme4” package via the “glmer” and “glm” functions respectively[18]. P-values were determined using the lmerTest function [19] with the level of statistical significance set at $p \leq 0.05$. All data are reported as mean ± standard deviation (SD) unless noted otherwise. Pearson’s correlation coefficients (r) were calculated for each circadian rhythm indicator to evaluate the strength of the relationship. Root Mean Square Error (RMSE) was calculated for each circadian rhythm indicator as the square root of the mean of the squared differences between ECTemp™ and CT.

RESULTS

Figure 2 displays CT over time of day across all data points. CT remained elevated after the exercise protocol until returning to close to pre-exercise values after approximately 1.5 hr. Heart rate also remained well above pre-exercise values for approximately 1.5 hr (Figure 3). Dotted lines represent time period that was excluded from analysis due to masking effects from the exercise protocol, gap in data represents time between the end and start of the experimental period

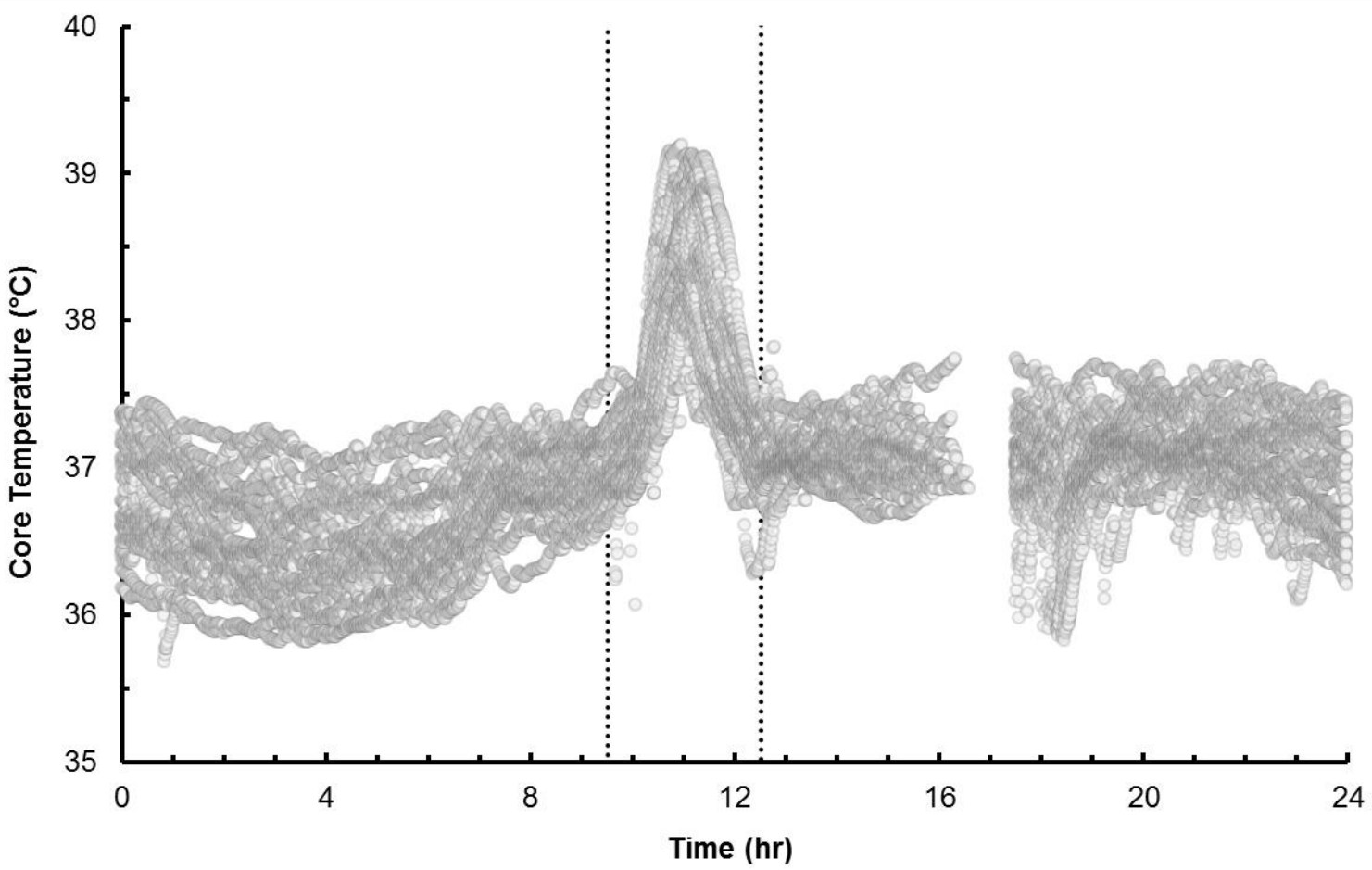
Figure 4 contains all of the temperatures estimated by ECTemp^{TM} and the corresponding measured CT across all data points. A moderately strong positive correlation was observed between ECTemp^{TM} and CT ($r = 0.68$). Overall, CT had both higher mean and standard deviation (36.82 ± 0.38 °C) than estimated CT by ECTemp^{TM} (36.65 ± 0.23 °C).

Table 2 displays the fixed and random effects estimates as well as model fit indices for each mixed effect model. Across both models, significant interactions were detected for the fixed effects estimates of β_0, β_1, and β_2. Trend lines of the fixed effects estimates of the core temperature circadian rhythm by CT and ECTemp^{TM} can be seen in Figure 5. ECTemp^{TM} estimates were slightly lower for MESOR (36.70 °C vs. 36.86 °C) and amplitude (0.24 °C vs. 0.31°C) as well as an earlier acrophase (1456 hr vs. 1639 hr) compared to CT.

The mean MESOR, amplitude, acrophase values across all participants and visits for ECTemp^{TM} and CT can be seen in Table 3. There were no significant differences between $Visit_1$ and $Visit_2$ in MESOR, amplitude, or acrophase for either CT ($p = 0.10$, 0.24, and 0.67 respectively) or ECTemp^{TM} ($p = 0.16$, 0.26, and 0.74 respectively). Subsequently, circadian rhythm indicators from both visits were compiled together and compared between CT and ECTemp^{TM}. Estimates of MESOR, amplitude, and acrophase were significantly lower for ECTemp^{TM} than CT ($p < 0.01$ for each).

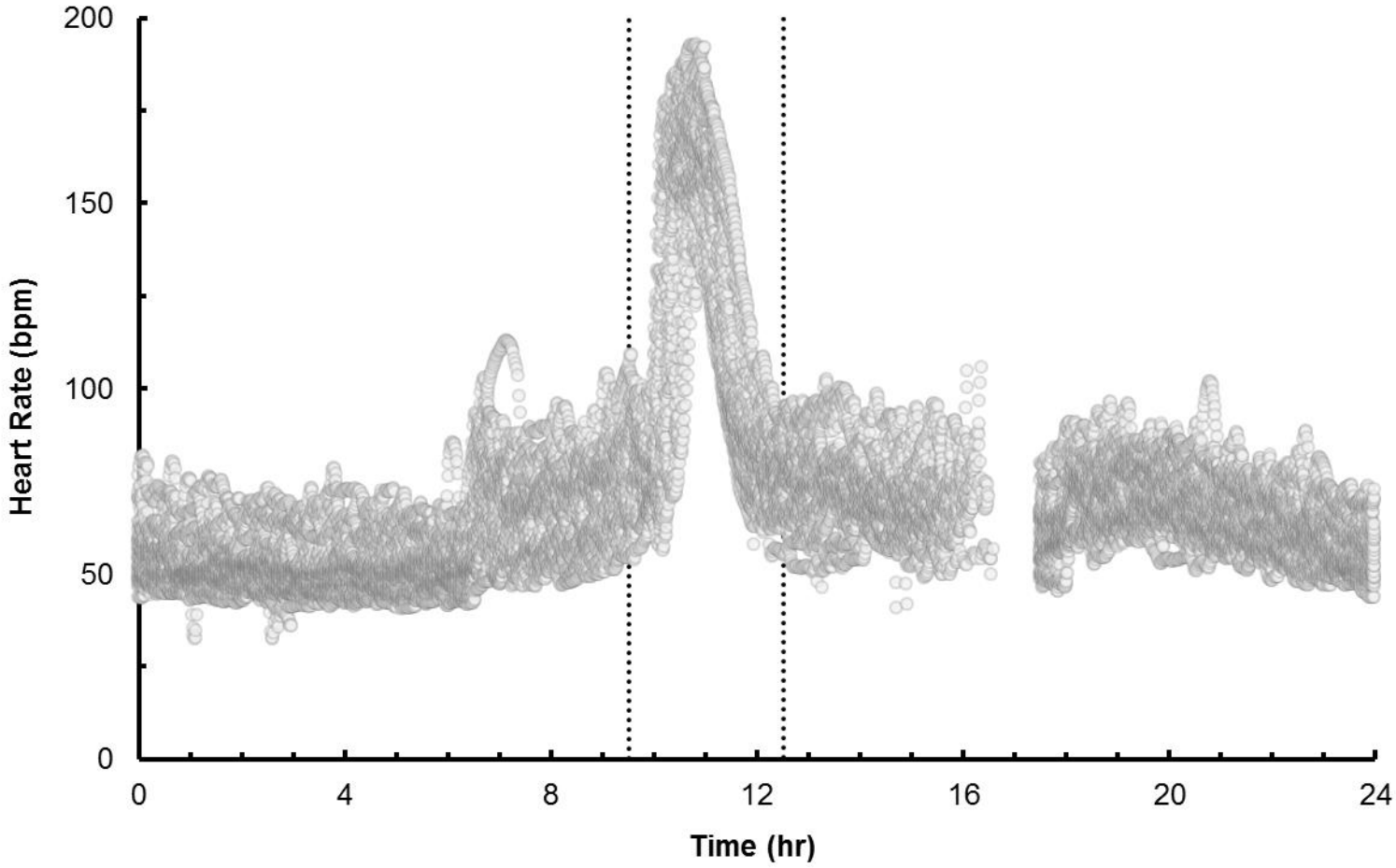
Figure 6 displays the individual circadian rhythm indicator estimates from both visits combined for ECTemp^{TM} and CT. Positive correlations were observed between ECTemp^{TM} and CT for MESOR ($r = 0.66$), amplitude ($r = 0.55$), and acrophase ($r = 0.43$).

Figure 2. Scatter plot of observed core temperatures over time of day.



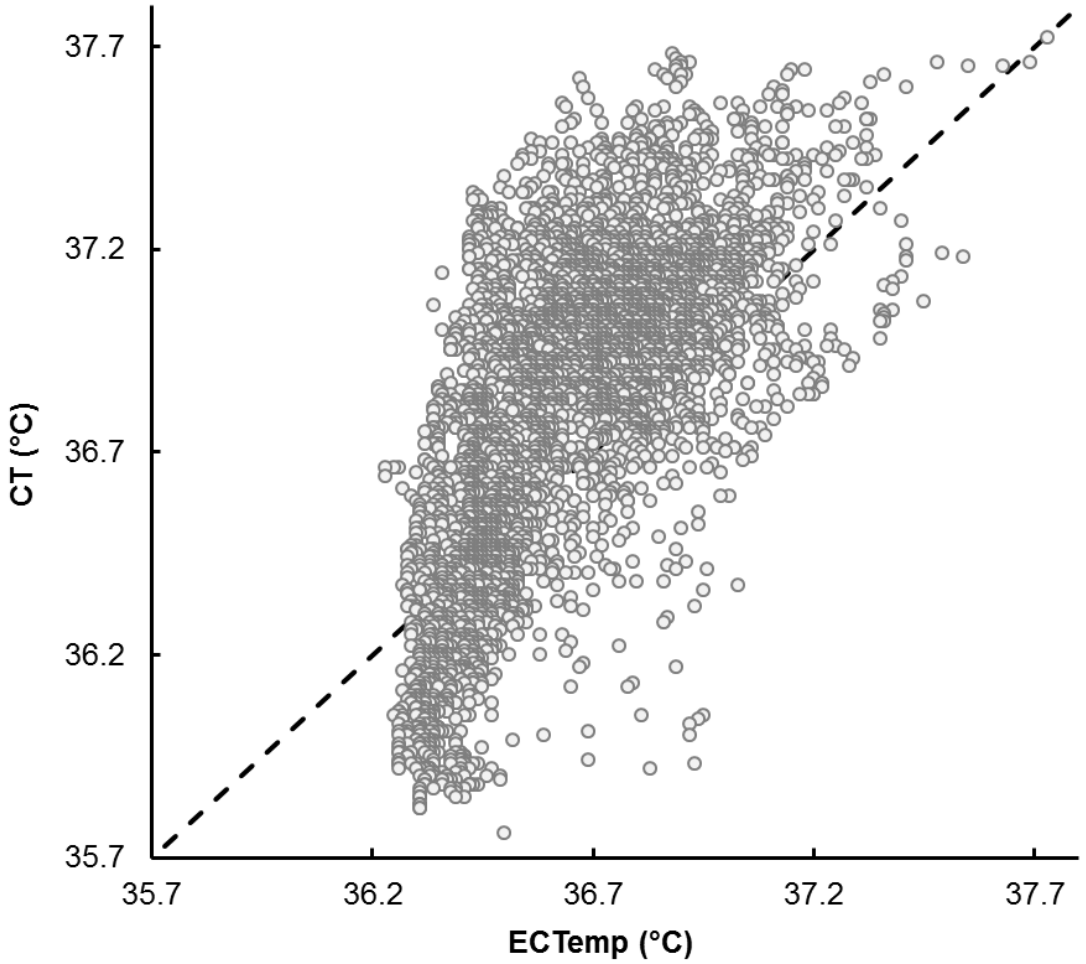
Dotted lines represent time period that was excluded from analysis due to masking effects from the exercise protocol, gap in data represents time between the end and start of the experimental period

Figure 3. Scatter plot of observed heart rates over time of day.



Dotted lines represent time period that was excluded from analysis due to masking effects from the exercise protocol, gap in data represents time between the end and start of the experimental period

Figure 4. Scatter plot of ECTemp™ by CT.



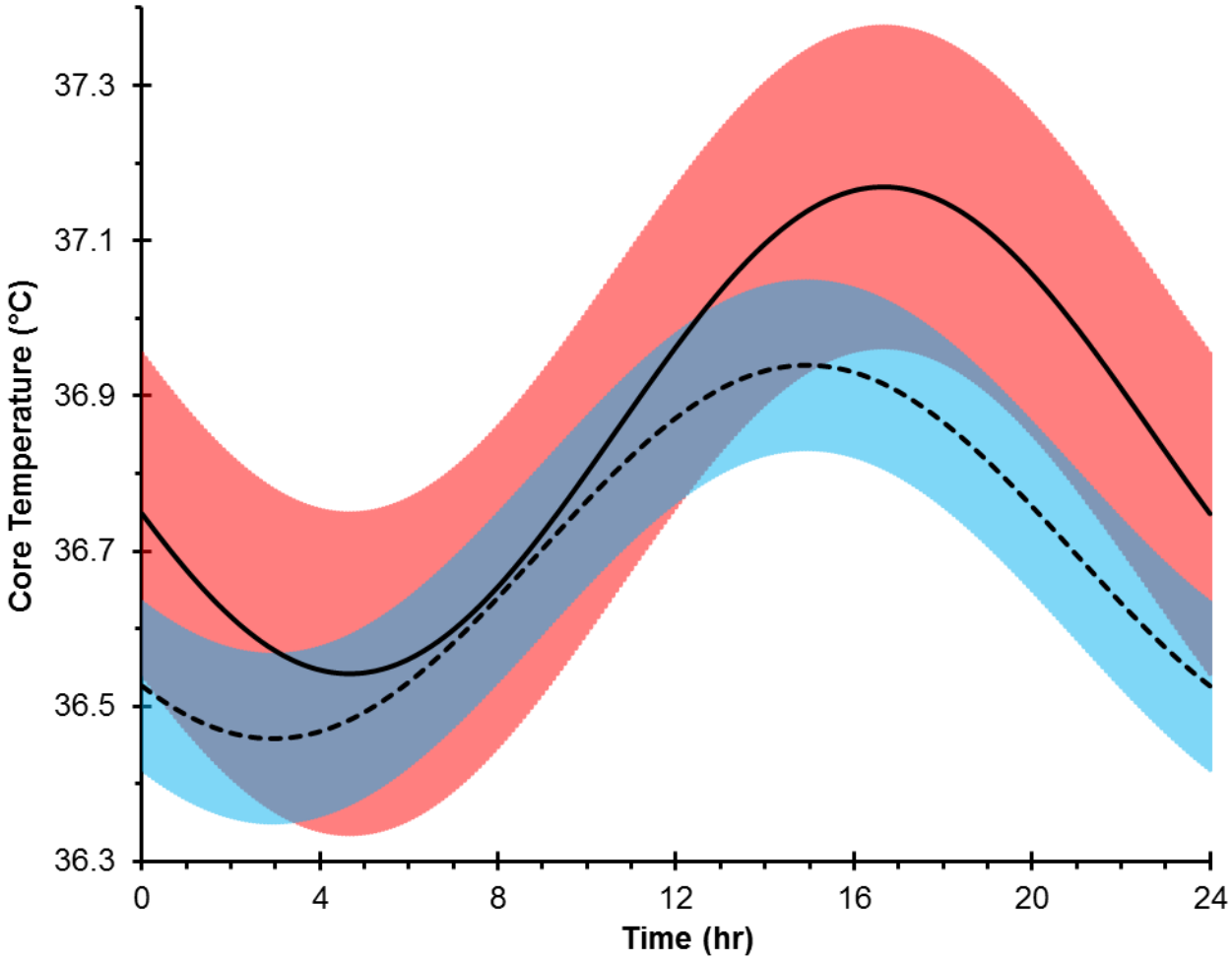
CT, observed core temperature; ECTemp™, Kalman Filter-estimated core temperature, dotted line, line of identity.

Table 2. Fixed and random effects for mixed effects models.

Model	Fixed Effects (Mean ± SE)			Random Effects (SD)						
				(| Visit : ID)			*(| ID)*			
	B_0	B_1	B_2	B_0	B_1	B_2	B_0	B_1	B_2	ε
CT	36.86 ± 0.05*	-0.11 ± 0.04*	-0.29 ± 0.04*	0.09	0.11	0.07	0.14	0.11	0.13	0.21
ECTemp™	36.70 ± 0.04*	-0.17 ± 0.02*	-0.17 ± 0.01*	0.08	0.06	0.04	0.11	0.05	0.03	0.11

SE, standard error; SD, standard deviation; *Visit*, experimental visit; ID, participant; B_0, intercept; B_1, coefficient for the $\cos(2\pi t/\tau)$ term; B_2, coefficient for the $\sin(2\pi t/\tau)$ term; ε, residual error; CT, observed core temperature; ECTemp™, Kalman Filter-estimated core temperature; *, significant interaction ($p < 0.05$).

Figure 5. Fixed effects estimates of core temperature circadian rhythms.



Solid and dotted lines represent the population-mean estimates of circadian rhythm waveforms for observed core temperature and ECTemp™ respectively; Red and blue fills represent the standard deviations of the errors for the CT and ECTemp™ models respectively.

Table 3. Between-visit comparisons in circadian rhythm indicators.

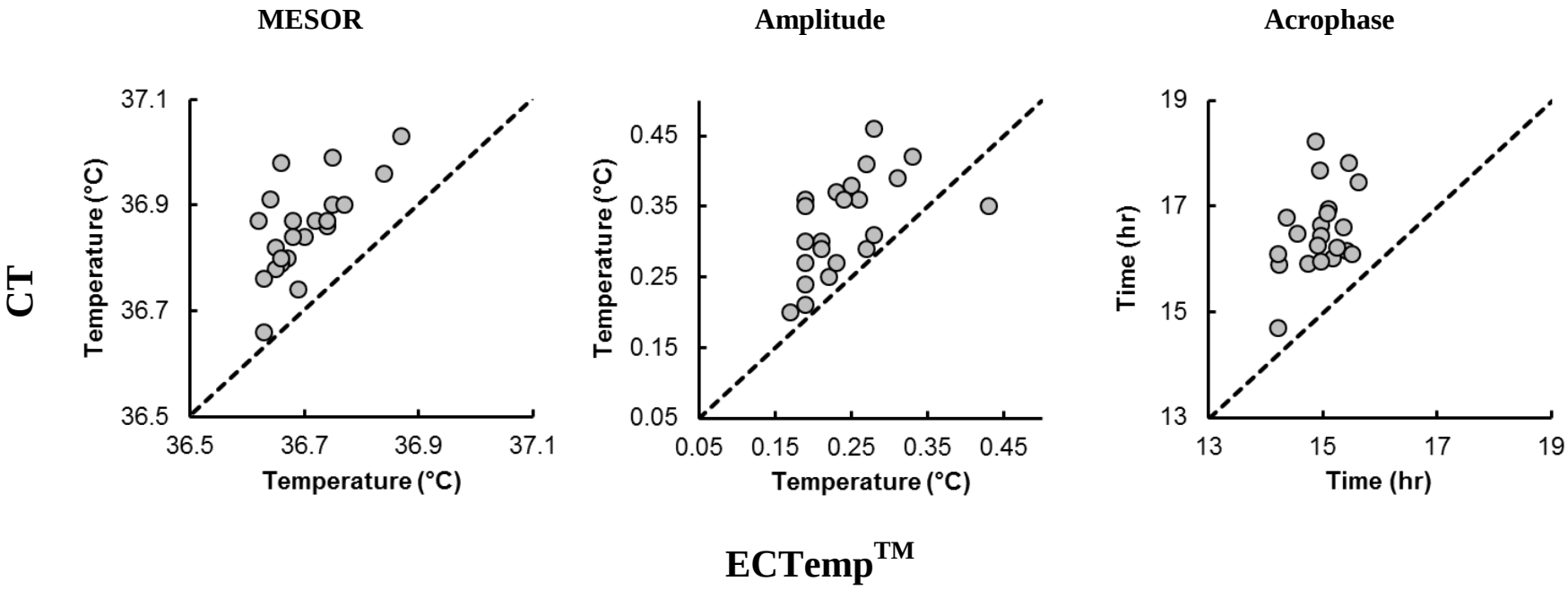
Indicator	Visit	ECTemp™	CT
MESOR	1	36.72 ± 0.07	36.89 ± 0.08
(°C)	2	36.68 ± 0.05	36.82 ± 0.08
	Δ1-2	0.04 ± 0.10	0.07 ± 0.12
Amplitude	1	0.26 ± 0.07	0.35 ± 0.08
(°C)	2	0.23 ± 0.04	0.30 ± 0.06
	Δ1-2	0.03 ± 0.09	0.04 ± 0.11
Acrophase	1	14.93 ± 0.41	16.78 ± 1.03
(hr)	2	15.01 ± 0.47	16.55 ± 0.99
	Δ1-2	-0.08 ± 0.76	0.21 ± 1.62

Table 4. Comparison of circadian rhythm indicators between ECTemp™ and CT.

Indicator	CT	Mean ± SD
MESOR	ECTemp™	36.70 ± 0.08
(°C)	CT	36.86 ± 0.09
	Bias	-0.24 ± 0.08*
	RMSE	0.17
Amplitude	ECTemp™	0.24 ± 0.06
(°C)	CT	0.32 ± 0.07
	Bias	-0.08 ± 0.06*
	RMSE	0.10
Acrophase	ECTemp™	14.97 ± 0.43
(hr)	CT	16.67 ± 0.99
	Bias	-1.55 ± 0.98*
	RMSE	1.91

ECTemp™, Kalman Filter-estimated core temperature; CT, observed core temperature; *, significant difference between CT and ECTemp™ ($p < 0.05$); RMSE, Root mean square error; MESOR, Midline Estimating Statistic Of Rhythm.

Figure 6. Relationships between ECTemp™ and CT estimates of MESOR, amplitude, and acrophase.



MESOR, Midline Estimating Statistic of Rhythm; CT, observed core temperature; ECTemp™, Kalman Filter-estimated core temperature, dotted line, line of identity.

DISCUSSION

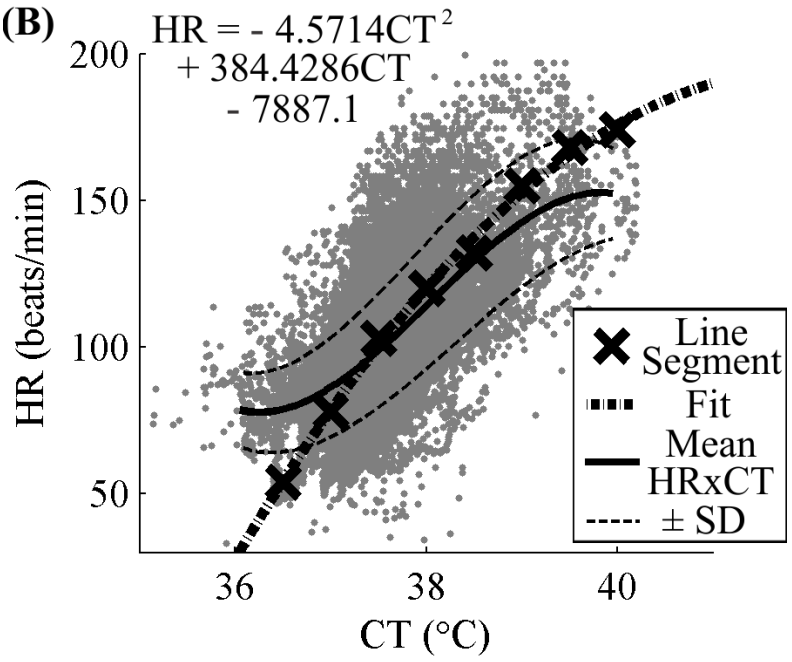
The results of this investigation show that ECTemp™ provides close estimates of circadian rhythm indicators. Specifically, mean estimates for MESOR and amplitude were within 0.25°C and 0.10°C respectively. Though ECTemp™ estimates of MESOR and amplitude were consistently lower than CT, the differences were well within the error of measurement of CT devices[20]. Furthermore, core temperature, MESOR, amplitude, and acrophase were all positively correlated between ECTemp™ and CT.

ECTemp™ performance compared favorably to the findings of Sim et al.[7]. In the present study, twenty heart rate-based parameters were fitted to CT data using polynomial regression and extended Kalman filter models. The order of each polynomial and extended filter model (between 1st and 8th) was selected based on lowest RMSE. Compared to all of the models that were analyzed, ECTemp™ had a lower RMSE than the best fitting model for MESOR (0.17 vs. 0.22°C) and amplitude (0.10 vs. 0.20°C). While ECTemp™ was not as accurate in estimating the acrophase as the best model (1.91 vs. 1.10 hr), it provided a closer estimate than 31 of the 40 models reported.

The observed correlation ($r = 0.68$) between ECTemp™ and CT shows that ECTemp™ sufficiently reflected the directionality of the oscillations in CT. However, the reduced amplitude indicates that ECTemp™ somewhat underestimates the magnitude of the oscillations. This is also evident in the overall lower variance displayed by ECTemp™ (SD = 0.23) versus CT (SD = 0.38). When the lower MESOR estimates are taken into consideration, it appears that ECTemp™ provides slightly conservative estimates of CT during resting conditions.

Of the three circadian rhythm indicators assessed, ECTemp™ was least accurate in estimating acrophase (mean bias, -1.55 ± 0.98 hr). However, this disparity may have stemmed from some of the limitations of the current study. For example, participants entered the calorimeter chamber at 1730 hr and left at 1600 hr the following day. This gap in data collection is notable in that previous studies have shown that the acrophase of CT to occur around this time[2]. Additionally, participants were provided CT pills at various times prior to entering the chamber, some in close proximity to the start of data collection. Consequently, some of the initial CT data was lost due to artifacts caused by water consumption[21]. Although data were excluded for the 1.5 hr that followed the exercise protocol, differences between CT and heart rate in post-exercise recovery rates [22] may have partially explained the discrepancies in acrophases.

Figure 7. Scatter plot of the development data points from the original investigation showing HR by CT.



Regardless, the findings of the current investigation are encouraging given that ECTemp™ was originally developed with the purpose of estimating CT during strenuous physical activity in hot environments[14]. Figure 7 displays the original developmental data points used for the ECTemp™ model. Notably, there were few core temperature datapoints below 36°C that were included. Although ECTemp™ was validated against data compiled from nine studies, only one of the studies[23] included data collected during sedentary periods. The precision of ECTemp™ estimates of circadian rhythm indicators could be further improved if the algorithm is updated to fit additional data from periods of low CT and heart rate.

CONCLUSION

In summary, this investigation determined that ECTemp™ provided reasonable estimates of CT circadian rhythm indicators. Additionally, the RMSE of ECTemp™ estimates of circadian rhythm indicators was lower than the majority of models assessed in prior research. Although further research is required, ECTemp™ appears to be a viable alternative to direct measurement of CT during circadian rhythm analysis particularly if the algorithm is adapted to better estimate CT during sedentary periods.

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