Chronobiologic Aspects of Heart Rate Variability

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HEART RATE VARIABILITY — 2006
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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)

Overview

- Morning peak in cardiovascular risk
- Potential factors involved
Model of Triggering Coronary Thrombus

Physical or mental stress *triggers* plaque rupture

Coagulability increase or vasoconstriction trigger complete *occlusion* by thrombus

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

Triggering of MI by Heavy Exertion (>METS)

Reduction of triggering of MI by regular exercise

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

- Morning peak in cardiovascular risk
- Potential factors involved
- “Circadian” what does it mean?
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Circadian rhythm
“About a day”
endogenous rhythm of ~24 hours
coined by Franz Halberg in 1959

Nycthemeral rhythm
“Daily”
no endogenous nature implied
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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Human biological clock
Suprachiasmatic nucleus projects to the heart via multisynaptic pathway

Pseudorabies staining of SCN neurons 4 days after myocardial inoculation

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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 Desynchronization 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

**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?

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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Unpublished data not shown
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
Heart

Human: Scheer et al., JBR, 1999
Rat: Scheer et al., AJP, 2001

Adrenal
Corticosteroids

Human: Scheer et al., JCEM, 1999
Rat: Buijs et al., Eur J Neurosci, 1999

melatonin

Rat: Klein and Weller, Science, 1972
Human: Lewy et al., Science, 1980

Suprachiasmatic nucleus
(the "biologic clock")

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- Circadian vs. nycthemeral
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- Circadian rhythm in responsiveness?
- Clinical implications?
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
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