Chronobiologic Aspects of Heart Rate Variability

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HEART RATE VARIABILITY — 2006
April 20-22, 2006

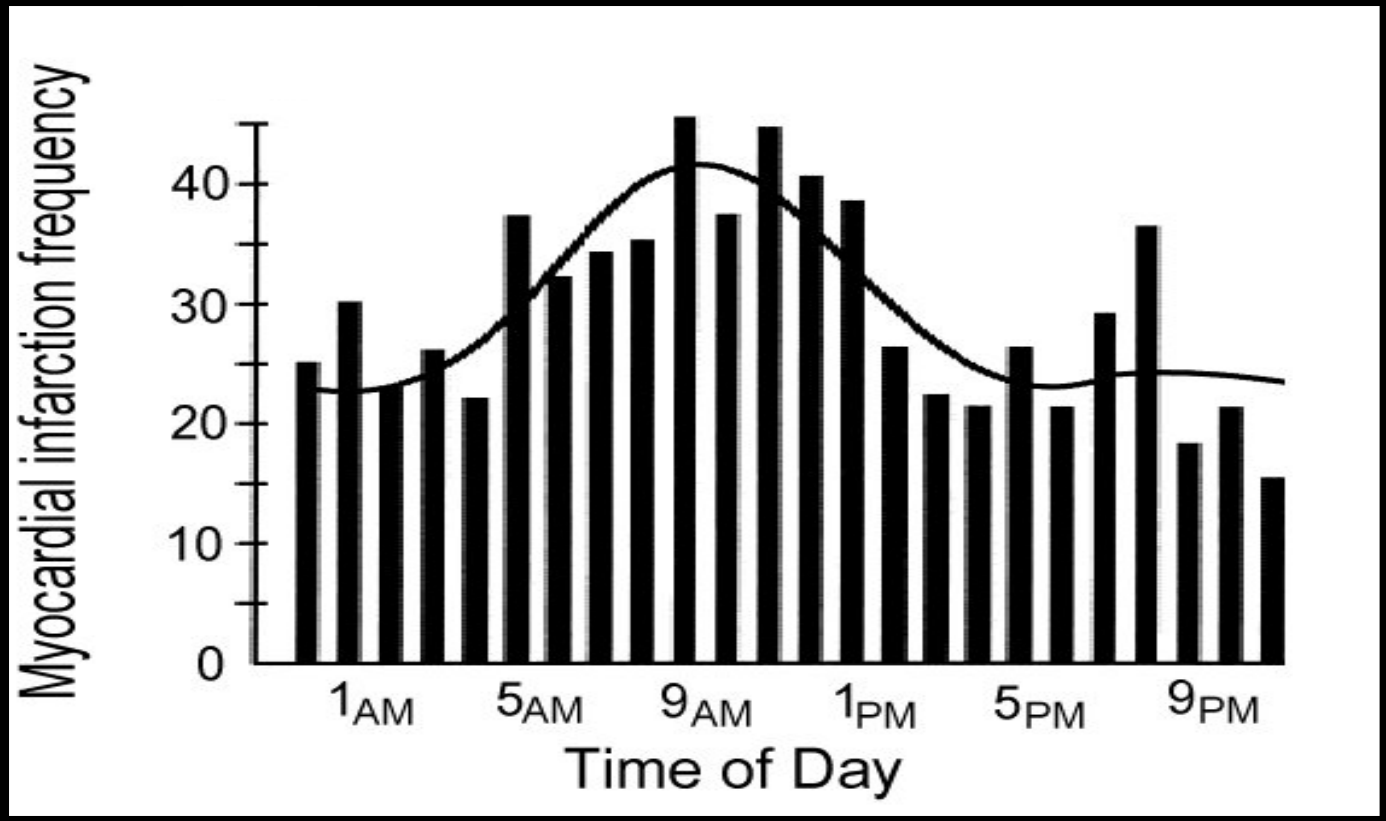
Overview

- Morning peak in cardiovascular risk
- Potential factors involved
- “Circadian” what does it mean?
- Circadian pacemaker & the heart
- Circadian rhythm in human cardiovascular physiology?
- Circadian rhythm in responsiveness?
- Clinical implications?

Overview

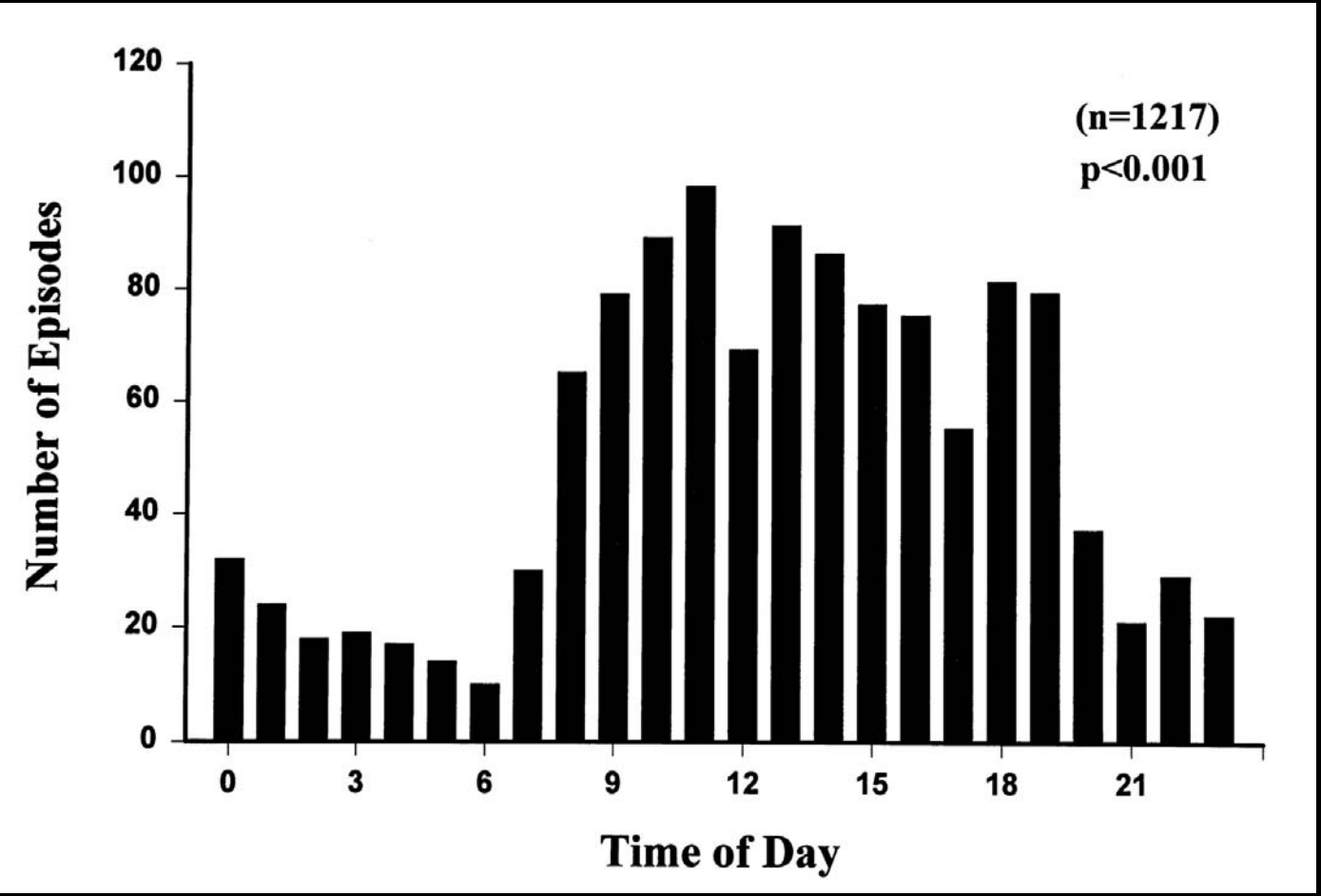
- Morning peak in cardiovascular risk

Robust epidemiological data show day/night pattern in incidence of myocardial infarction, with a peak at ~9AM



Muller, *Am J Hypertens.*, 1999

Day/night pattern in episodes of rapid ventricular tachyarrhythmias (HR >250 bpm)

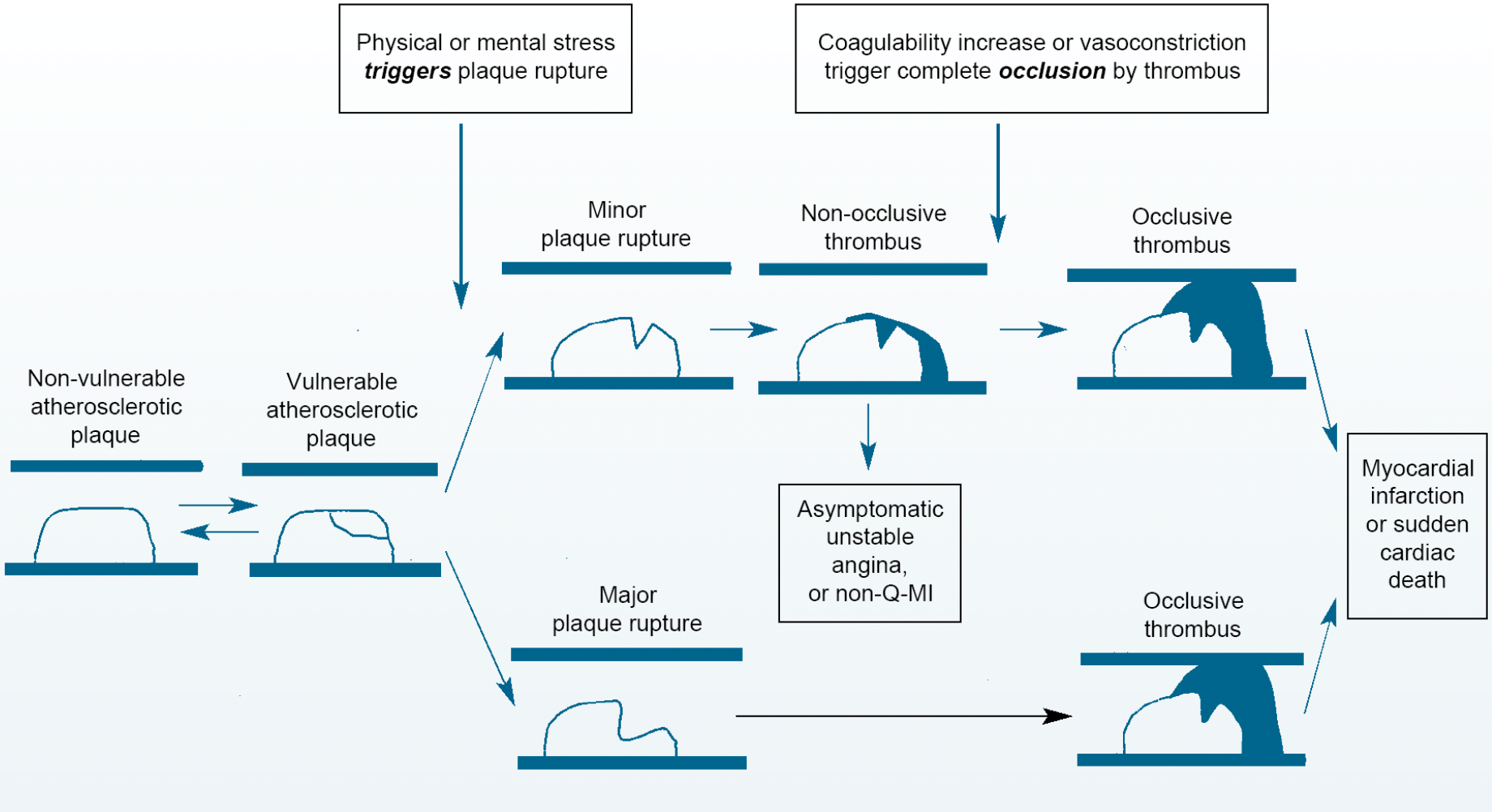


Tofler, G. H. et al. *Circulation* 1995;92:1203-1208

Overview

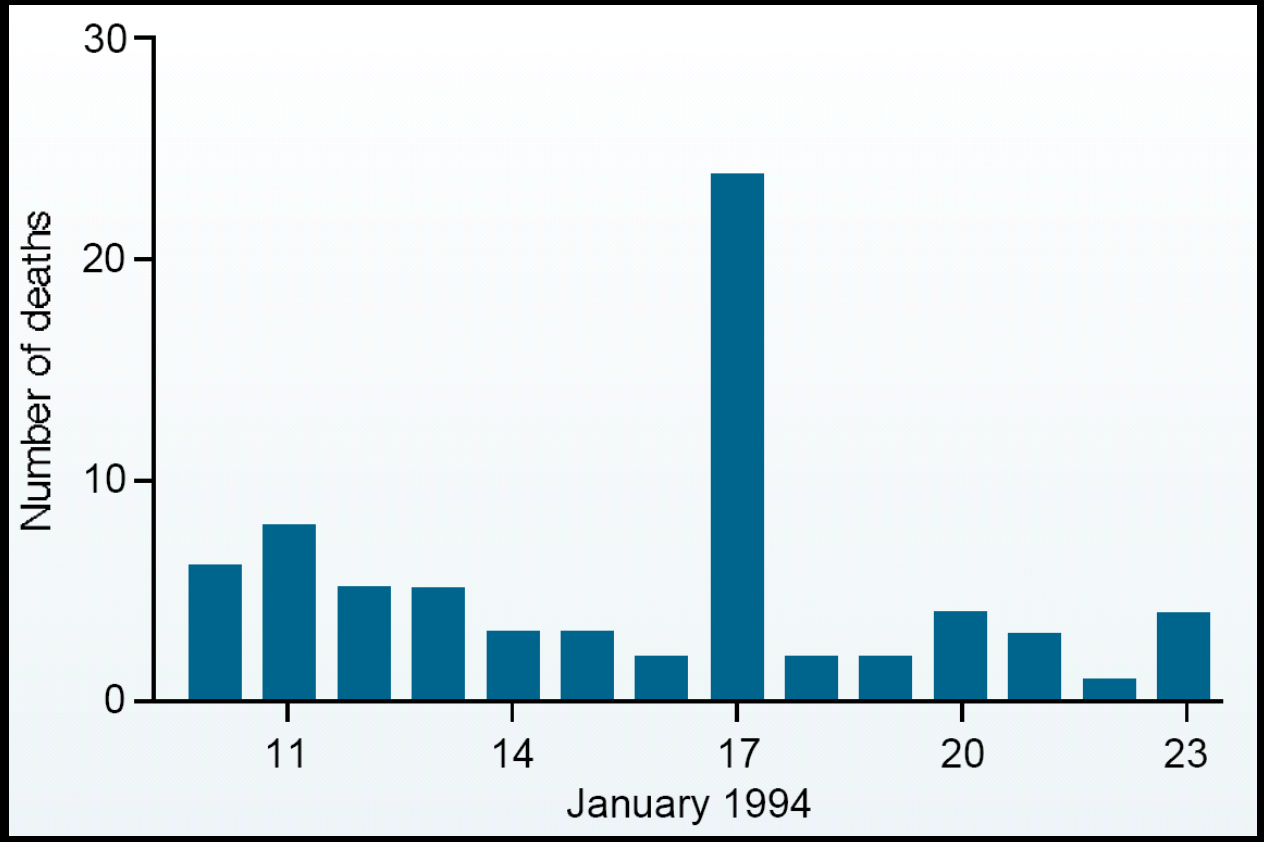
- Morning peak in cardiovascular risk
- Potential factors involved

Model of Triggering Coronary Thrombus



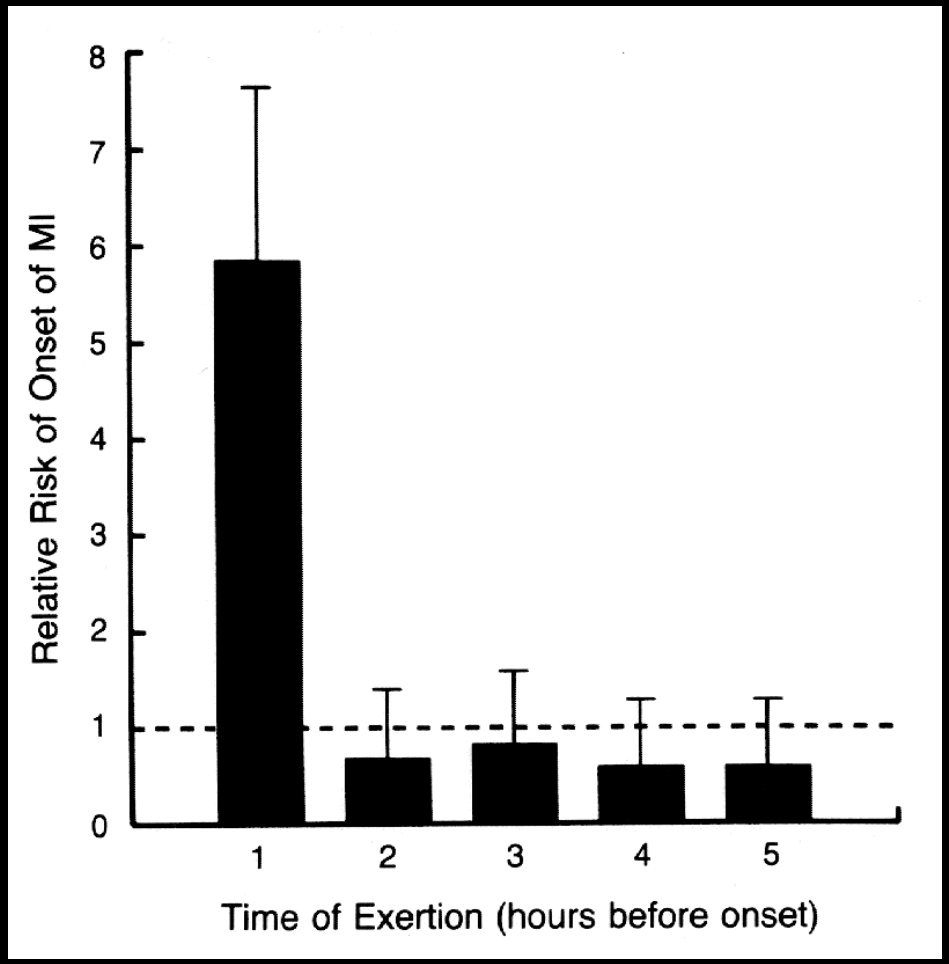
Adapted from Muller J, *Am Heart J*, 1999: 12: 355-425

Increase in SCD on Jan. 17, 1994 - the day of the Northridge Earthquake



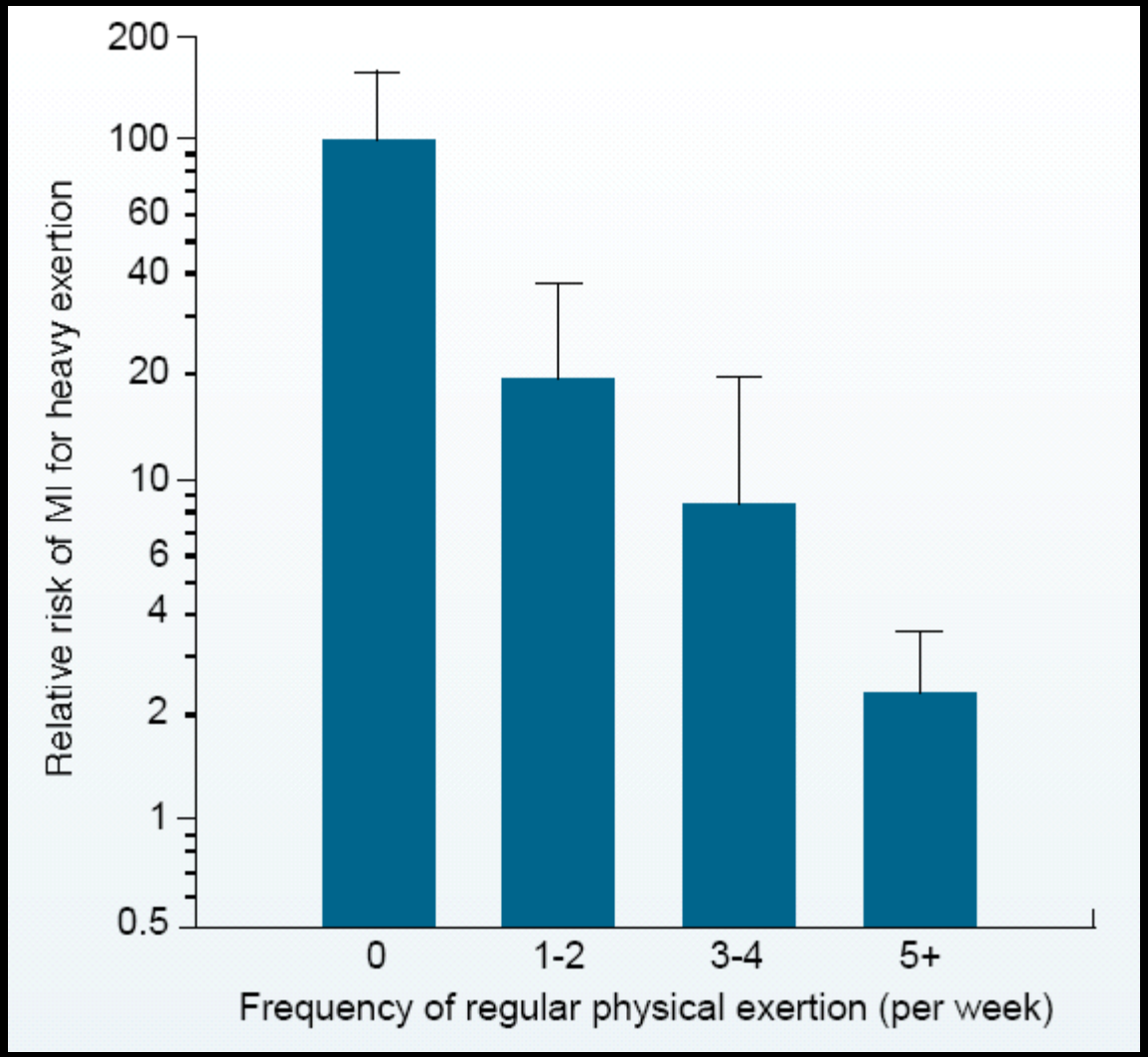
Leor J, et al. *N Engl J Med* 1996;334:413-19

Triggering of MI by Heavy Exertion (>METS)



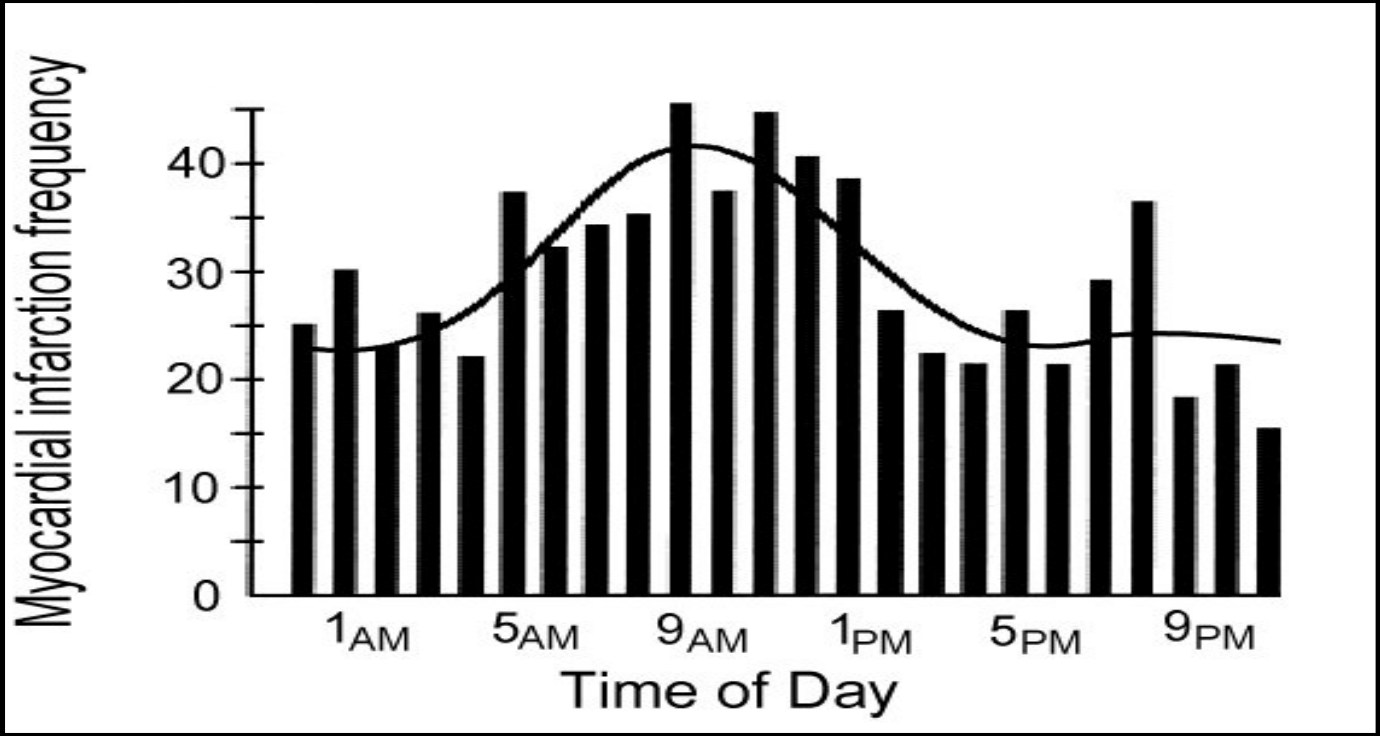
Mittleman MA et al. *N Engl J Med* 1993;329:1677-83

Reduction of triggering of MI by regular exercise



Mittleman MA et al. *N Engl J Med* 1993;329:1677-83

Aside of behavioral influences (sleep/wake, posture/activity) , are there endogenous circadian rhythms that may contribute to the morning peak in cardiovascular incidents?



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- “Circadian” what does it mean?

“Circadian” what does it mean?

Circadian rhythm

“About a day”

endogenous rhythm of ~24 hours

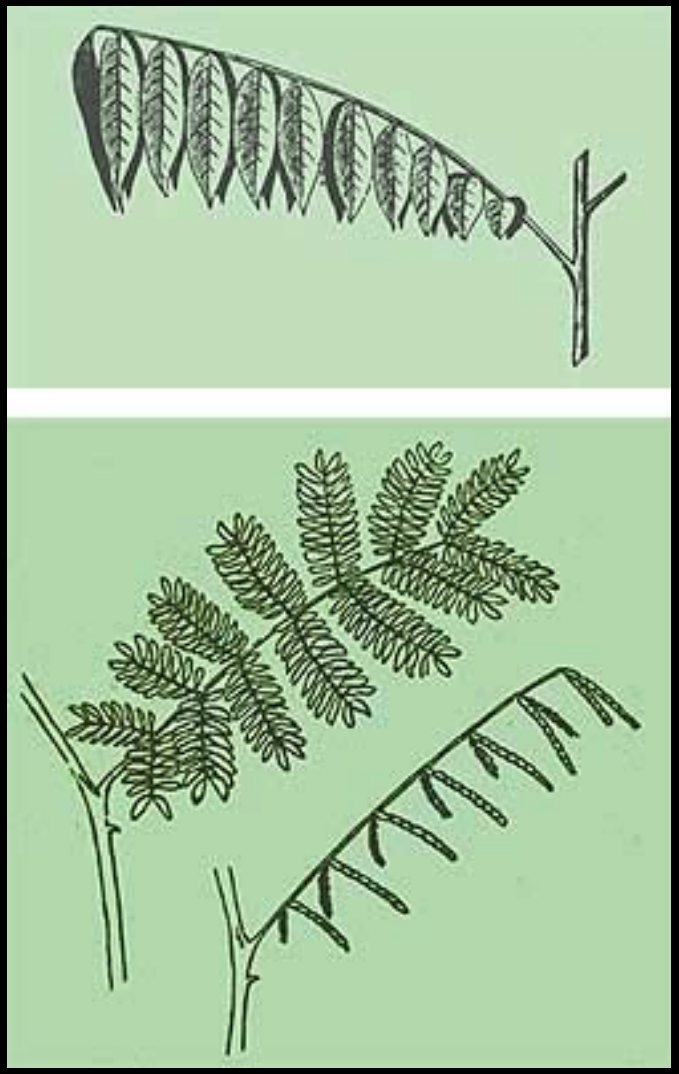
coined by Franz Halberg in 1959

Nycthemeral rhythm

“Daily”

no endogenous nature implied

First demonstration



In 1729, Jean-Jacques d'Ortous de Mairan placed a Heliotrope plant in the dark to test whether the daily opening and closing of the leaves would be dependent on the sun.

The rhythm persisted, suggesting the rhythm may be of endogenous origin.

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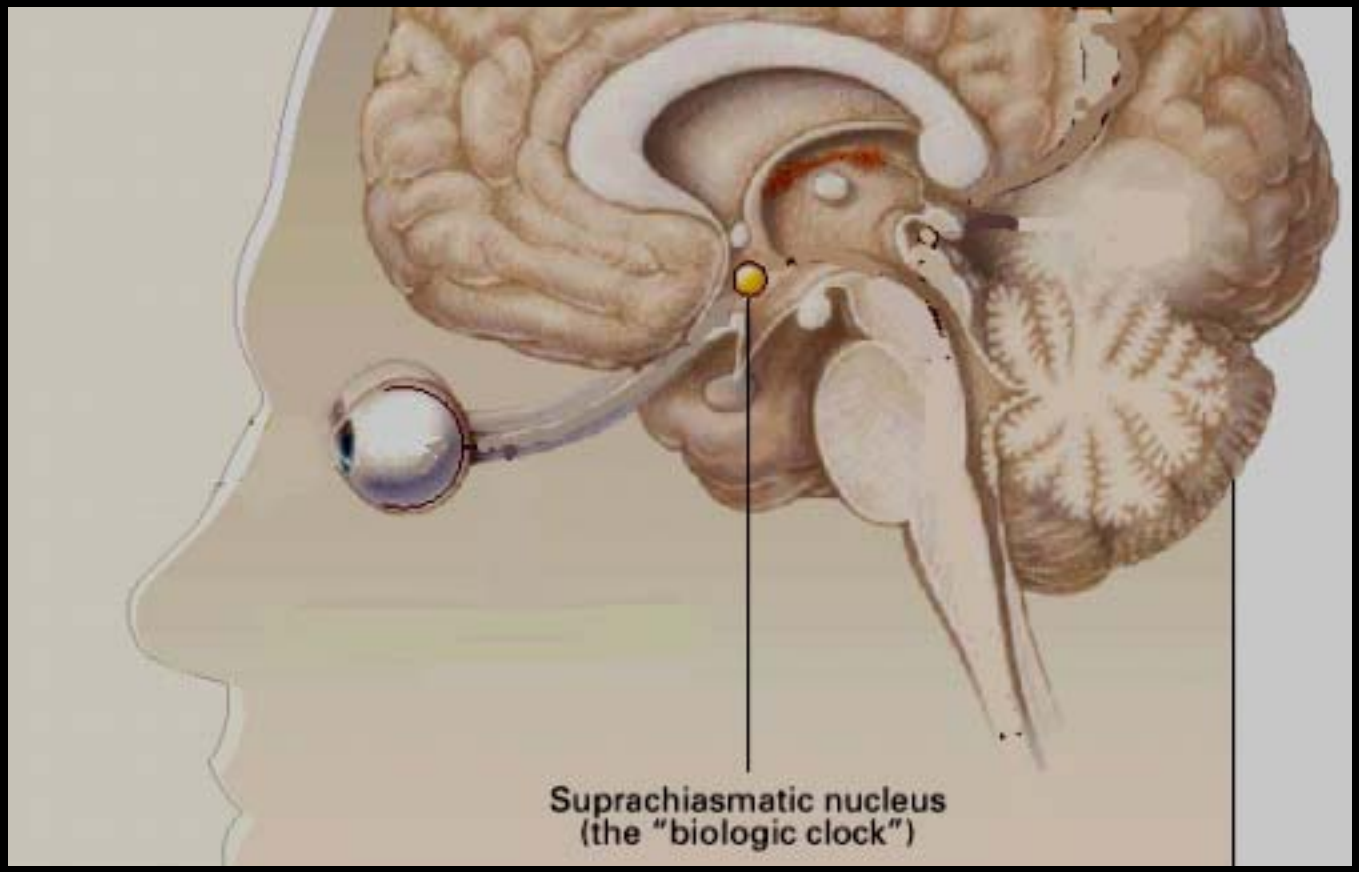
- Circadian pacemaker & the heart

Human biological clock



Suprachiasmatic nucleus projects to the heart via multisynaptic pathway

Pseudorabies staining of SCN neurons 4 days after myocardial inoculation

Scheer FAJL et al., Am J Physiol. 2001;280:H1391-9

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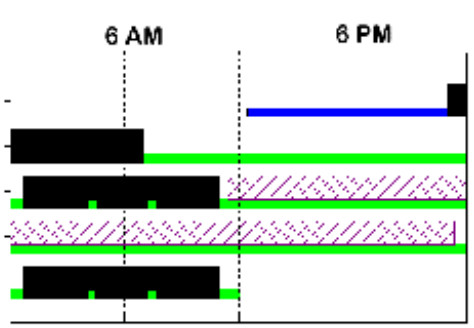
Techniques to assess human circadian rhythmicity are based on two principles:

Minimizing the influence of behavioral and environmental 'masking' factors
-> Constant Routine protocol

or

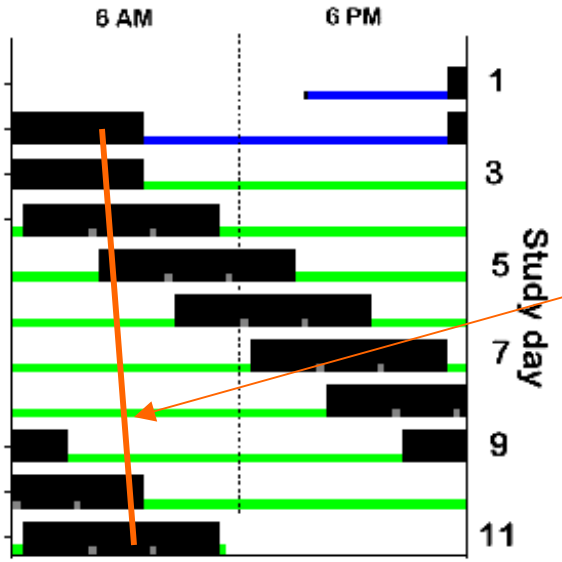
Distributing the influence equally across the circadian cycle
-> Forced Desynchrony protocol

Circadian rhythm in human cardiovascular functioning?



Constant Routine:

- 9 healthy young subjects
- 38 h awake
- Constant posture
- Constant temperature
- Constant dim light (<5 lux)
- Snacks every 2 h



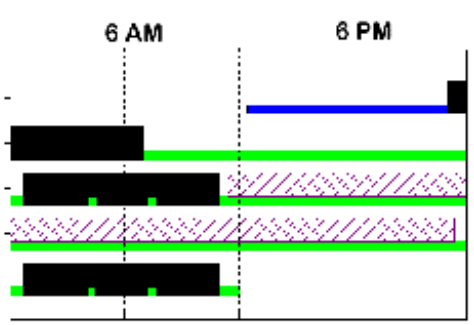
Fitted core body temperature minimum

Forced Desynchrony:

- 5 healthy young subjects
- Dim light (<5 lux)
- 2 baseline days
- 7 cycles of 28-h sleep-wake period
- Measurements at all circadian phases

Data with courtesy of Steven Shea, Michael Hilton, and coworkers

Circadian rhythm in human cardiovascular functioning?



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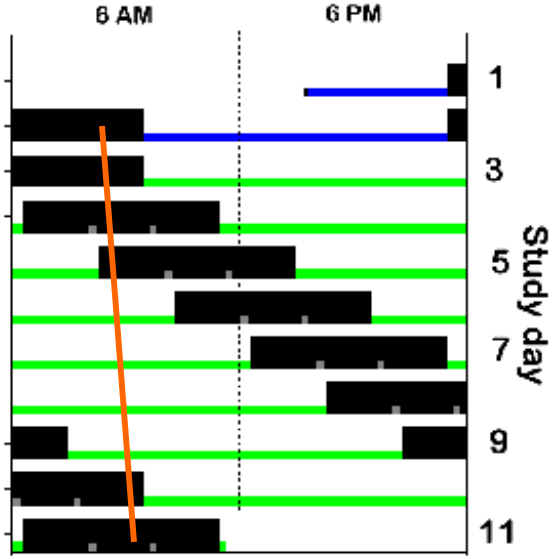

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Measurements:

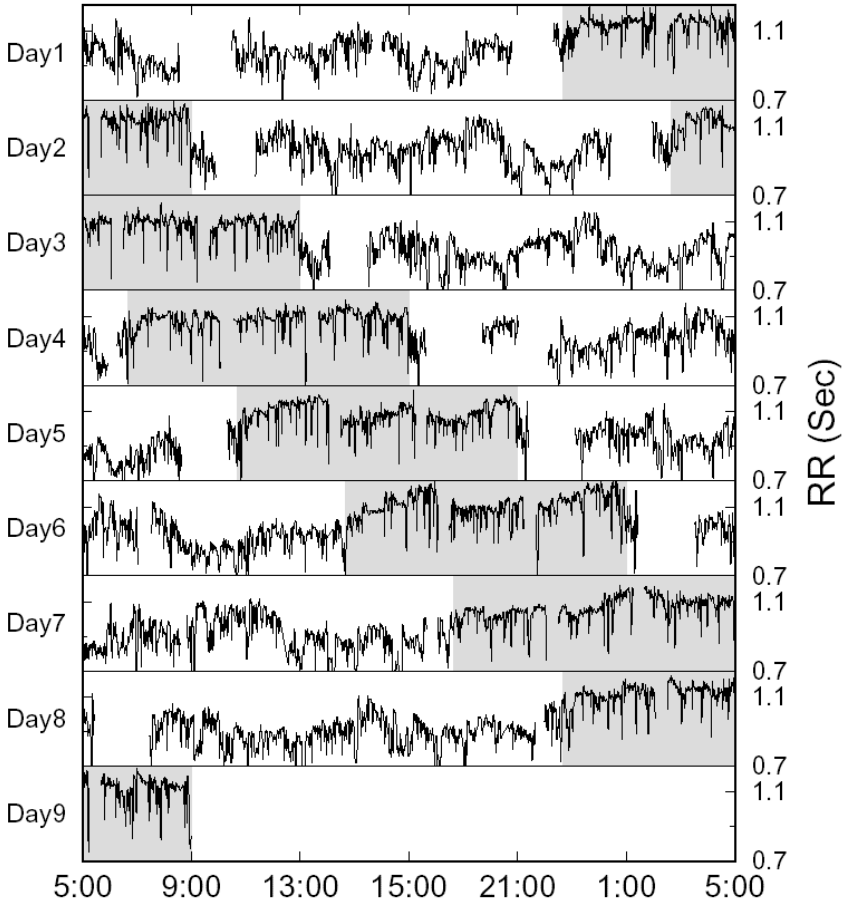
- Cardiac vagal tone (power of high frequency band in ECG inter-beat interval)
- Cardiac sympathetic tone (iso-volumetric ventricular contraction time)
- Urinary epinephrine and norepinephrine
- Circulating cortisol
- Systemic blood pressure
- Core body temperature to assess endogenous circadian phase

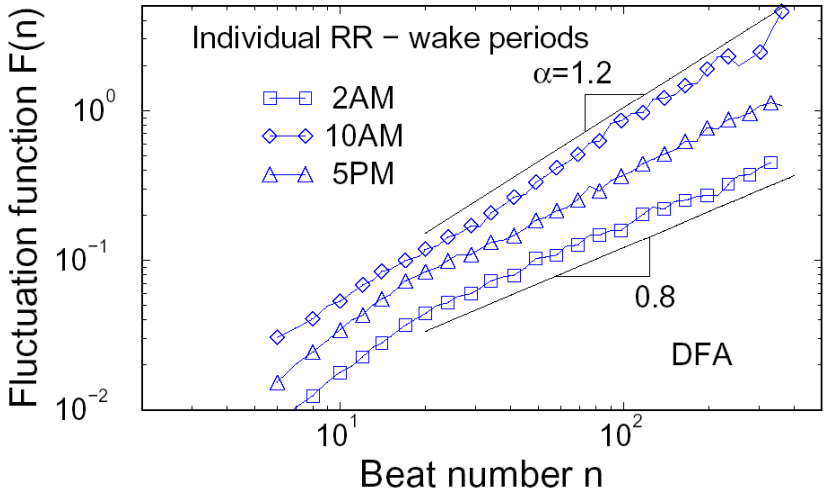
Data with courtesy of Steven Shea, Michael Hilton, and coworkers

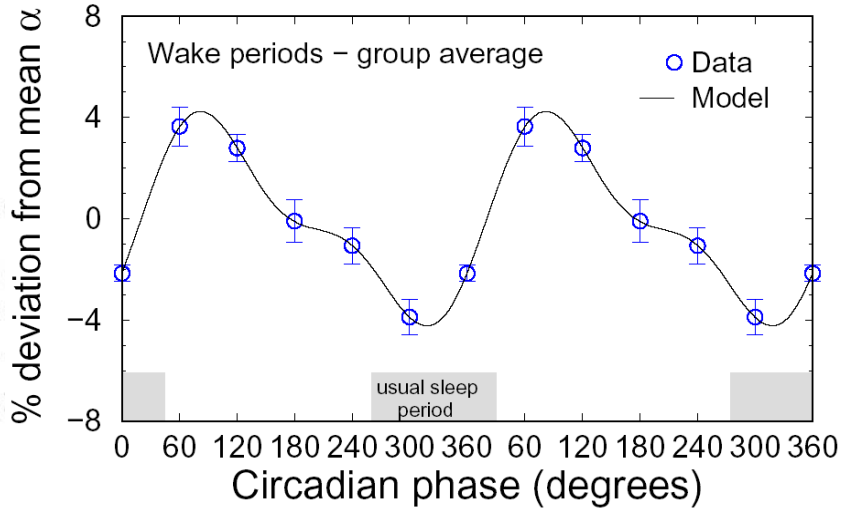
Unpublished data not shown

Unpublished data not shown

Circadian rhythms in heartbeat correlations
Individual during wake periods







Hu, K et al, PNAS 2005

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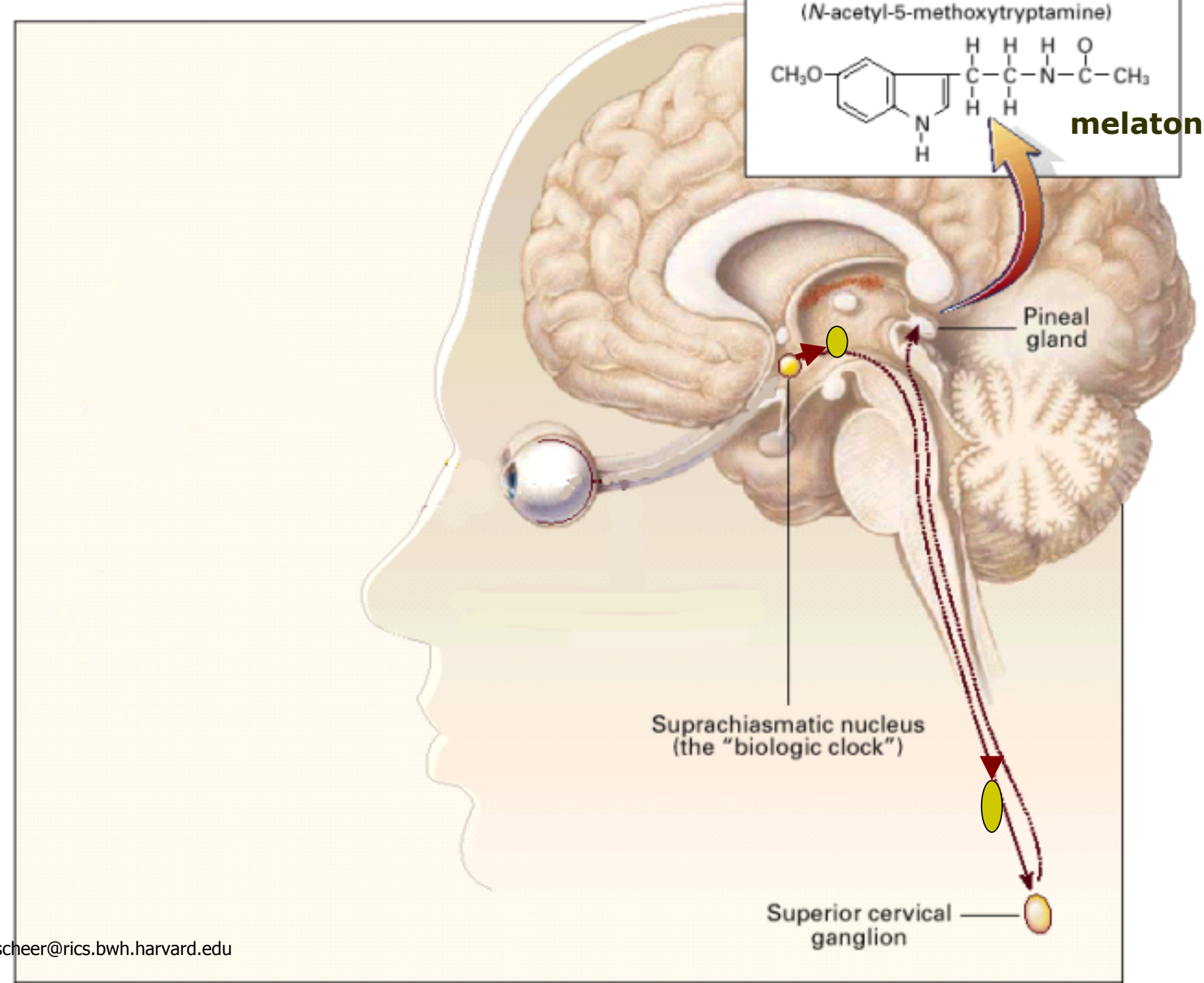

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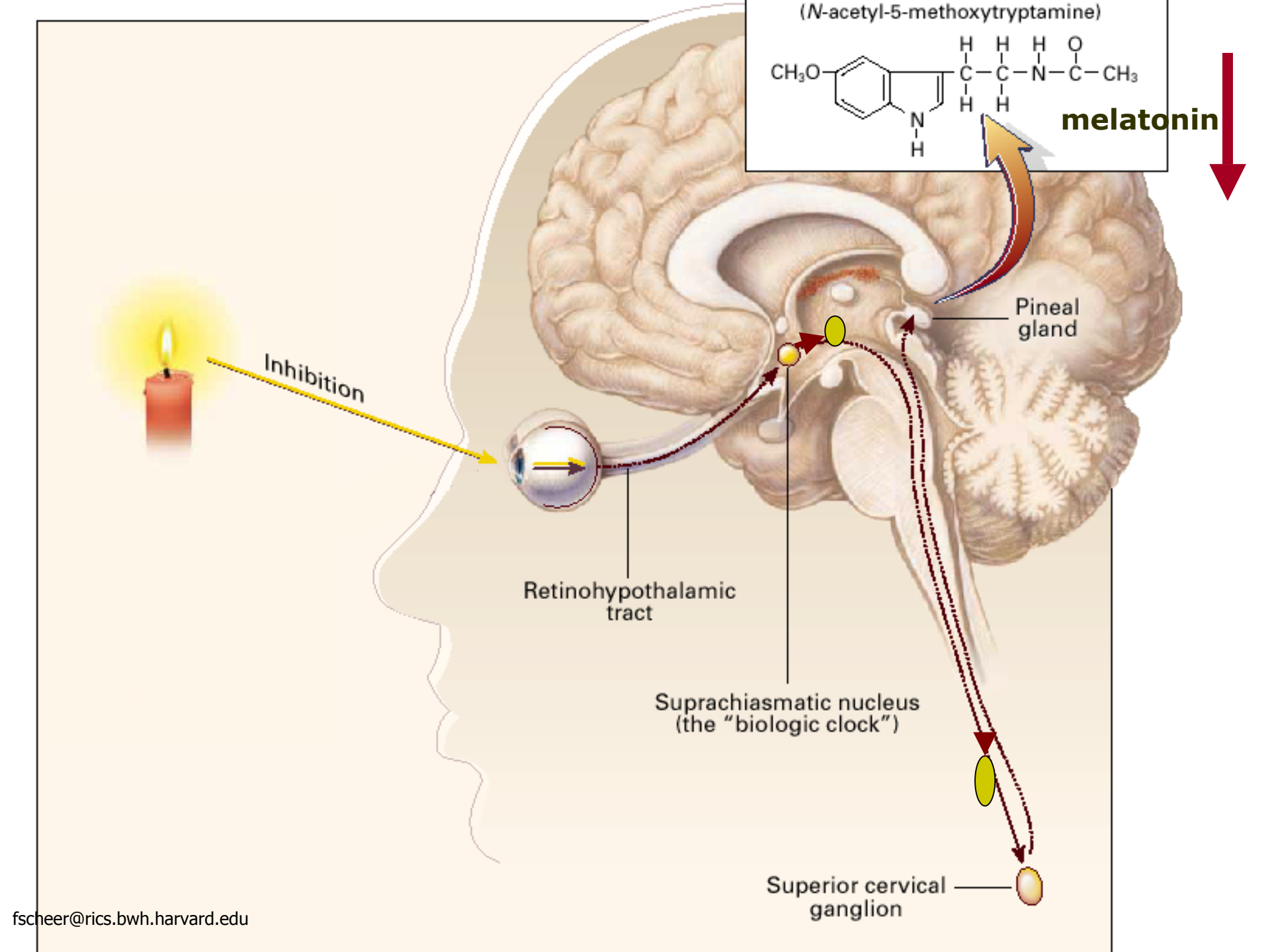

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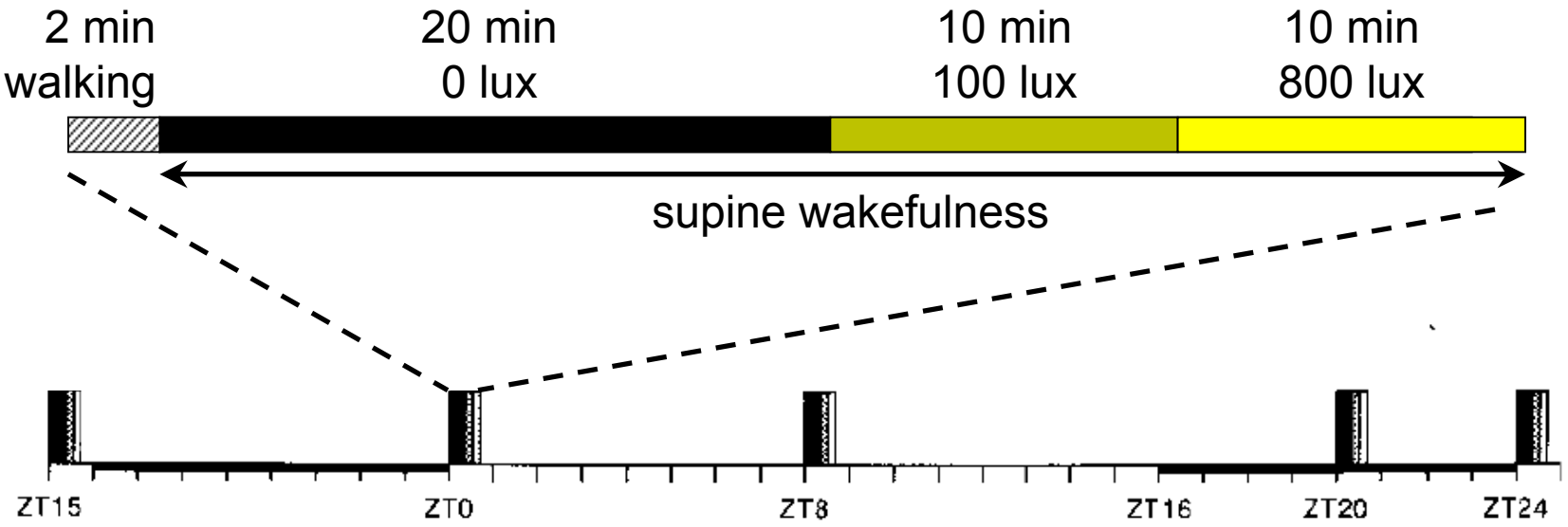
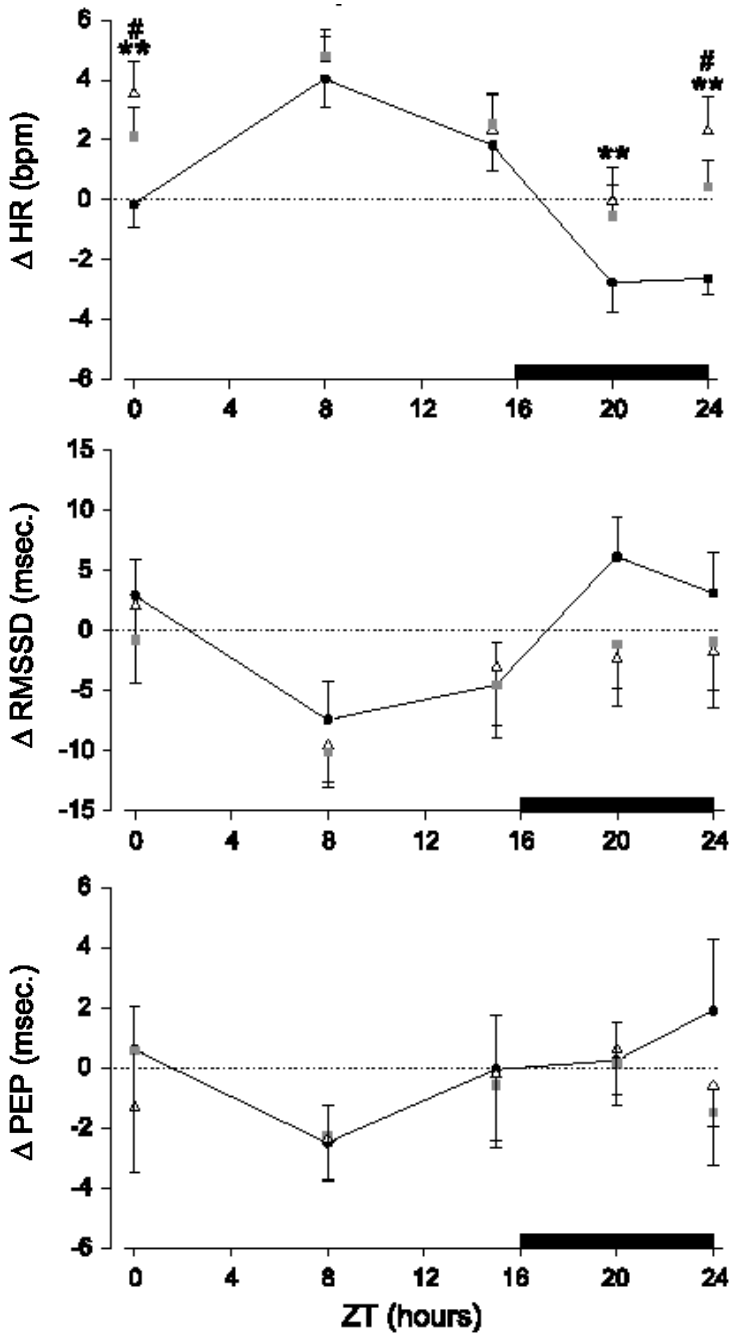
Acute effect of light on autonomic regulation of the heart in humans?



Subjects:10 healthy men 20-40 y, non smoking, no medication
Recordings: under awake, supine, resting conditions
Illumination: Reproducible exposure to the same light intensities
Measuring system: VU-AMS (Free University, Amsterdam, the Netherlands)
Measures: HR, RMSSD, PEP (ECG & ICG)

Scheer et al., *Autonomic Neurosci*, 2004



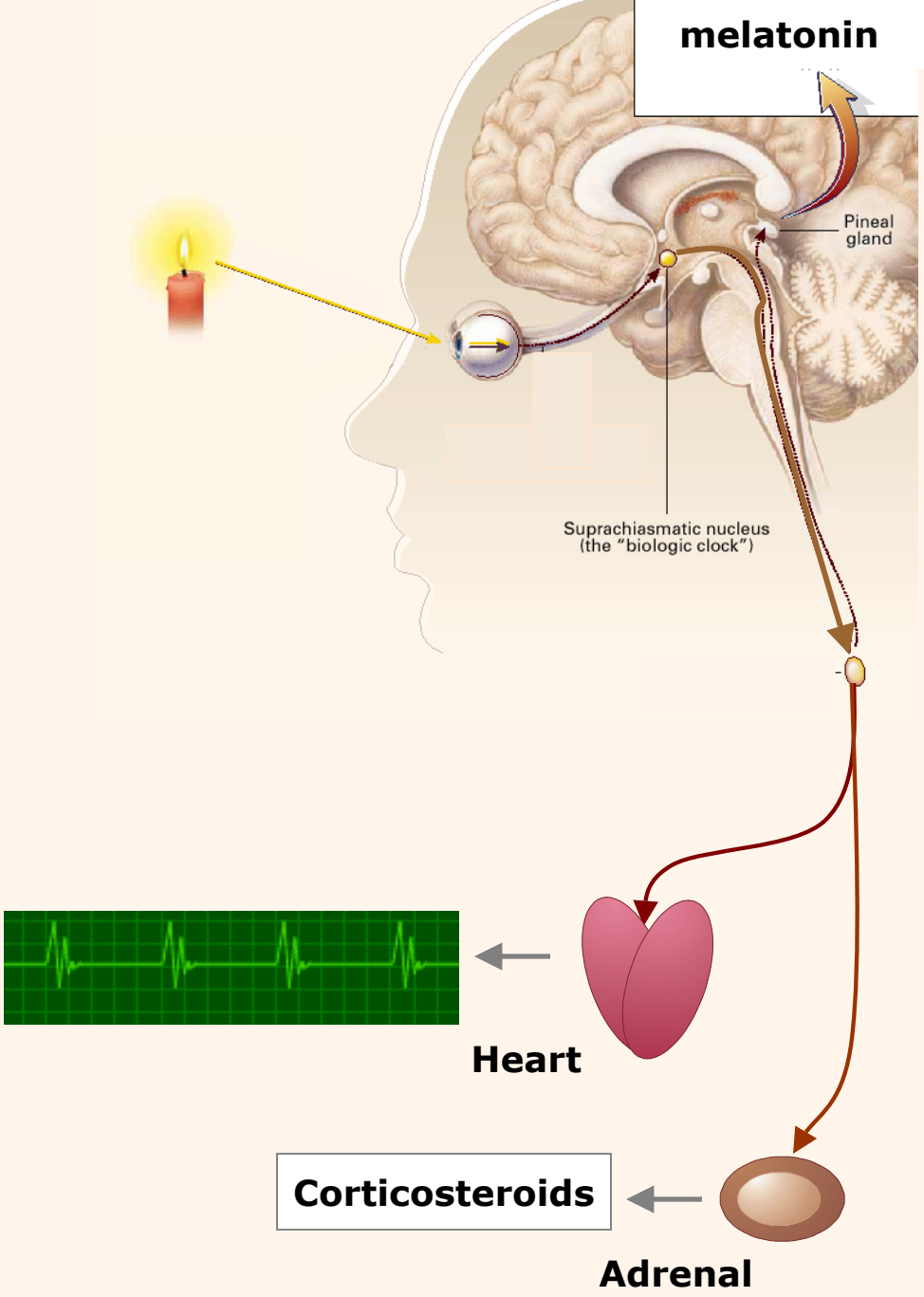
Acute effect of light on the heart in humans

- Significant daily rhythm in HR and RMSSD but not PEP

- Light stimulates HR
- time-of-day dependent
- Intensity dependent
- involvement of sympathetic n.s.?

significant difference compared to 0 lx: * P= < 0.05; ** P < 0.01;
significant difference compared to 100 lx: # P < 0.05.

Scheer et al., *Autonomic Neurosci*, 2004



Rat: Klein and Weller, Science, 1972

Human: Lewy et al., Science, 1980

Human: Scheer et al., JBR, 1999

Rat: Scheer et al., AJP, 2001

Human: Scheer et al., JCEM, 1999

Rat: Buijs et al., Eur J Neurosci, 1999

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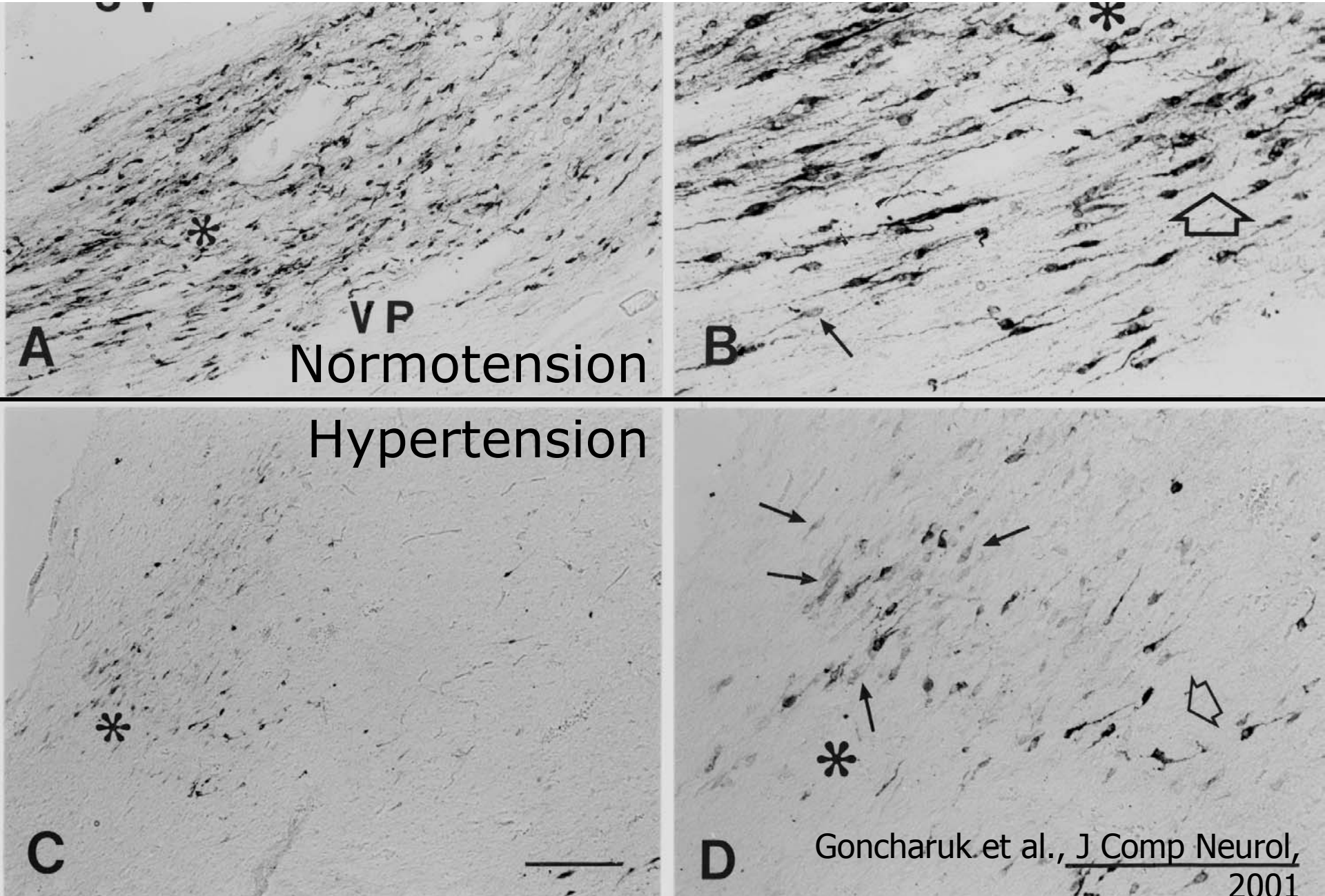
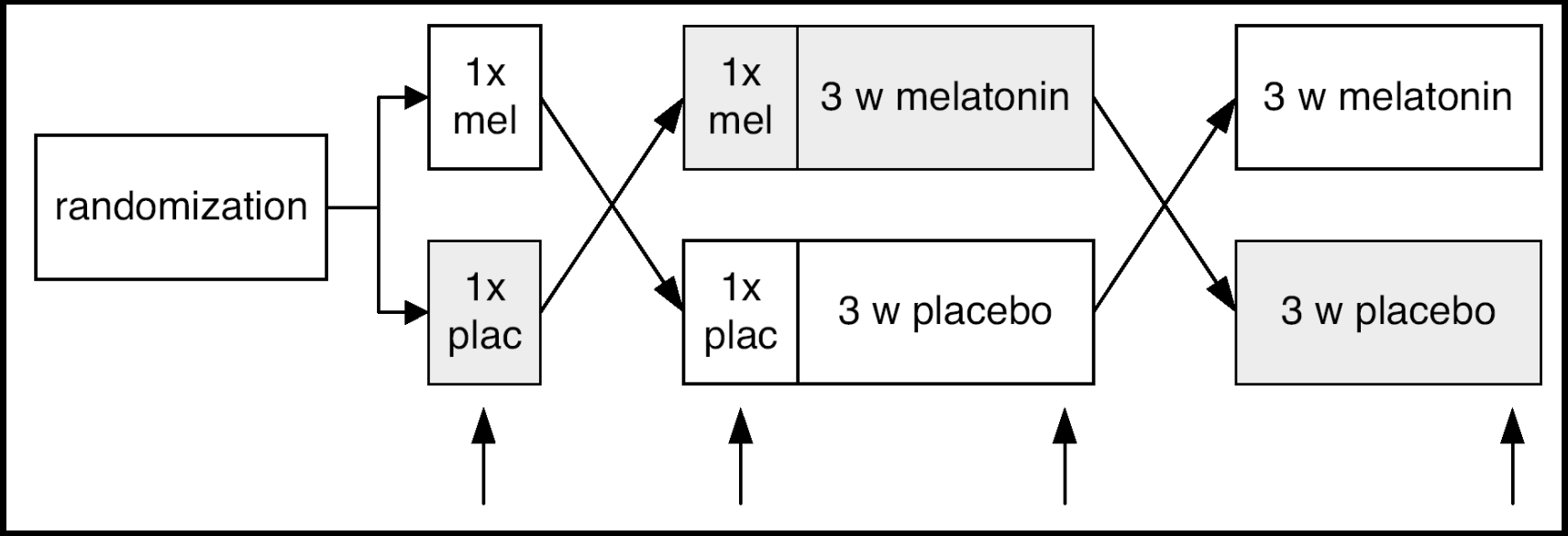
Suprachiasmatic nucleus neurotransmitter content and transcription is suppressed in hypertensive patients



Goncharuk et al., J Comp Neurol, 2001

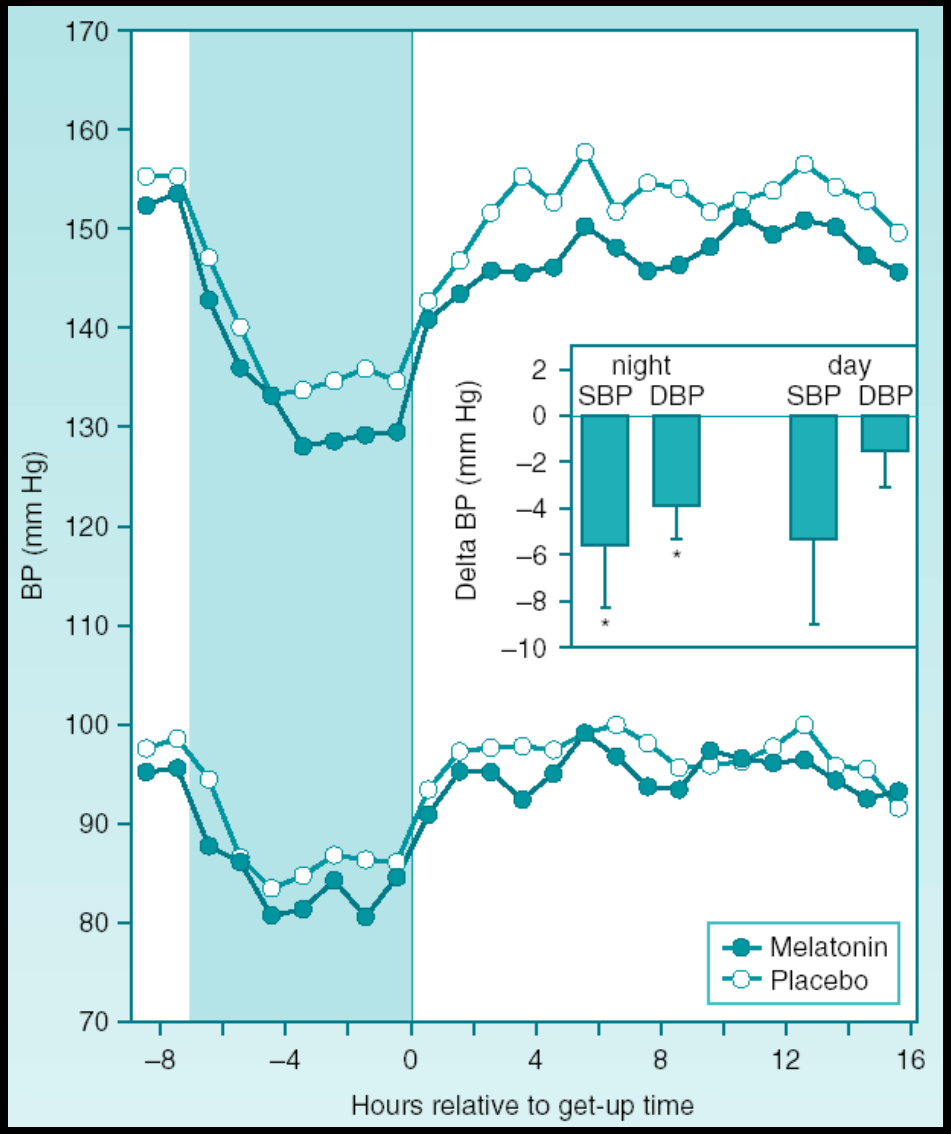
Can melatonin, the night time signal for the circadian timing system, ameliorate hypertension?



Arrows indicate ambulatory blood pressure recordings

Scheer FAJL et al., Hypertension. 2004;43:192-7

Prolonged nighttime melatonin administration lowers blood pressure in hypertensive men



Scheer FAJL et al., Hypertension. 2004;43:192-7

Summary of Main Findings

- Suprachiasmatic nucleus projects to the heart via multi-synaptic pathway
- Significant endogenous circadian rhythms in most cardiovascular variables – independent of changes in behavior (robust finding: CR & FD)
- Circadian peaks in cardiac sympathetic indices and circadian trough in cardiac vagal tone occurred around usual time of awakening (although subjects remained awake)
- Magnitude of cardiac response to change in behavior and environment (arousal and light) varied with circadian phase
- Suprachiasmatic nucleus seems disturbed in hypertensive patients while nighttime melatonin ameliorates hypertension

Unpublished data not shown

Acknowledgements

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