



# **Circadian Rhythm**

## **Introduction and Cardiovascular Applications**

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**Friedrich-Alexander-Universität Erlangen-Nürnberg**

**21 - 25 Mar 2011**

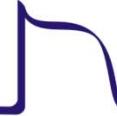
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## Agenda: Circadian Rhythm

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



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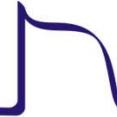
# Rhythm and Man



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

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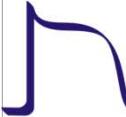
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# Rhythm and Fluctuations



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



# Daily Rhythms in Nature

## Eine Blumen-Uhr



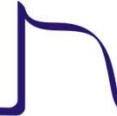
Linné (1745)

„A Clock of Flowers“

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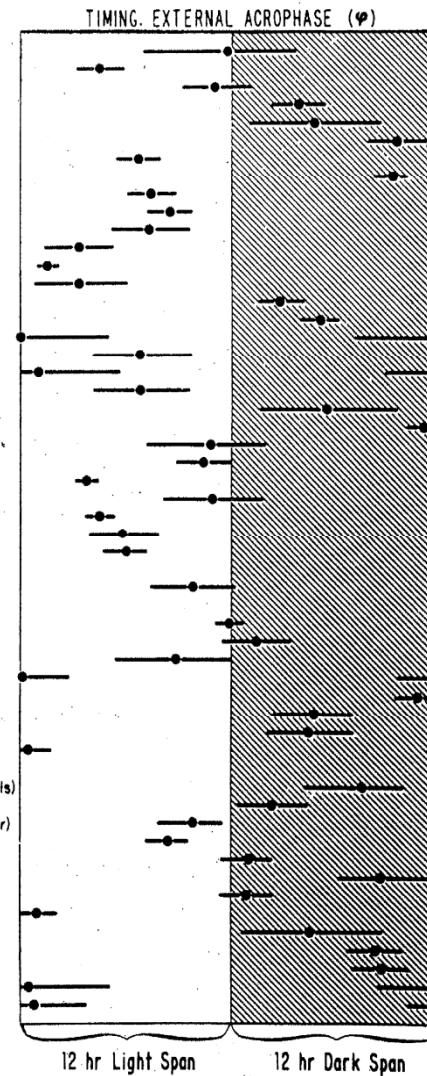
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# Variation of Physiological Parameters in Mice

SITE	VARIABLE
HYPOTHALAMUS	CRF
PITUITARY	ACTH
ADRENAL GLAND	Corticosterone Mitosis (parenchyma) Mitosis (stroma) Reactivity to ACTH
BRAIN	5-Hydroxytryptamine
CORNEA	Mitosis
EPIDERMIS	Mitosis (pinna) Tensile Strength
KIDNEY	Transaminidase Mitosis
LIVER	Glycogen Content Malic Dehydrogenase Phospholipids (RSA) RNA Metabolism (RSA) DNA Metabolism (RSA)
DUODENUM	Mitosis (parenchyma) $H^3$ -thymidine uptake
PANCREAS	Mitosis, $\alpha$ -cells " $\beta$ -cells " acini
BONE MARROW	$H^3$ -thymidine uptake
BLOOD	Corticosterone Phosphate Insulin Total Leukocytes Lymphocytes Eosinophils
WHOLE BODY	IgM Hemagglutination titers: Background Response to SRBC RES (Phagocytic index) Plaque-forming cells (spleen) Colony-forming cells (spleen) Temperature (colon) Gross Motor Activity Body Weight
<u>SUSCEPTIBILITY TO:</u>	
	X-ray (% no. nucleated bone marrow cells) White Noise (% convulsing) Dimethylbenzanthracene (% with tumor) Endotoxin (% deaths) Ethanol Librium (% survival time) Methopyrapone Ouabain Daunomycin Adriamycin Arabinosyl Cytosine Cyclophosphamide Vincristine

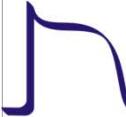


Halberg (1978)

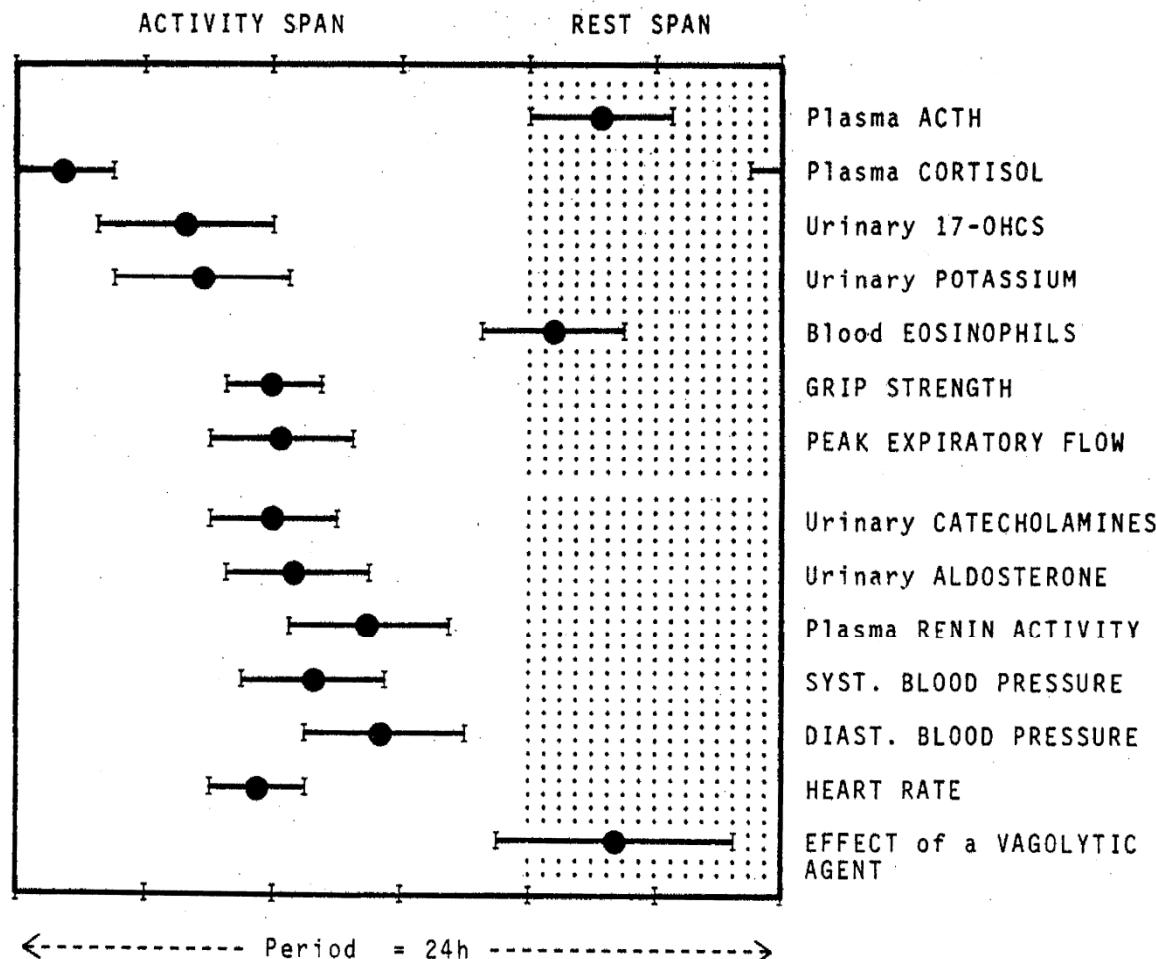
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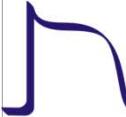
# Variation of Physiological Parameters in Man



Reinberg (1983)

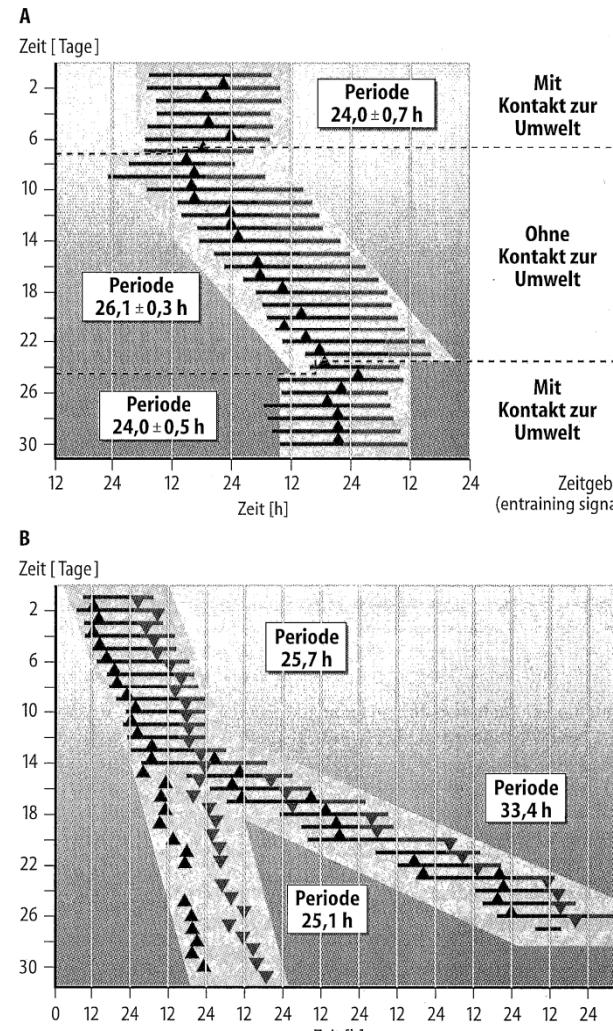
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# Free Running Cycles vs. Entrainment

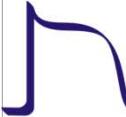
Temperature and  
Sleep Cycle under  
Temporary Isolation



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)**

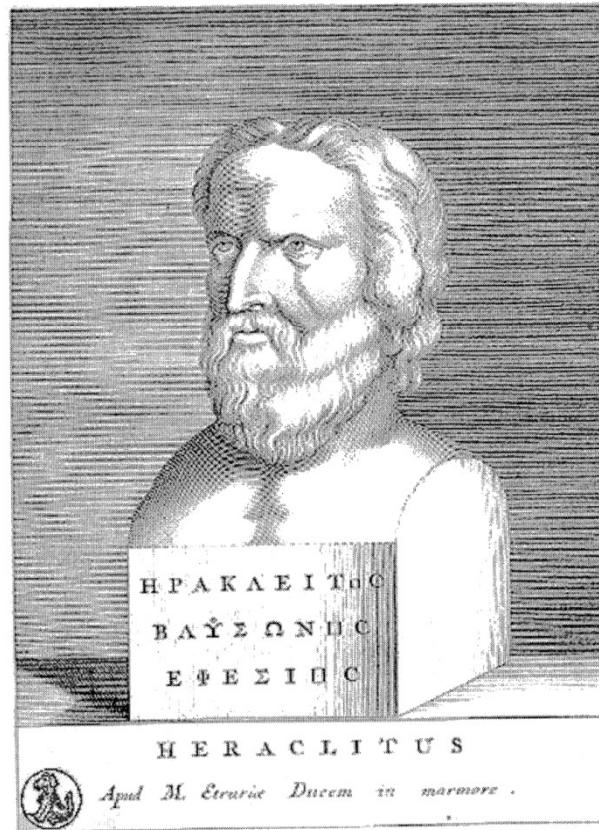


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# Circadian Rhythm of Fluctuations

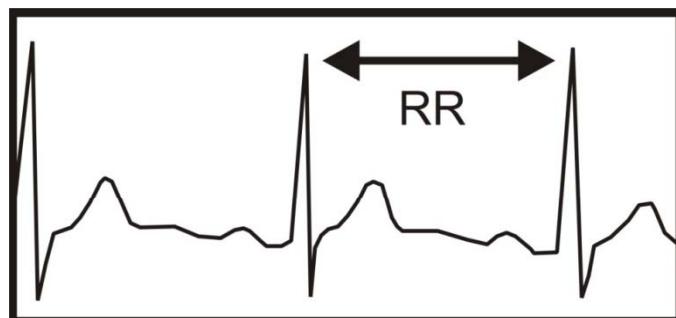


τὰ ὄντα ἔναι τε πάντα καὶ μένειν οὐδέν”  
Ta onta ienai te panta kai menein ouden  
"All things move and nothing remains still"

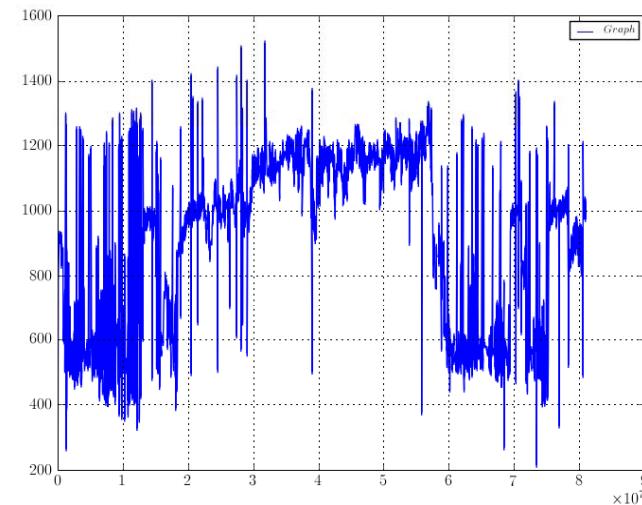
# Cardiovascular Fluctuation: Construction of Interbeat Intervals

Extraction of Regulation Mechanisms by “RRI”:

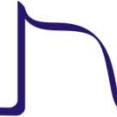
iEGM/ECG:



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



Time Dependent Analysis in Subintervals of 24h Measurements



# Characterization by Single Cosinor Analysis

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

$$y_j, j = 1, \dots, N$$

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

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

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

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

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

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

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

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

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

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

## Linear Approximation

## Least Squares Results



# Characterization by Single Cosinor Analysis

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

$$\hat{\phi} = K + \hat{\theta}$$

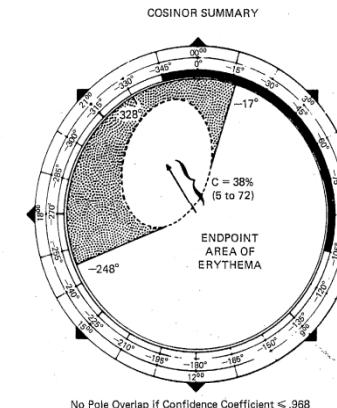
$$\hat{\sigma}^2 = \frac{RSS}{(n - 3)}$$

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

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

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

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



Amplitude and „Acrophase“

Confidence Area



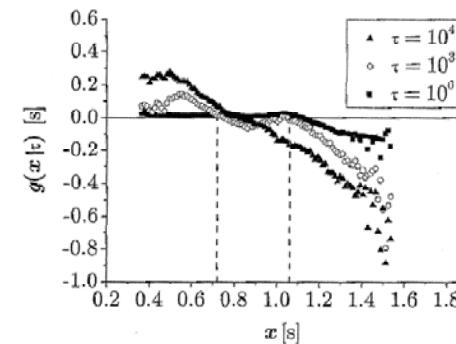
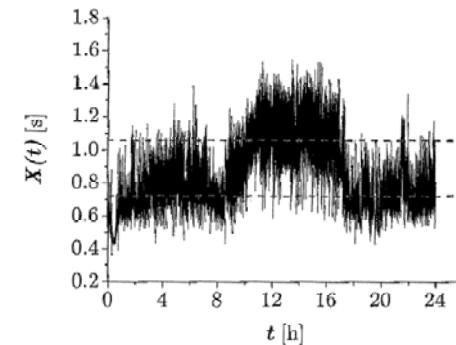
# Characterization by Langevin Equation

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

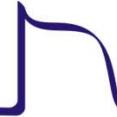
$$g[X(t), t, \tau] = \gamma(t + \tau) - X(t).$$

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

Stochastic noise  $\Gamma$ ,  
feedback term  $g$ ,  
piecewise constant  
trend  $\gamma$



Solution for the true  
piecewise levels  $\xi_1$  and  
 $\xi_2$  by linear  
approximation of  $g$

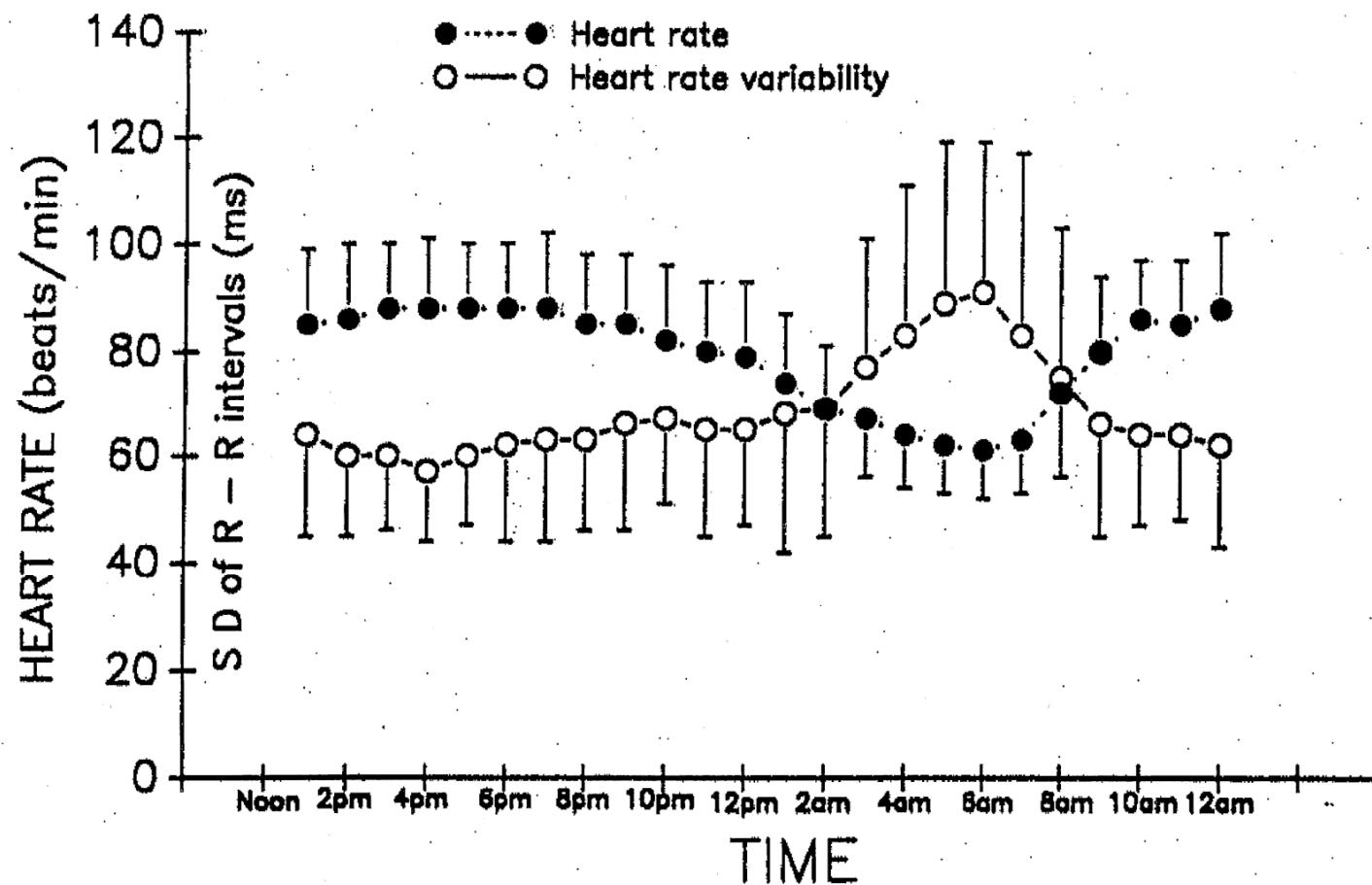


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# Circadian Rhythm of Cardiovascular Variables: Heart Rate

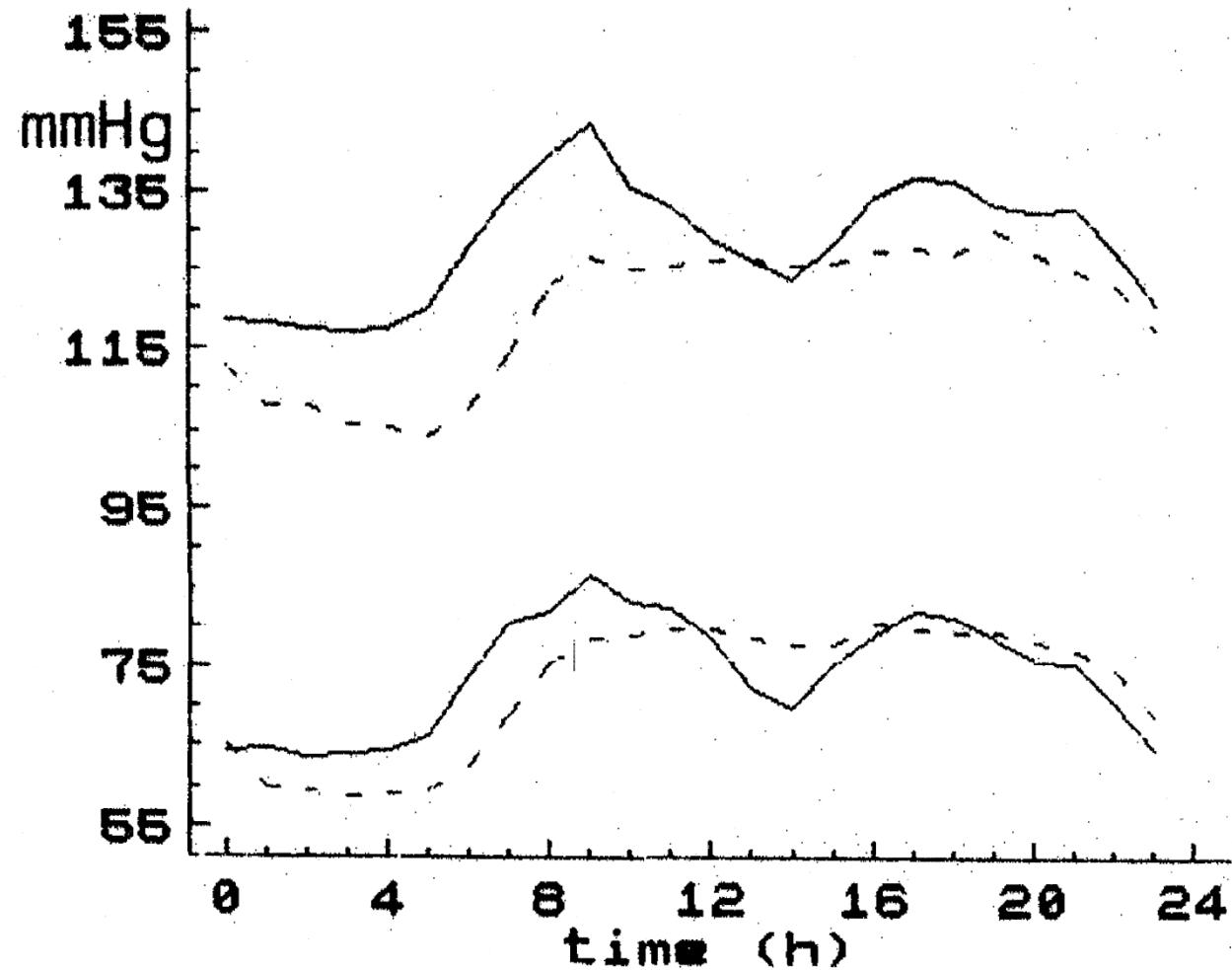


Huikuri (1990)

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# Circadian Rhythm of Cardiovascular Variables: Blood Pressure

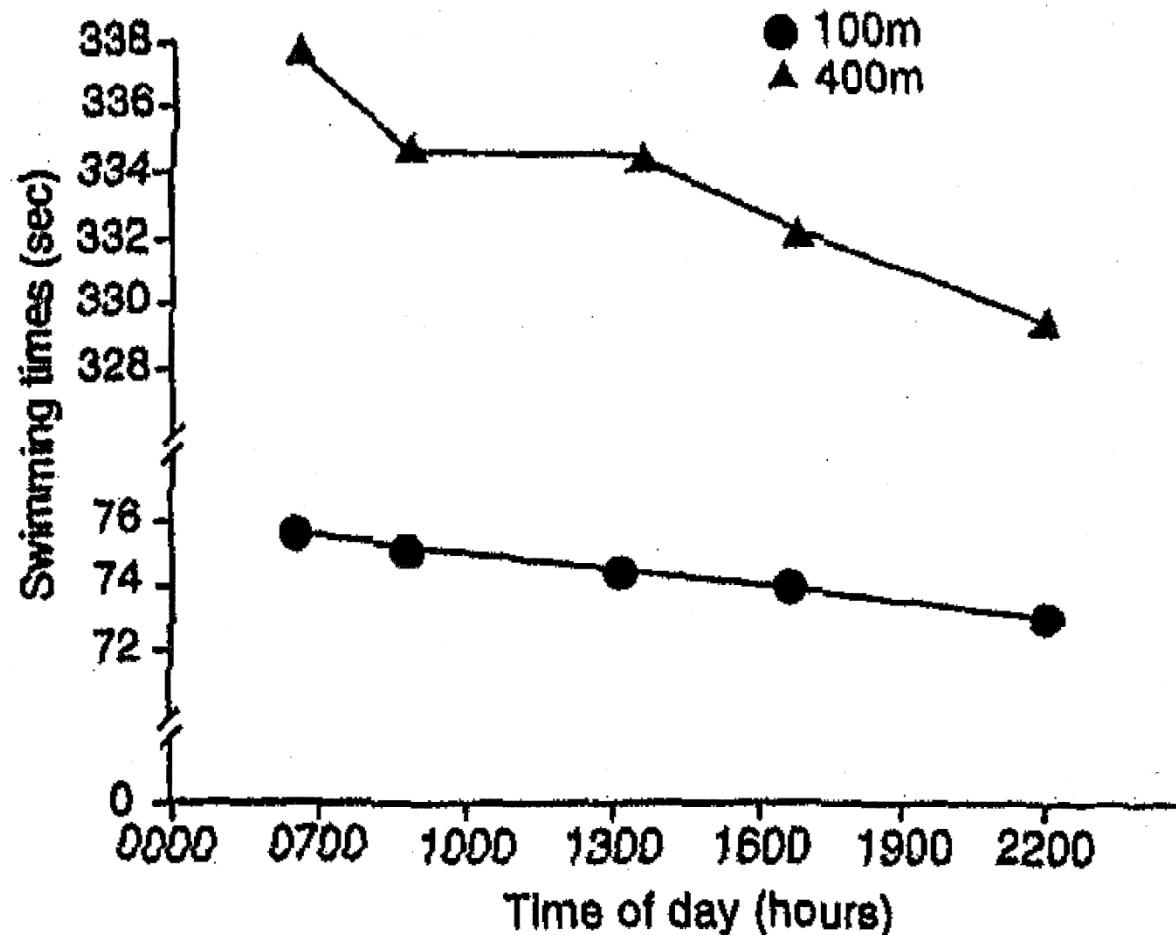


Baumgart (1991)

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# Circadian Rhythm of Cardiovascular Variables: Performance



Atkinson (1996)

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# Circadian Rhythm of Heart Disease: Stent Thrombosis

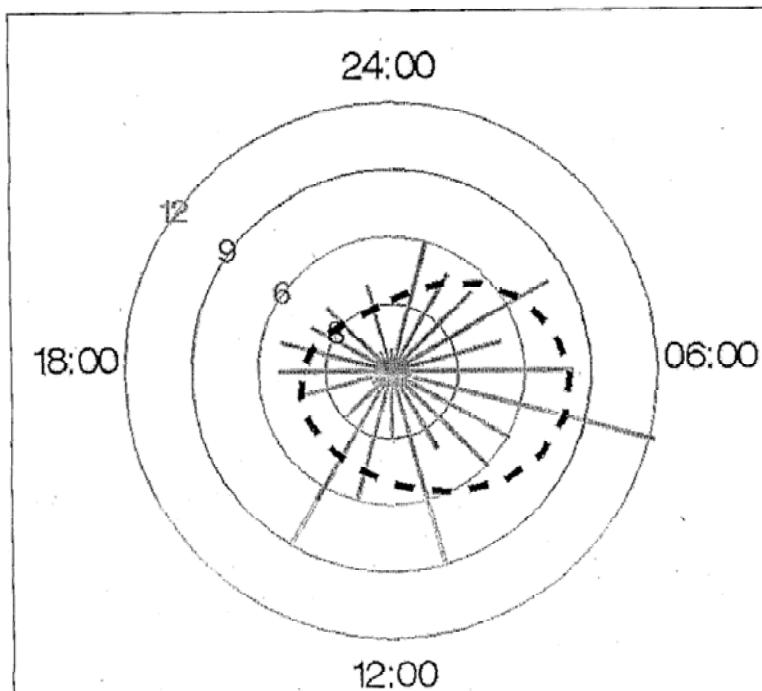


Figure 1. Circadian Variation of Overall Stent Thrombosis ( $n = 124$ )

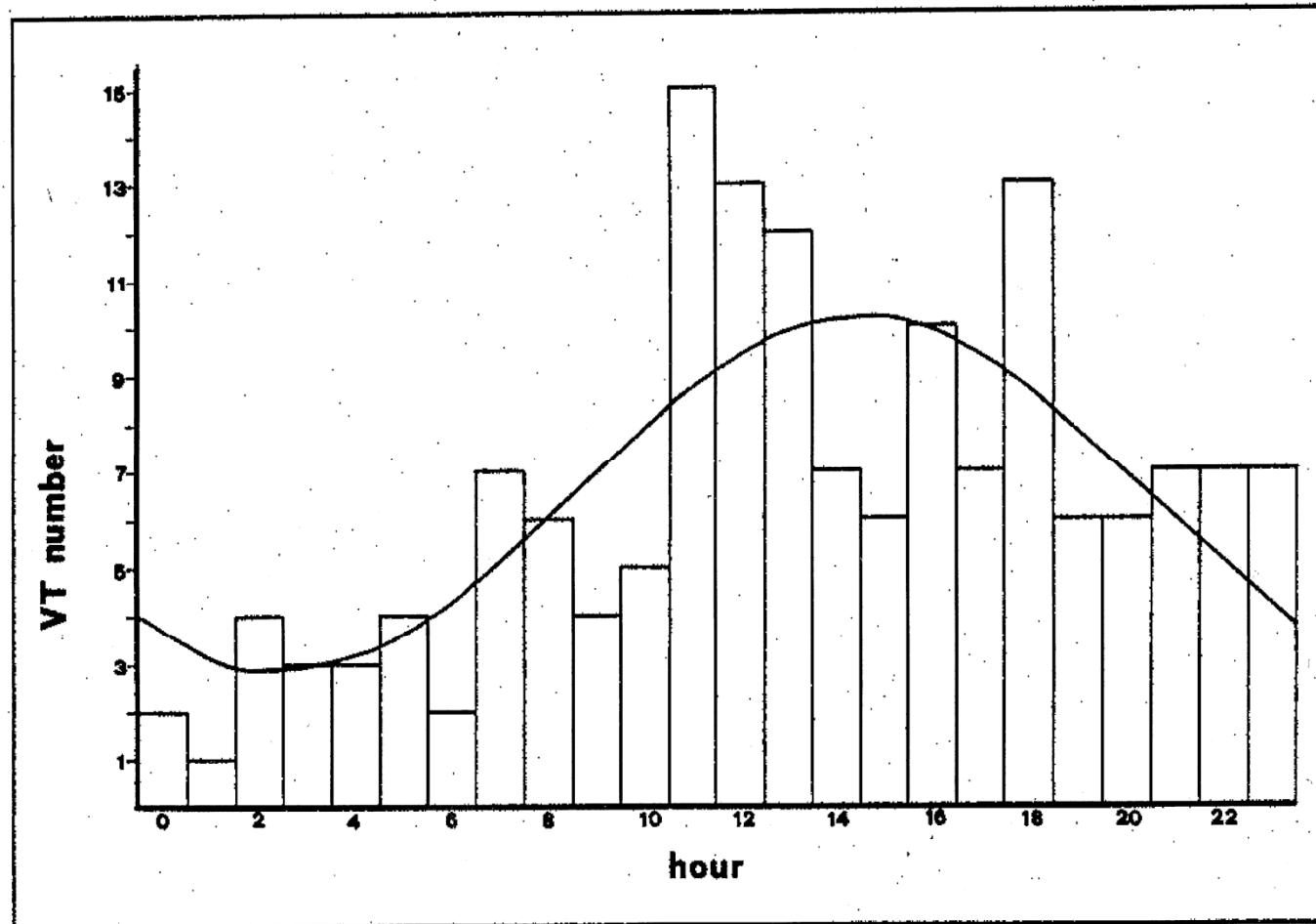
The **spokes** are drawn from the center of the circle to the number of stent thrombosis events that occurred that hour of the day; the **spoke angles** represent the time of day (rounded to the nearest hour). The scale is presented by concentric circles; the **center of the circles** represents 0 frequency; 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)

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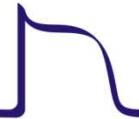
# Circadian Rhythm of Heart Disease: Ventricular Tachycardia



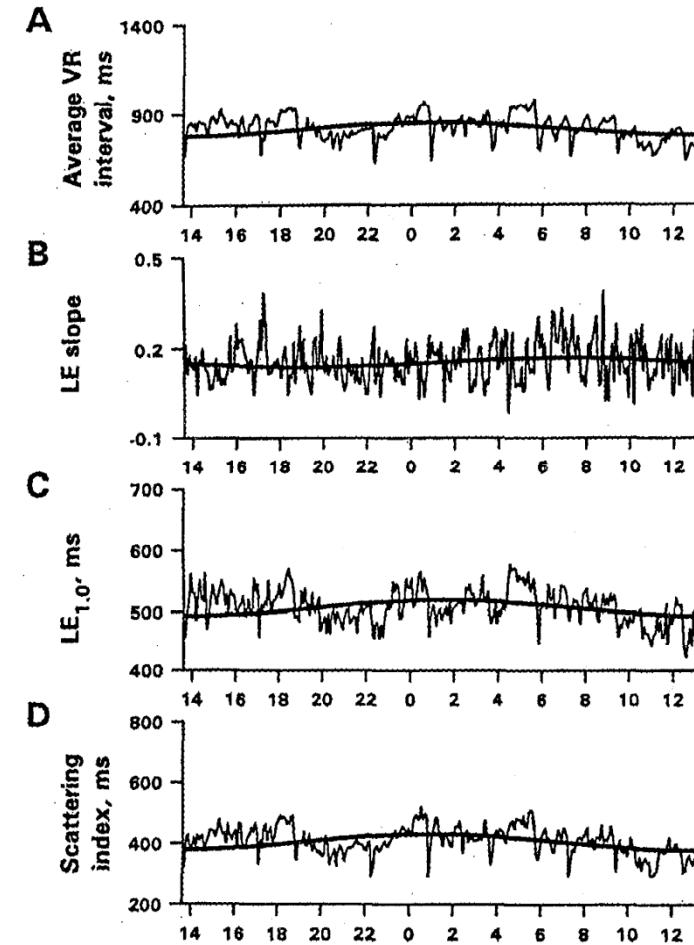
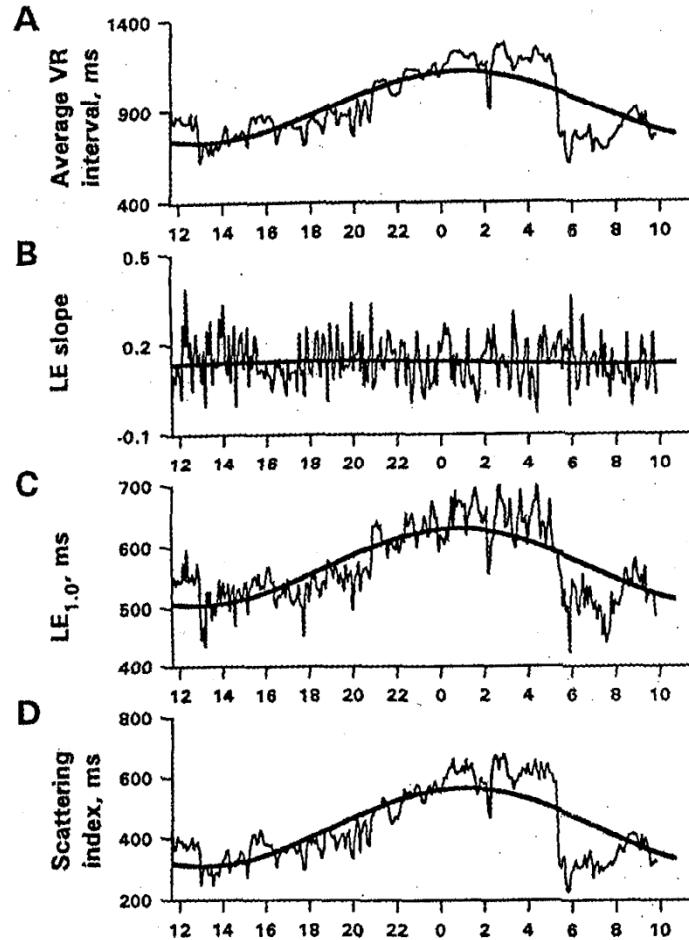
Lucente (1998)

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# Circadian Rhythm of Heart Disease: Atrial Fibrillation

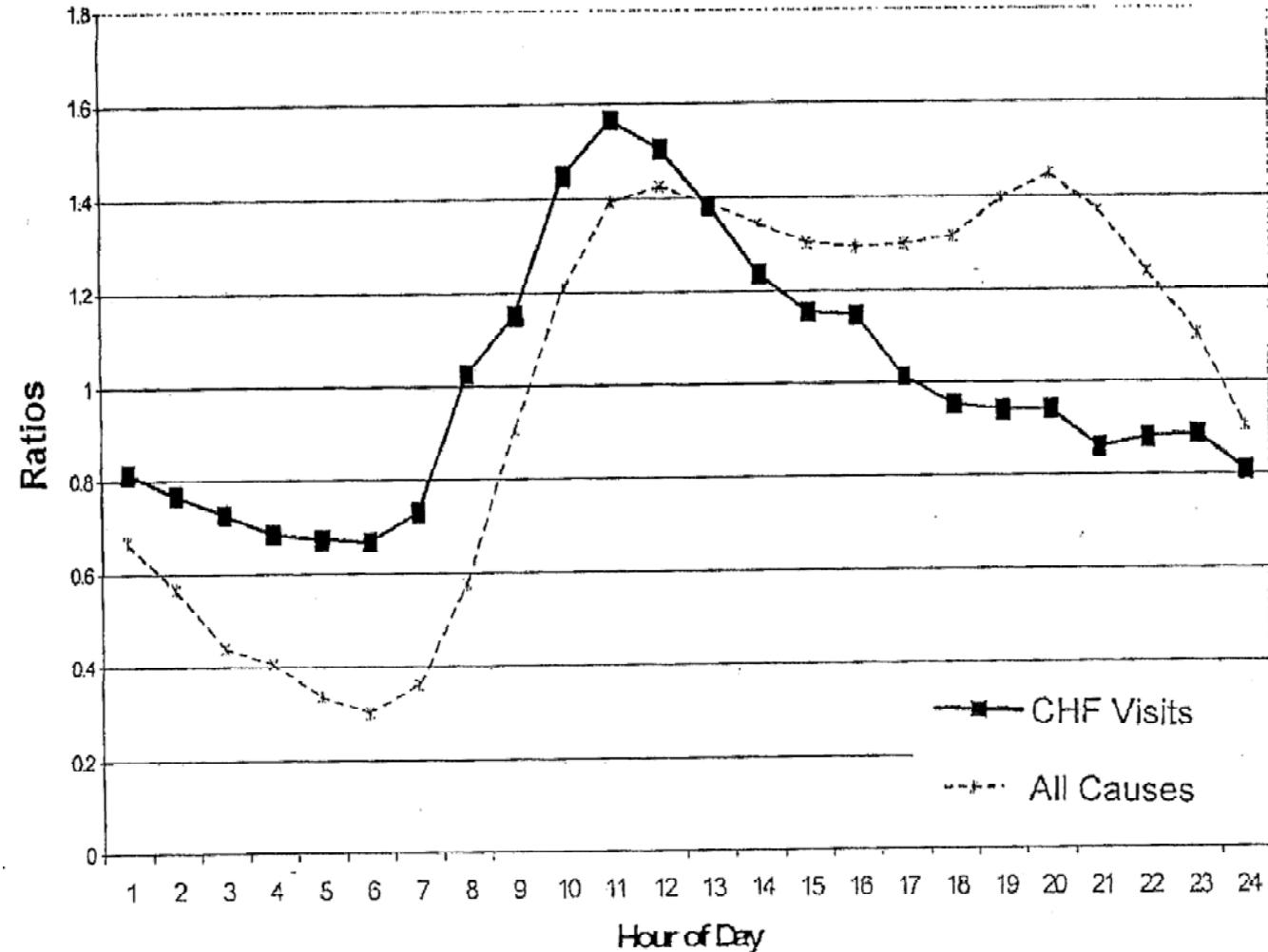


Hayano (1998)

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



Allegra (2001)

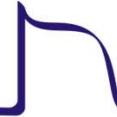
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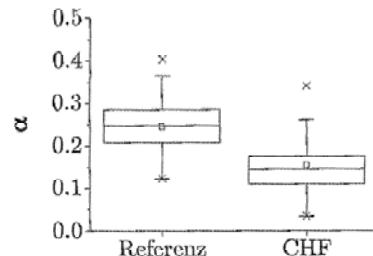


## Agenda: Circadian Rhythm

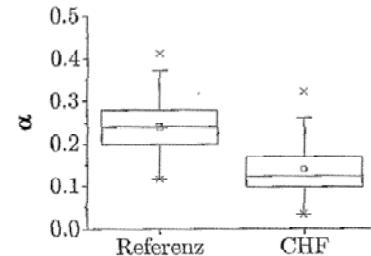
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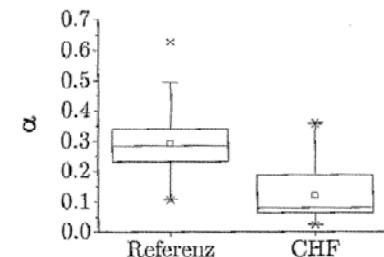
# Circadian Rhythm in Congestive Heart Failure (CHF)



(a) Fitmethode 1a



(b) Fitmethode 1b

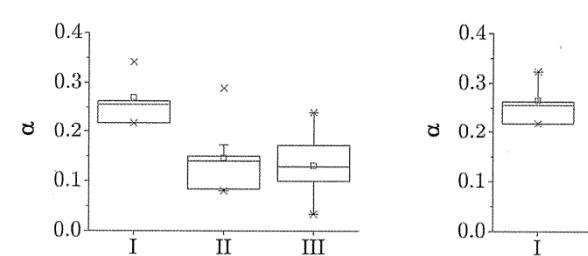


(c) Fitmethode 2

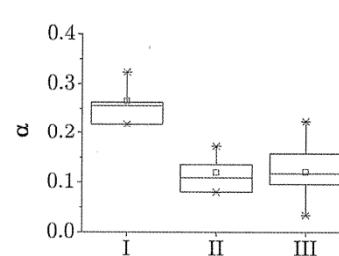
**Clear discrimination of healthy and CHF group by different methods of fit for g**

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

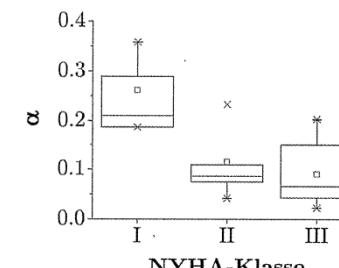
Kirchner (2008)



(a) Fitmethode 1a

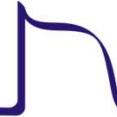


(b) Fitmethode 1b



(c) Fitmethode 2

**Discrimination of mild and advanced levels of heart failure**



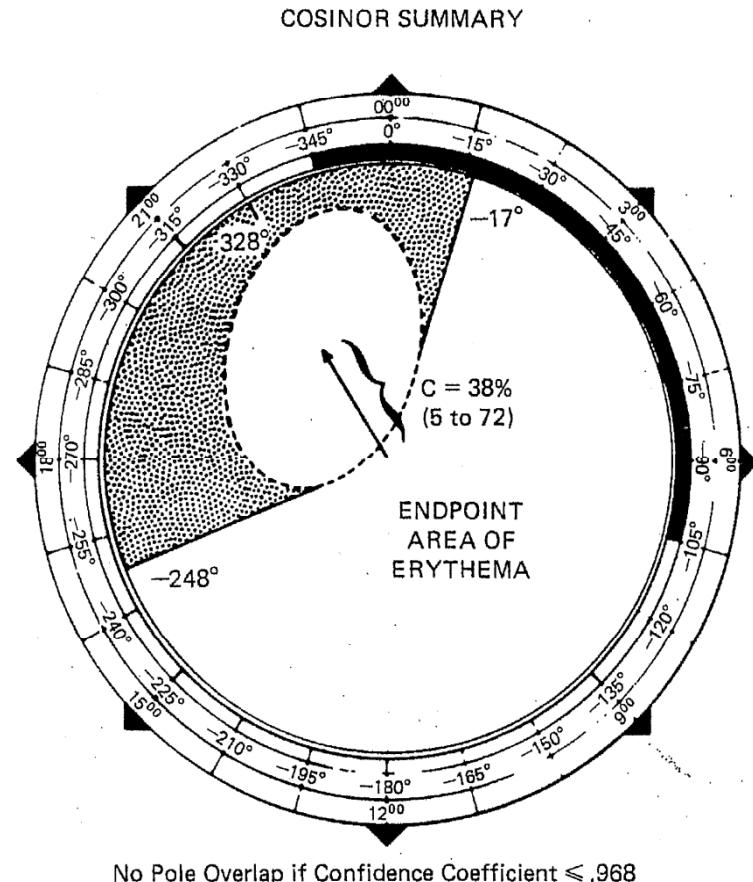
## Conclusion: The Importance of Circadian Rhythm

- 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

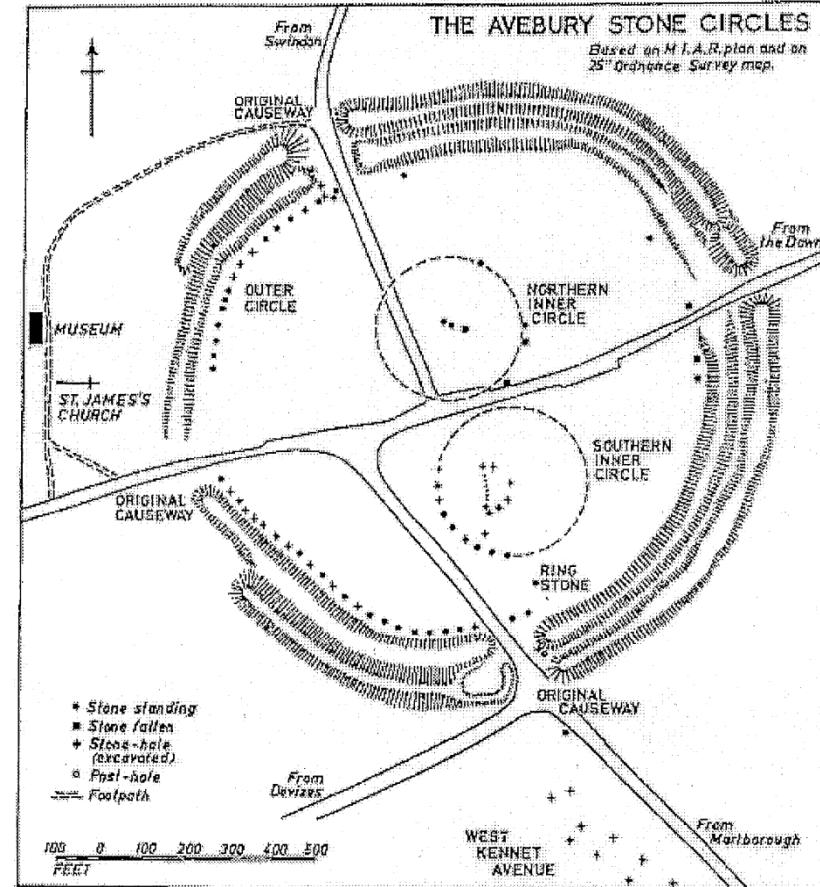


**Cardiovascular Variables Should Be Observed >24h Whenever Possible**

# Quantifying the Rhythm: An Old and New Challenge



Reinberg (1983)



Bolshoe Spasibo!  
Vielen Dank!

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