Circadian Rhythm

Introduction and Cardiovascular Applications

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Agenda: Circadian Rhythm

- Introduction
- Methods of Quantification
- Circadian Rhythm and Heart Disease
- Results and Conclusion

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Rhythm and Man

Annual Rhythms of Solstice, Sowing, and Harvest: >2000 B. C.

Rhythm and Fluctuations

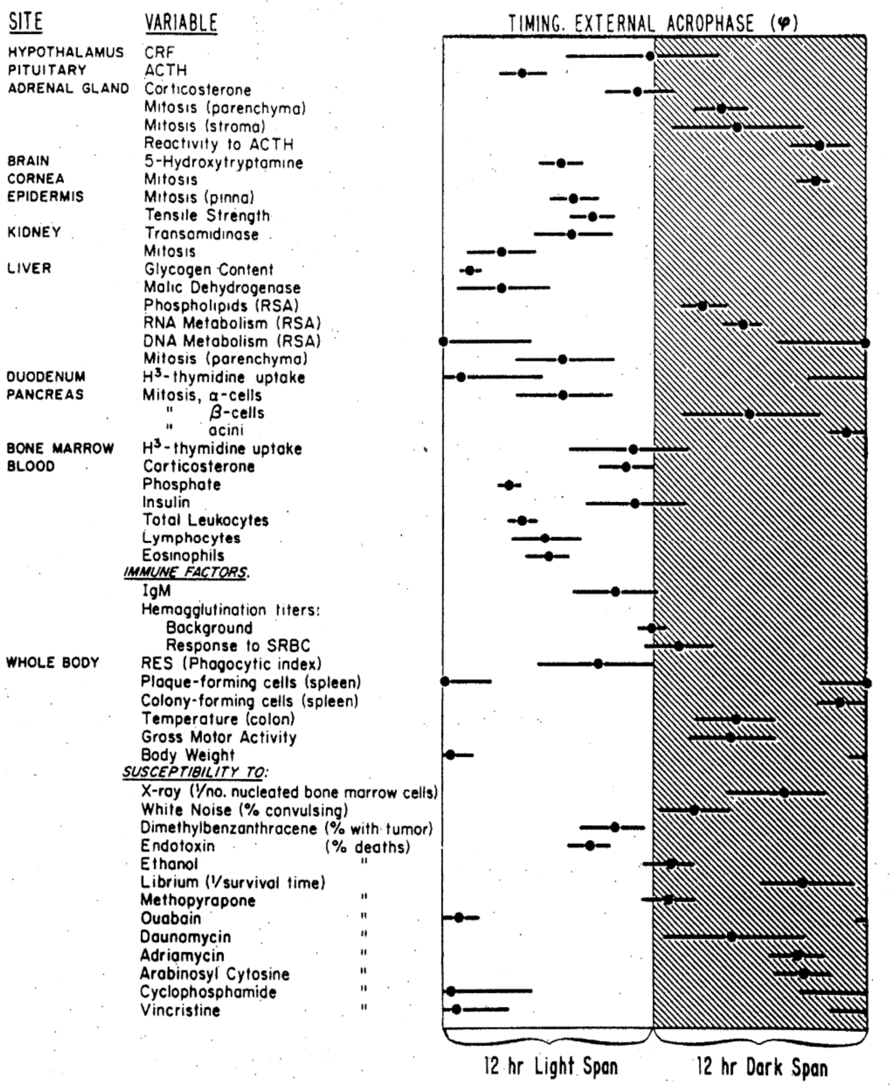
Approximation of Rhythm and Correction of Fluctuations: >1600 B. C.

Daily Rhythms in Nature

Linné (1745)

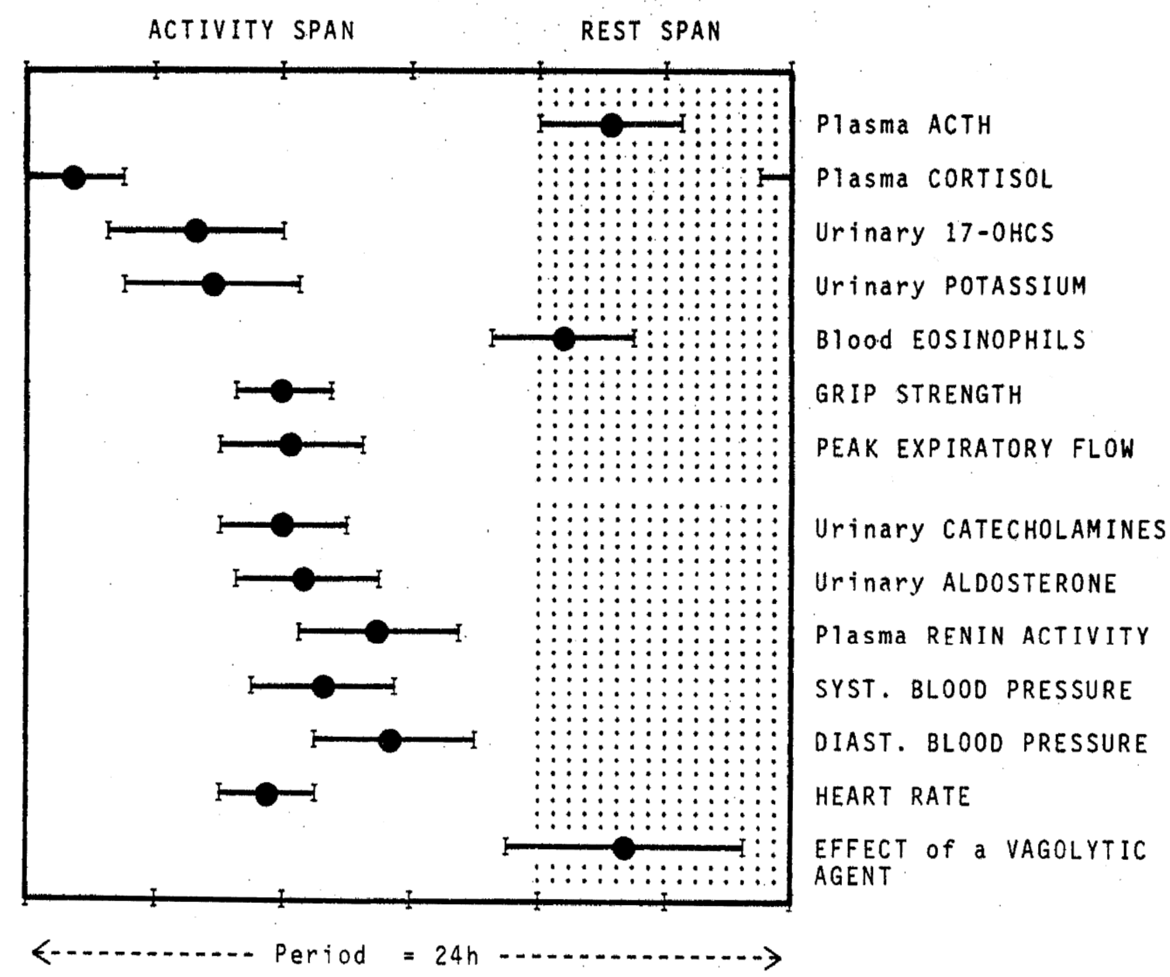
„A Clock of Flowers“

Variation of Physiological Parameters in Mice



Halberg (1978)

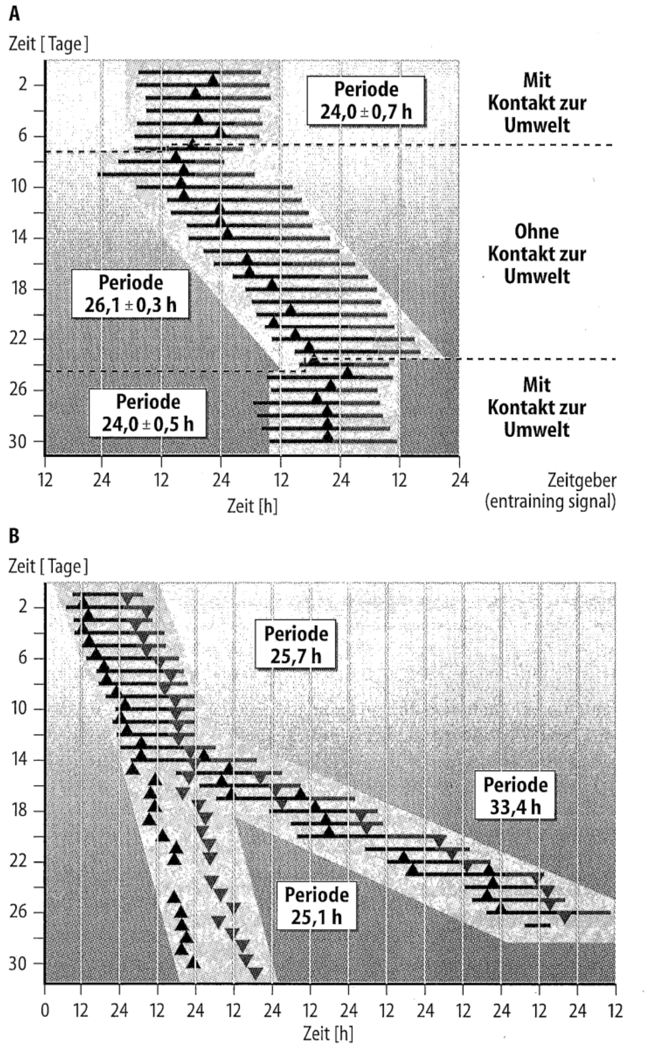
Variation of Physiological Parameters in Man



Reinberg (1983)

Free Running Cycles vs. Entrainment

Temperature and Sleep Cycle under Temporary Isolation



Schmidt (1997)

Slow Drift of Period

Dissociation of Rhythms

Circadian Rhythm in Medicine: Database Search

- „Circadian Rhythm“: 58664
- „Circadian Rhythm Review“: 6319
- „Circadian Rhythm Cardiac“: 5367
- „Circadian Rhythm Heart“: 4917
- „Circadian Rhythm Cardiovascular“: 3748

Growing Fast Due To Technological Progress In Observation (Telemedicine)

Pubmed 19 Mar 2011

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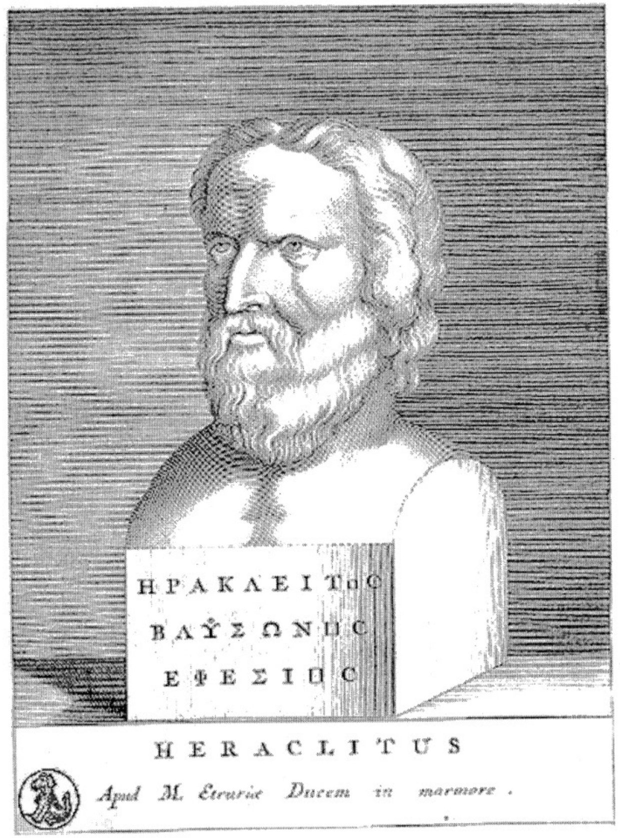
Circadian Rhythm of Fluctuations

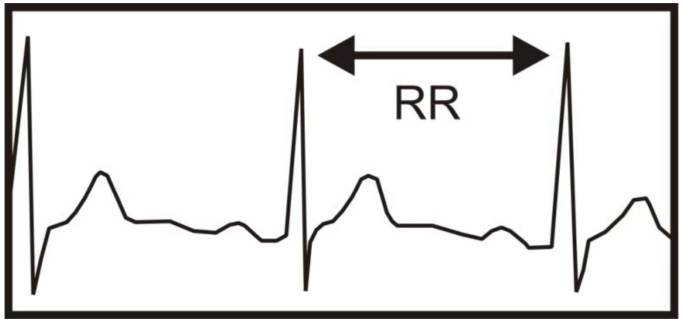


τὰ ὄντα ἰέναι τε πάντα καὶ μένειν οὐδέν”
Ta onta ienai te panta kai menein ouden
"All things move and nothing remains still“

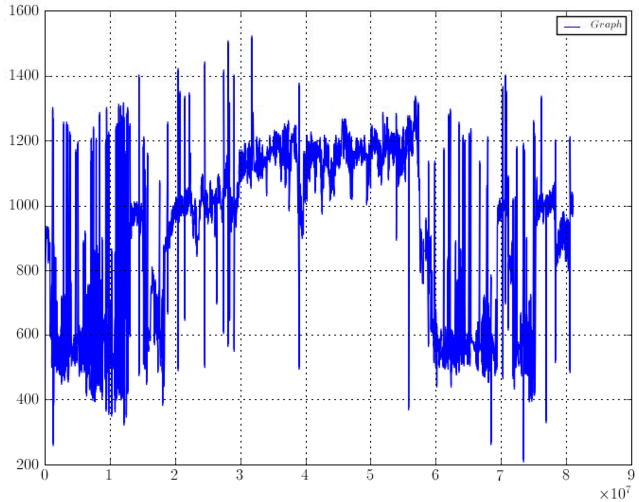
Cardiovascular Fluctuation: Construction of Interbeat Intervals

Extraction of Regulation Mechanisms by “RRI“:

iEGM/ECG:



Time Series of RR Intervals



Spontaneous Fluctuations of Interbeat Intervals:

Provides Physiological Information

Cardiovascular Signal Analysis

- Analysis of signal morphology (ECG, Impedance,…)
- Theory of excitable media (cellular interactions)
- (Spectral-)analysis of spontaneous fluctuations (HRV)
- Nonlinear dynamics and chaos theory
- Theory of stochastic systems
- Complex pattern recognition
- Several other approaches

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Time Dependent Analysis in Subintervals of 24h Measurements

Characterization by Single Cosinor Analysis

$$f(t) = M + A\cos(\omega t + \phi)$$

$$y_j, j = 1, ..., N$$

$$y_j = M + A\cos(\omega t_j + \phi)$$

$$y_j = M + A\cos(\phi)\cos(\omega t_j) - A\sin(\phi)\sin(\omega t_j) + e_j$$

$$\beta = A cos(\phi); \gamma = -A\sin(\phi)$$

$$x_j = \cos(\omega t_j); z_j = \sin(\omega t_j)$$

$$y_j = f(t_j) + e_j = M + \beta x_j + \gamma z_j + e_j$$

Linear Approximation

$$\sum_{j=1}^{n} x_j = \sum_{j=1}^{n} z_j = \sum_{j=1} x_j z_j = 0$$

$$\sum_{j=1}^{n} x_j^2 = \sum_{j=1}^{n} z_j^2 = \frac{n}{2}$$

$$\hat{M} = \frac{1}{n}\sum_{j=1}^{n} y_j$$

$$\hat{\beta} = \frac{2}{n}\sum_{j=1}^{n} x_j y_j$$

$$\hat{\gamma} = \frac{2}{n}\sum_{j=1}^{n} z_j y_j$$

Least Squares Results

Characterization by Single Cosinor Analysis

$$\hat{A} = (\hat{\beta}^2 + \hat{\gamma}^2)^{\frac{1}{2}}$$
$$\hat{\phi} = K + \hat{\theta}$$

$$\hat{\theta} = \arctan|\frac{\hat{\gamma}}{\hat{\beta}}| \quad , \quad 0 < \hat{\theta} < \frac{\pi}{2}$$

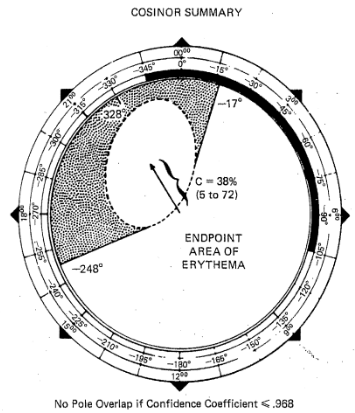
$$\begin{aligned} \hat{\phi} &= -\hat{\theta} &&, \quad \hat{\gamma} > 0, \hat{\beta} \geq 0 \\ \hat{\phi} &= -\pi + \hat{\theta} &&, \quad \hat{\gamma} \geq 0, \hat{\beta} < 0 \\ \hat{\phi} &= -\pi - \hat{\theta} &&, \quad \hat{\gamma} < 0, \hat{\beta} \leq 0 \\ \hat{\phi} &= -2\pi + \hat{\theta} &&, \quad \hat{\gamma} \leq 0, \hat{\beta} > 0 \end{aligned}$$

Amplitude and „Acrophase"

$$\hat{\sigma}^2 = \frac{RSS}{(n-3)}$$

$$\hat{M} \pm (t_{1-\frac{\alpha}{2}})(\frac{\hat{\sigma}}{\sqrt{n}})$$

$$(\beta^* - \hat{\beta})^2 + (\gamma^* - \hat{\gamma})^2 \leq \frac{4}{n}\hat{\sigma}^2 F_{1-\alpha}$$



Confidence Area

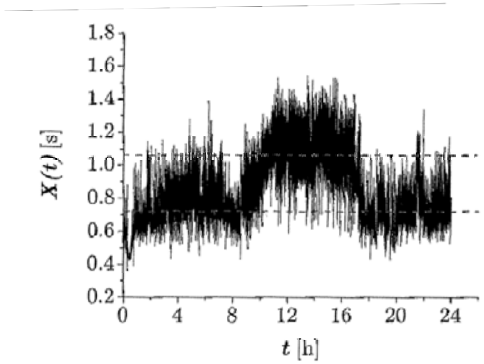
Characterization by Langevin Equation

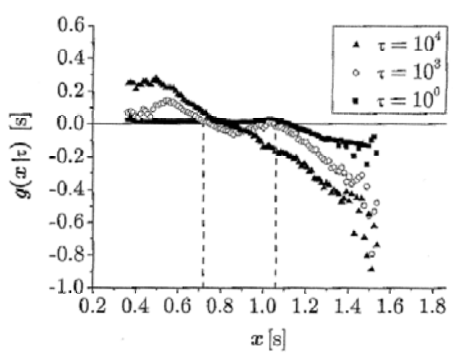
$$\frac{dX(t)}{dt} = g[X(t),t] + h[X(t),t]\Gamma(t),$$

$$g[X(t),t,\tau] = \gamma(t+\tau) - X(t).$$

$$\gamma(t) = \begin{cases} -1, & t \in [0, 0.3T], \\ -1 + \dfrac{2t}{0.4T}, & t \in [0.3T, 0.7T], \\ +1, & t \in [0.7T, T] \end{cases}$$

Stochastic noise Γ, feedback term g, piecewise constant trend γ





Solution for the true piecewise levels ξ_1 and ξ_2 by linear approximation of g

Kirchner (2008)

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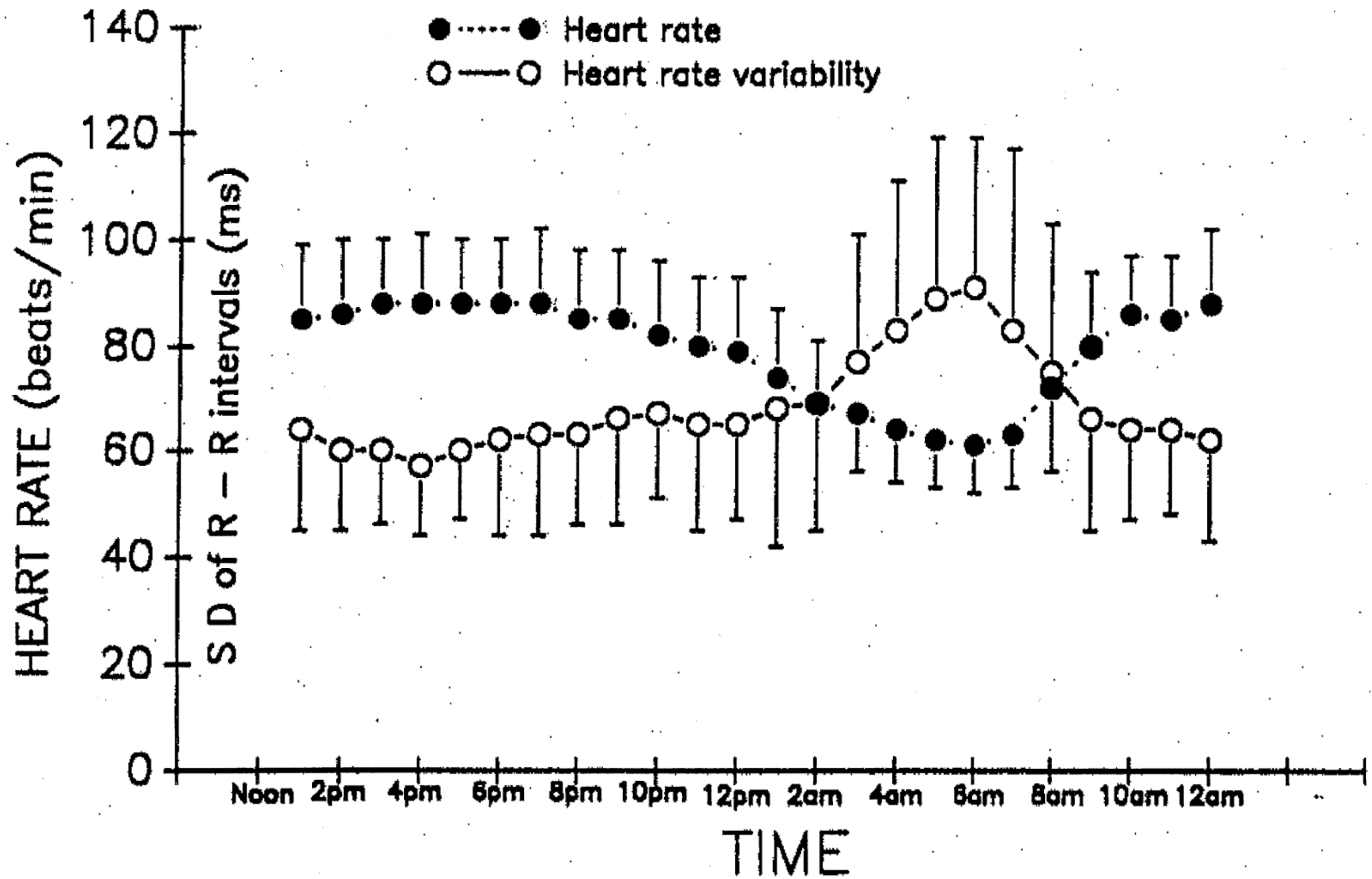
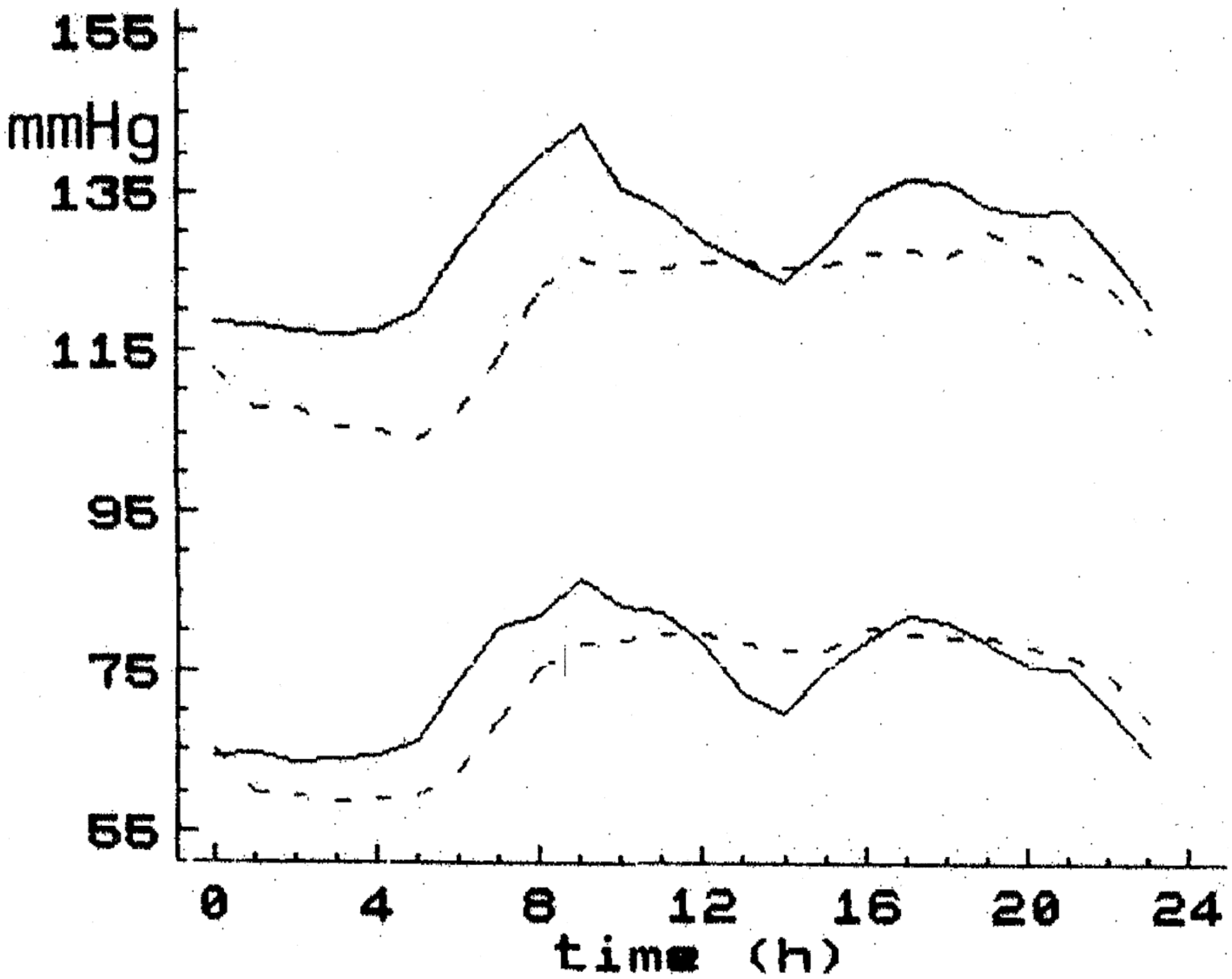
Circadian Rhythm of Cardiovascular Variables: Heart Rate



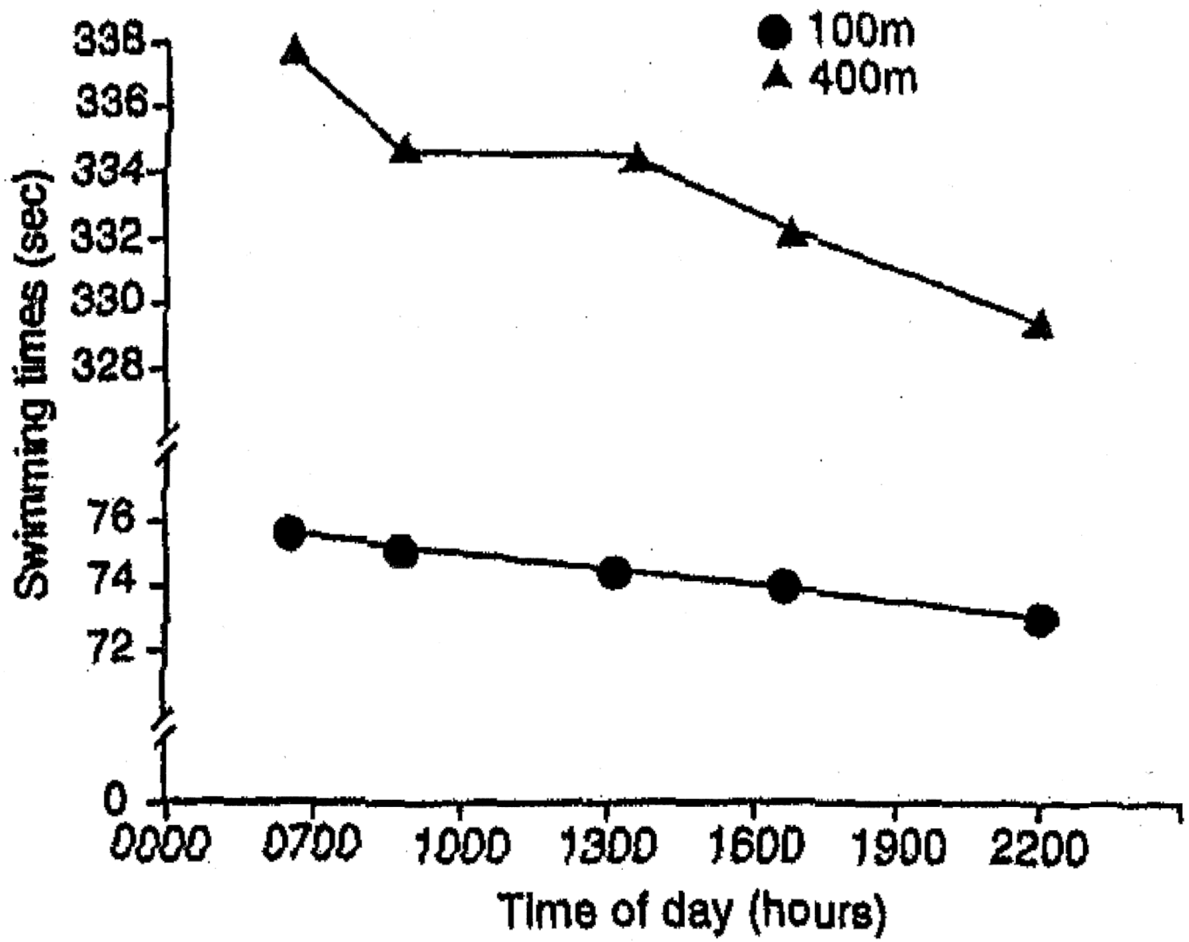
Huikuri (1990)

Circadian Rhythm of Cardiovascular Variables: Blood Pressure



Baumgart (1991)

Circadian Rhythm of Cardiovascular Variables: Performance



Atkinson (1996)

Circadian Rhythm of Heart Disease: Stent Thrombosis

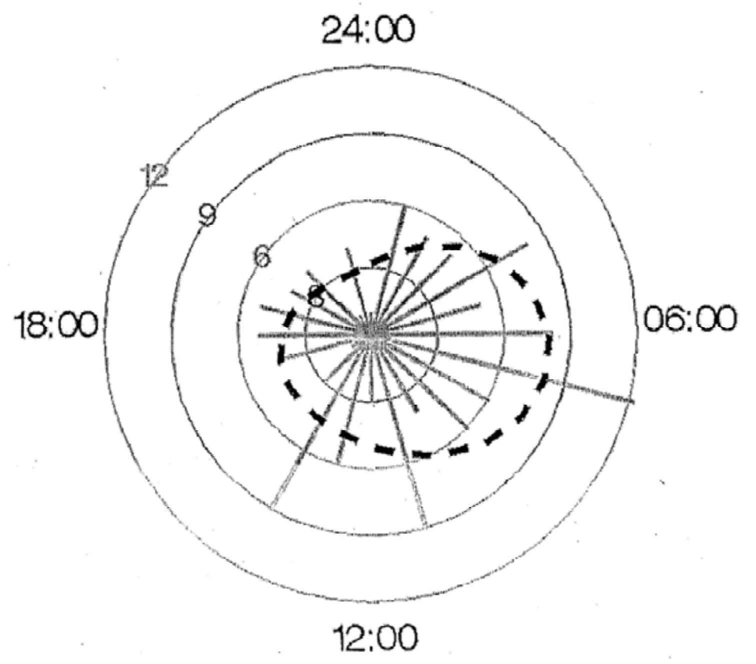
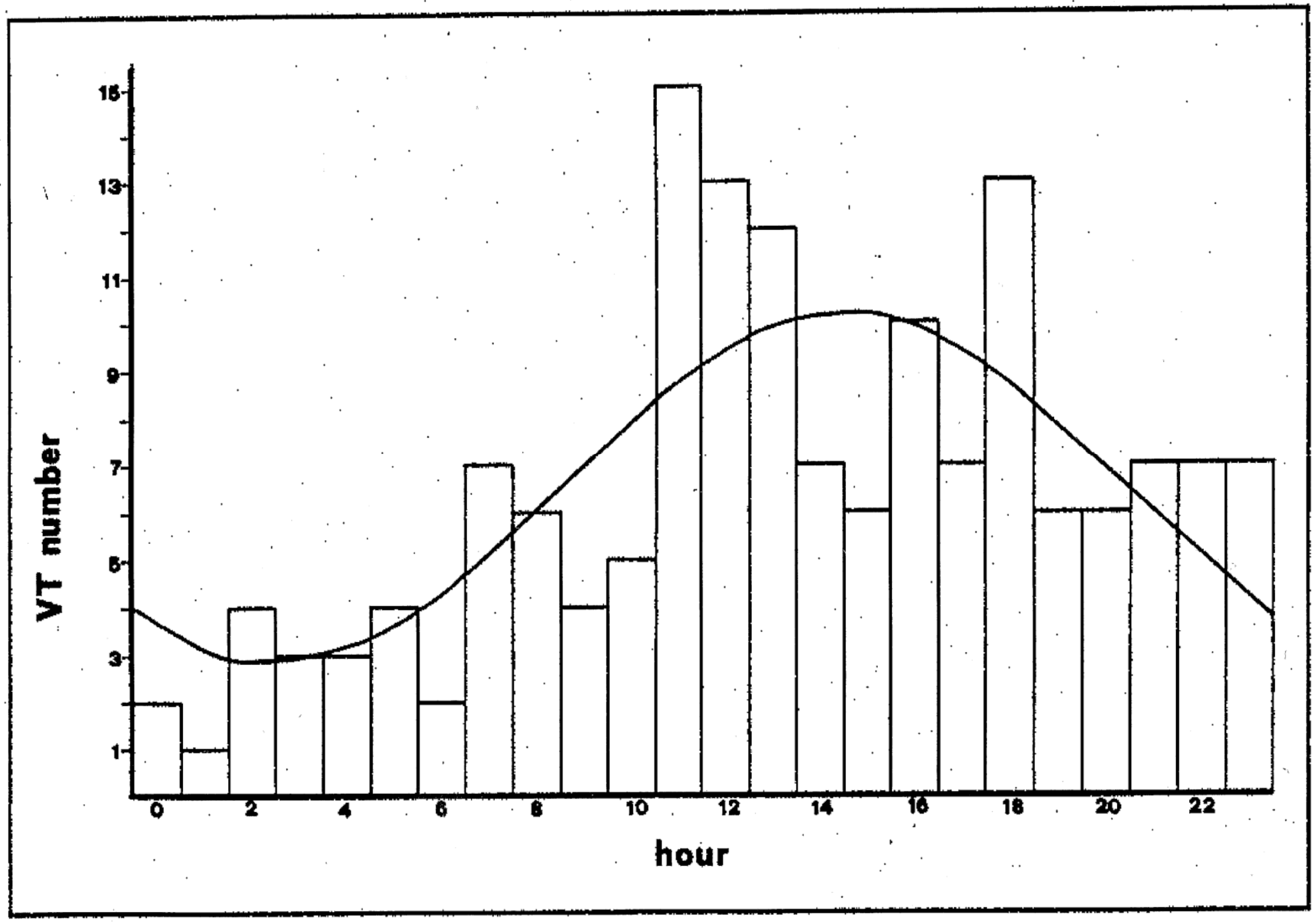


Figure 1. Circadian Variation of Overall Stent Thrombosis (n = 124)

The **spokes** are drawn from the center of the circle to the number of stent thrombosis events that occurred that hour of the day; the **spoke angles** represent the time of day (rounded to the nearest hour). The scale is presented by concentric circles; the **center of the circles** represents 0 frequency; and the **outer circle** represents 12 stent thrombosis events. The **dashed line** is a sinusoidal smoothing function indicating the average circadian trends. The plot indicates that there was a low incidence of stent thrombosis at approximately 7:00 PM to 12:00 AM and a peak incidence at approximately 7:00 AM. The association between onset of stent thrombosis and time of day was significant ($p = 0.006$).

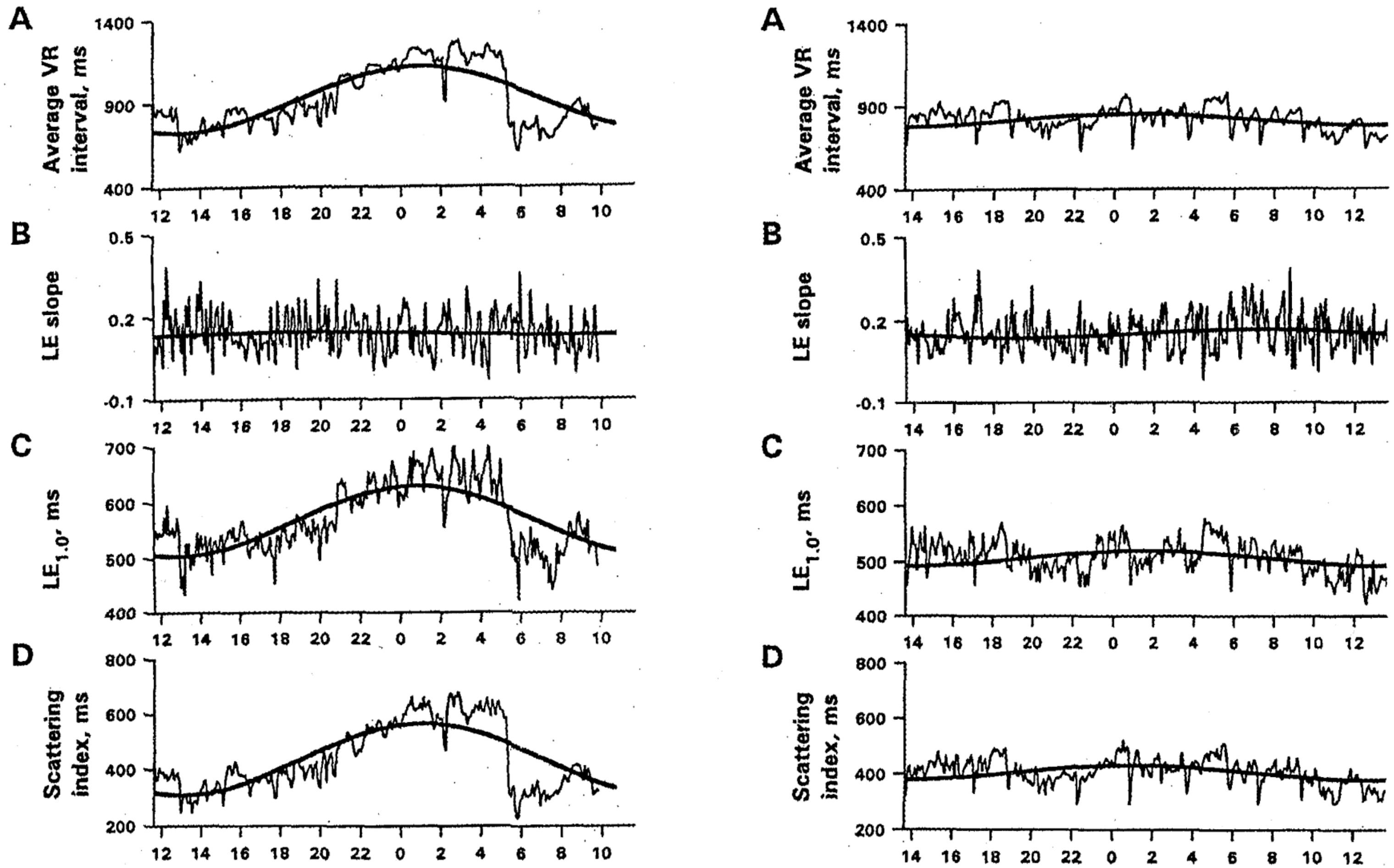
Mahmoud (2011)

Circadian Rhythm of Heart Disease: Ventricular Tachycardia



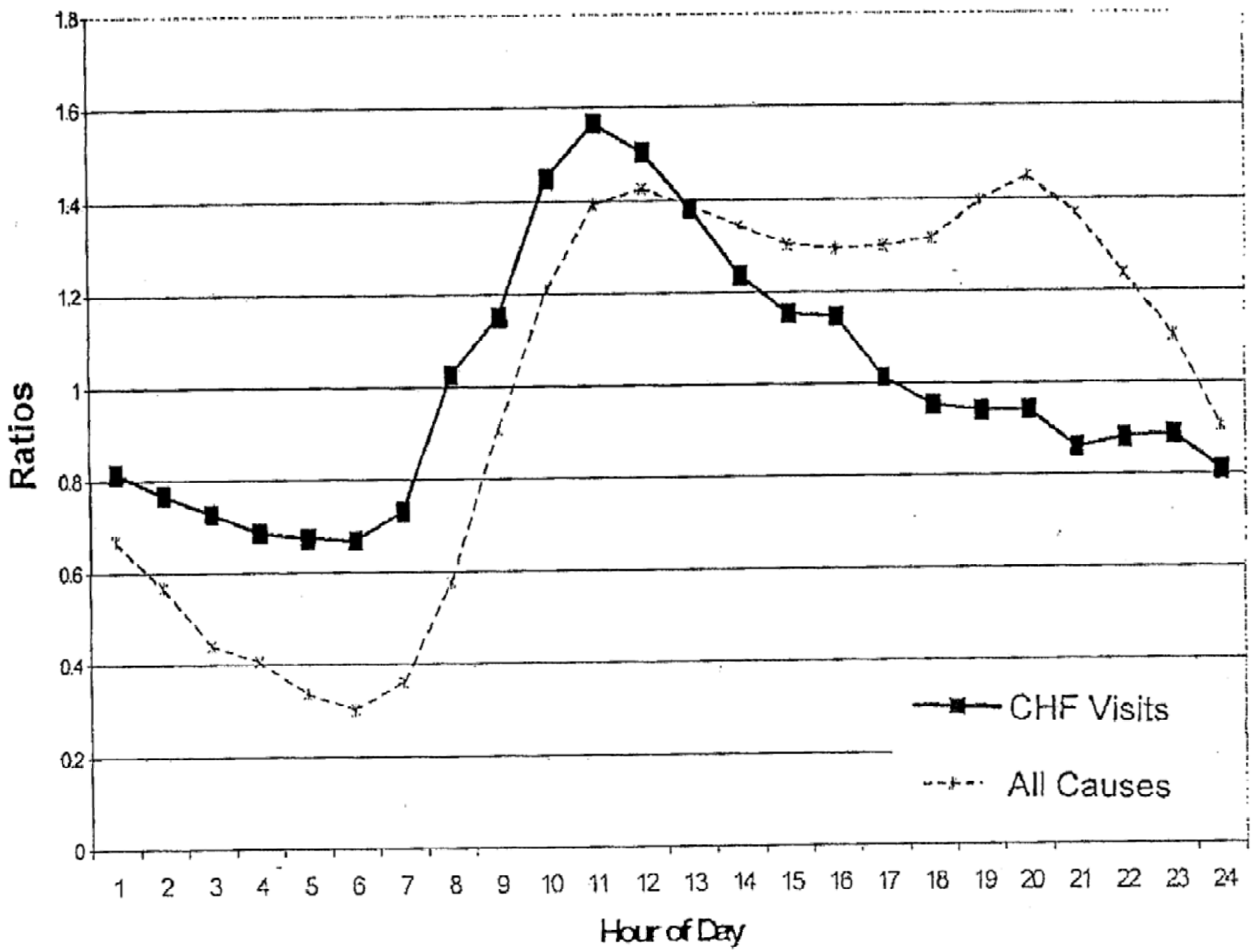
Lucente (1998)

Circadian Rhythm of Heart Disease: Atrial Fibrillation



Hayano (1998)

Circadian Rhythm of Heart Disease: Heart Failure Events (CHF)



Allegra (2001)

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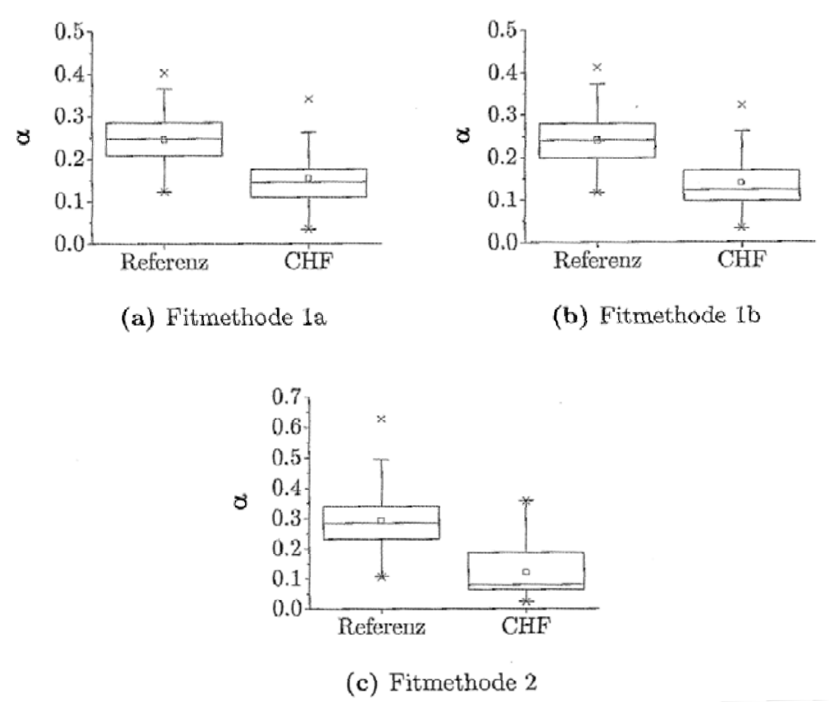
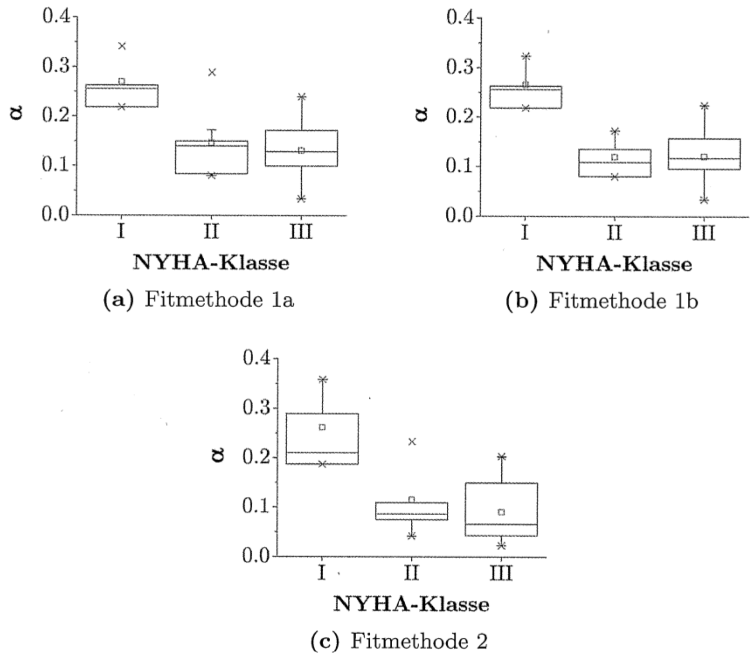
Circadian Rhythm in Congestive Heart Failure (CHF)





Clear discrimination of healthy and CHF group by different methods of fit for g

$$\alpha = \frac{\xi_2 - \xi_1}{\xi_2}.$$

Discrimination of mild and advanced levels of heart failure

Kirchner (2008)

Conclusion: The Importance of Circadian Rhythm

- Circadian rhythm is observed everywhere in world and human physiology
- Circadian rhythm analysis may help to understand cardiovascular system
- Circadian rhythm allows for quantification of risk or disease status
- Circadian rhythm may mask or mimic other relations
- Circadian rhythm may interfere with experiments

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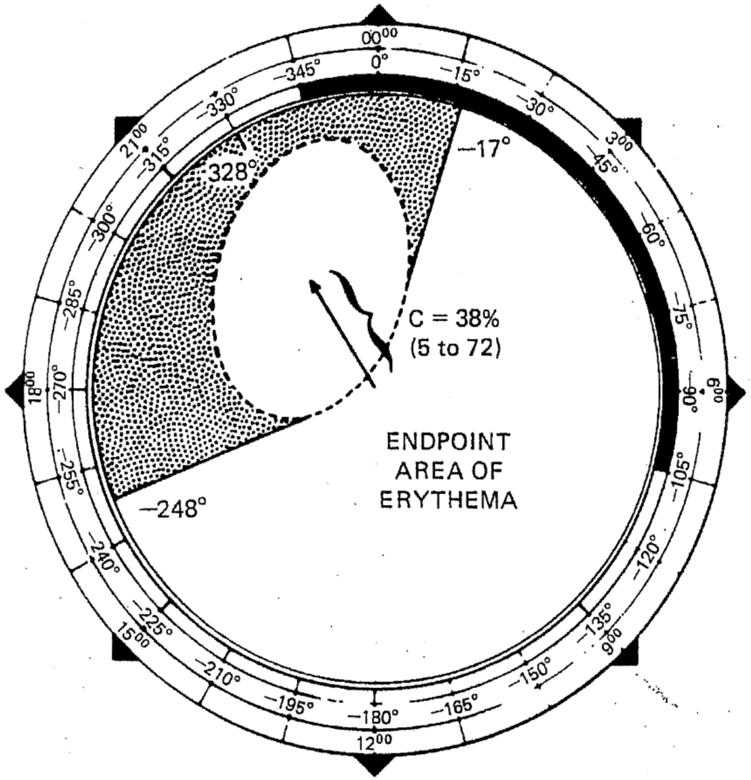
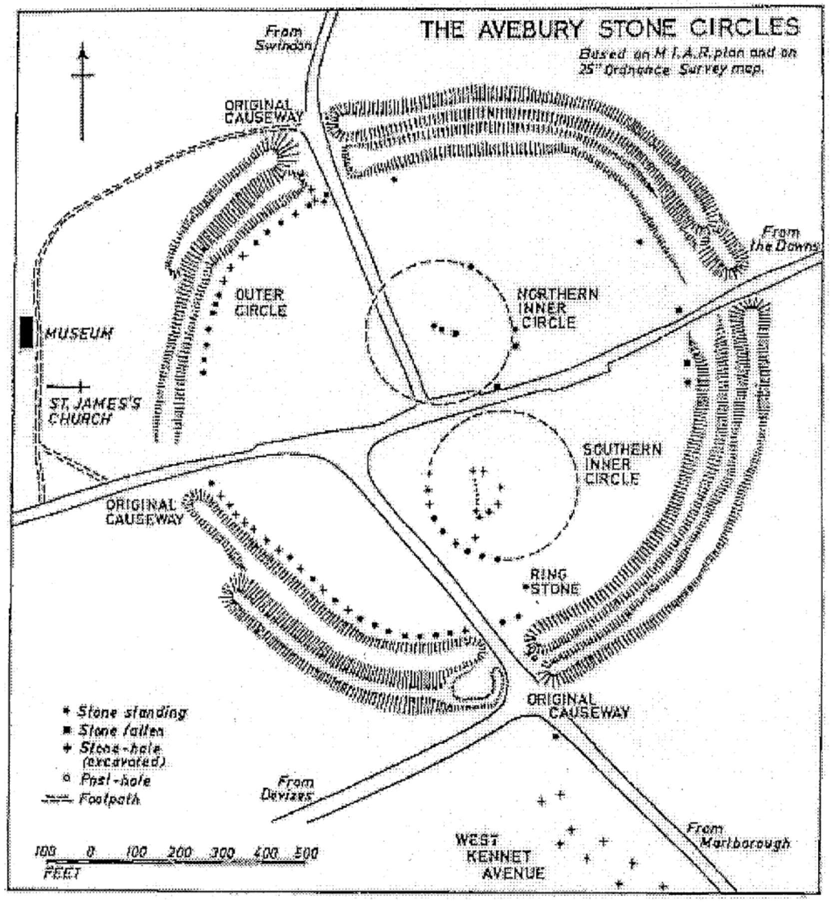
Cardiovascular Variables Should Be Observed >24h Whenever Possible

Quantifying the Rhythm: An Old and New Challenge

COSINOR SUMMARY



No Pole Overlap if Confidence Coefficient ≤ .968



Reinberg (1983)

Bolshoe Spasibo!

Vielen Dank!