Network Physiology in adults and **infants**

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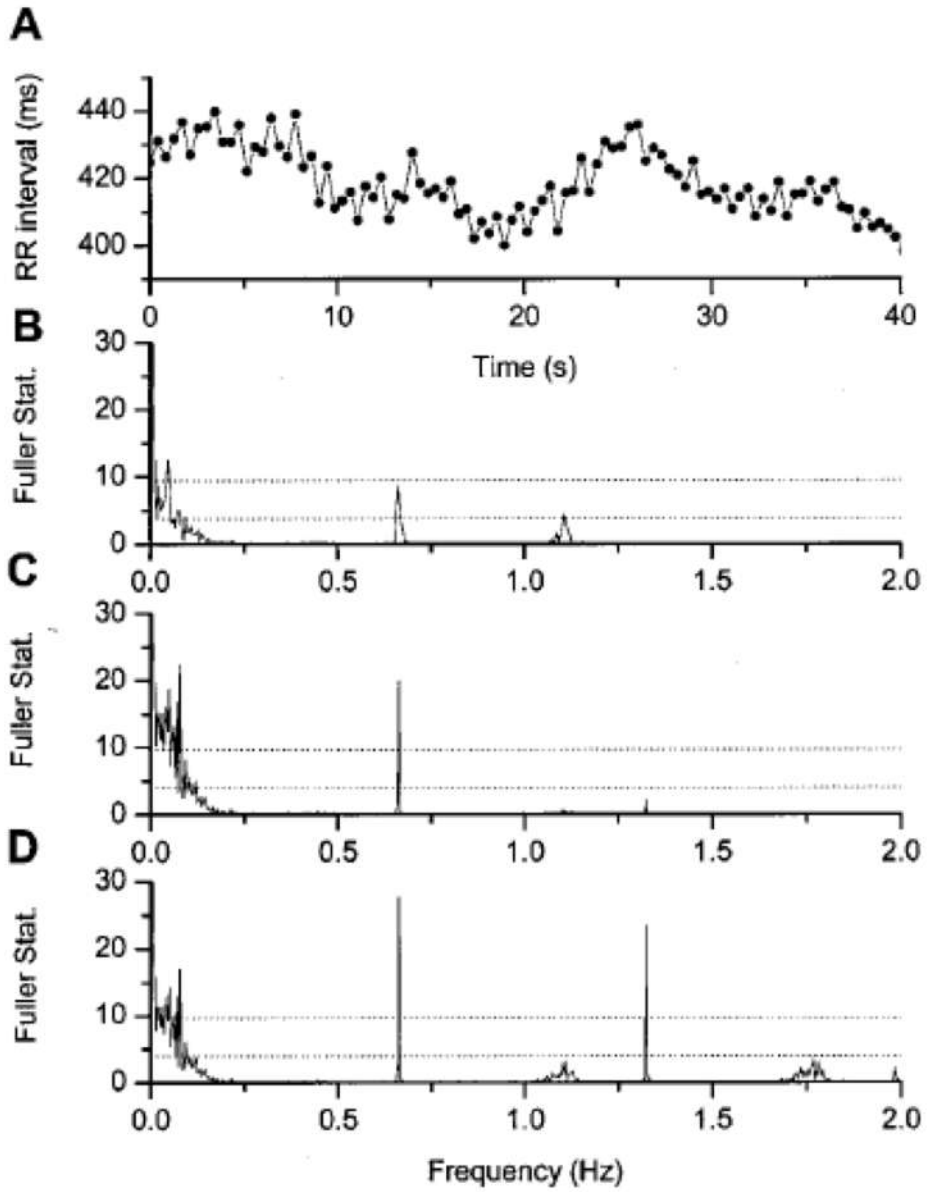
Outline

- **Network Physiology in infants**
- Examples that make sense, up to a point
- A prismatic, important counter-example
- Questions for the field

- Story line: entrainment of heart and lungs, normal and abnormal doses, and mechanisms that make sense and those that do not

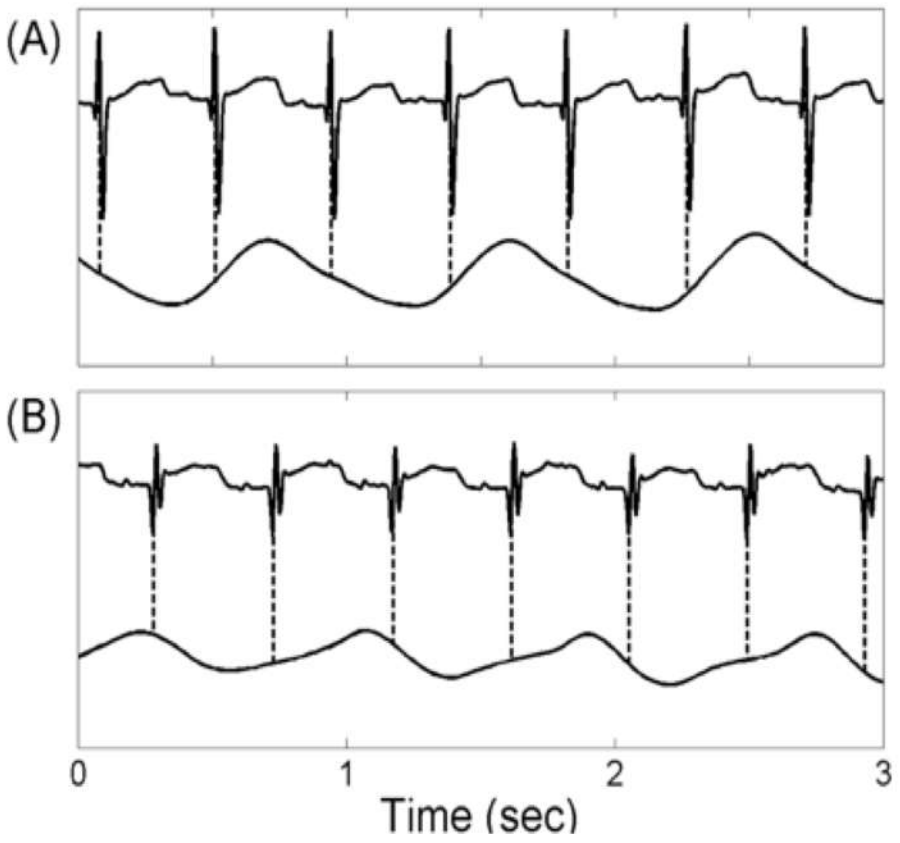
- Yesterday we spoke of how the lungs entrain the heartbeat in healthy adults as respiratory sinus arrhythmia, or RSA.

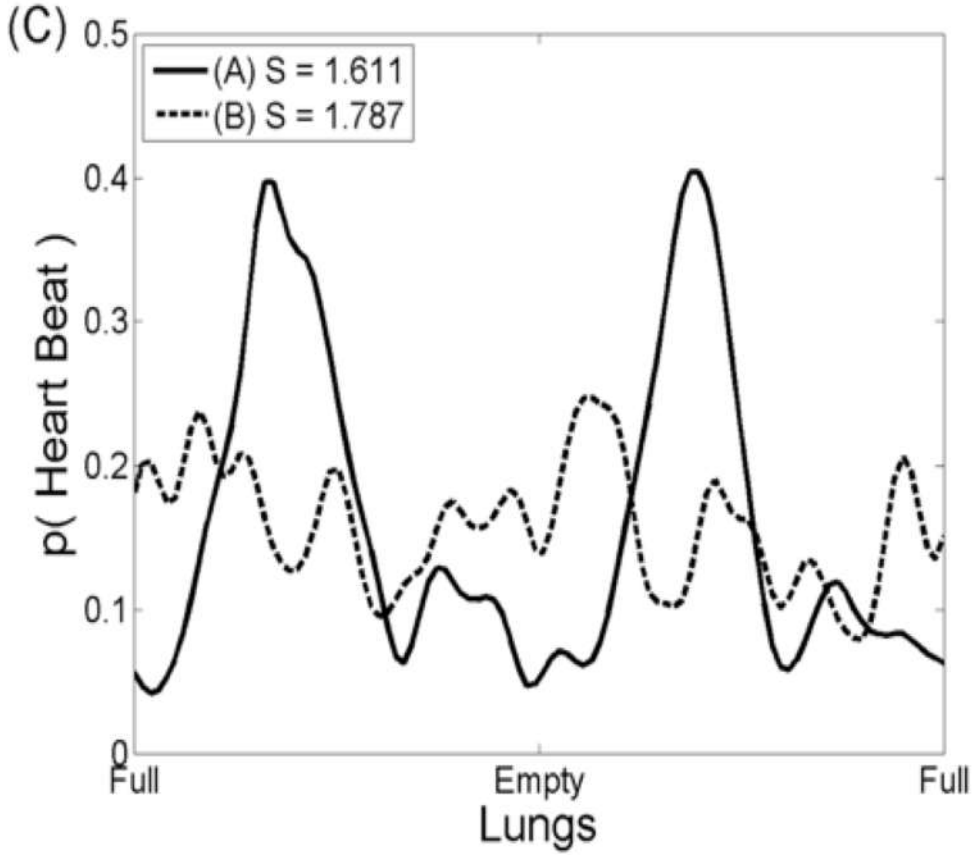
Infants have RSA, but it's difficult



2001

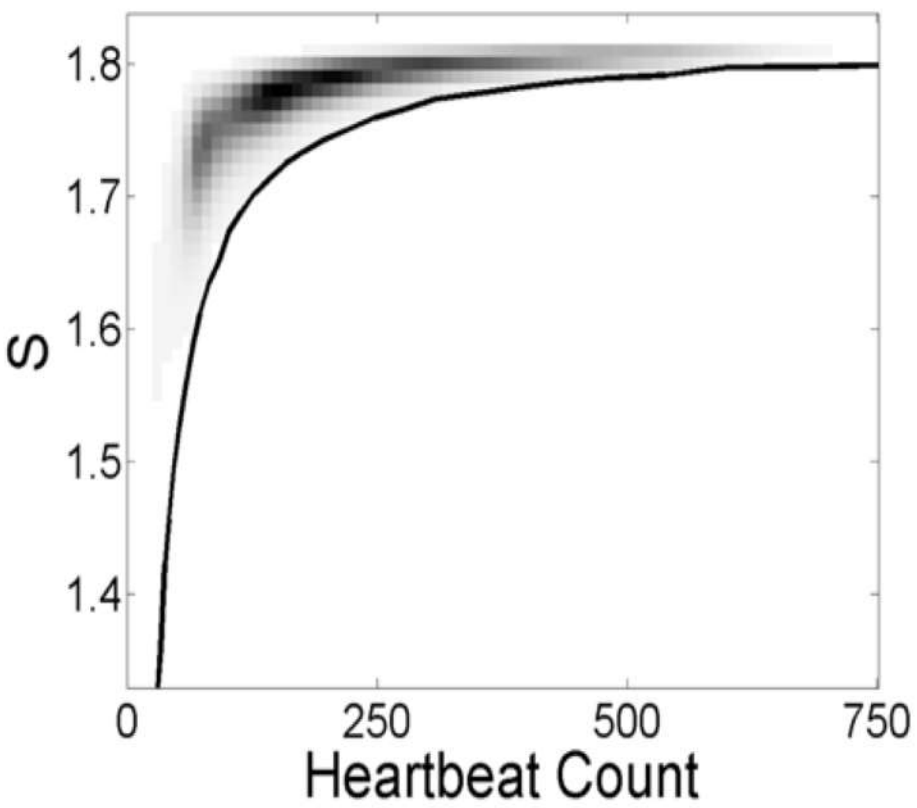
Breath-by-breath respiratory sinus arrhythmia

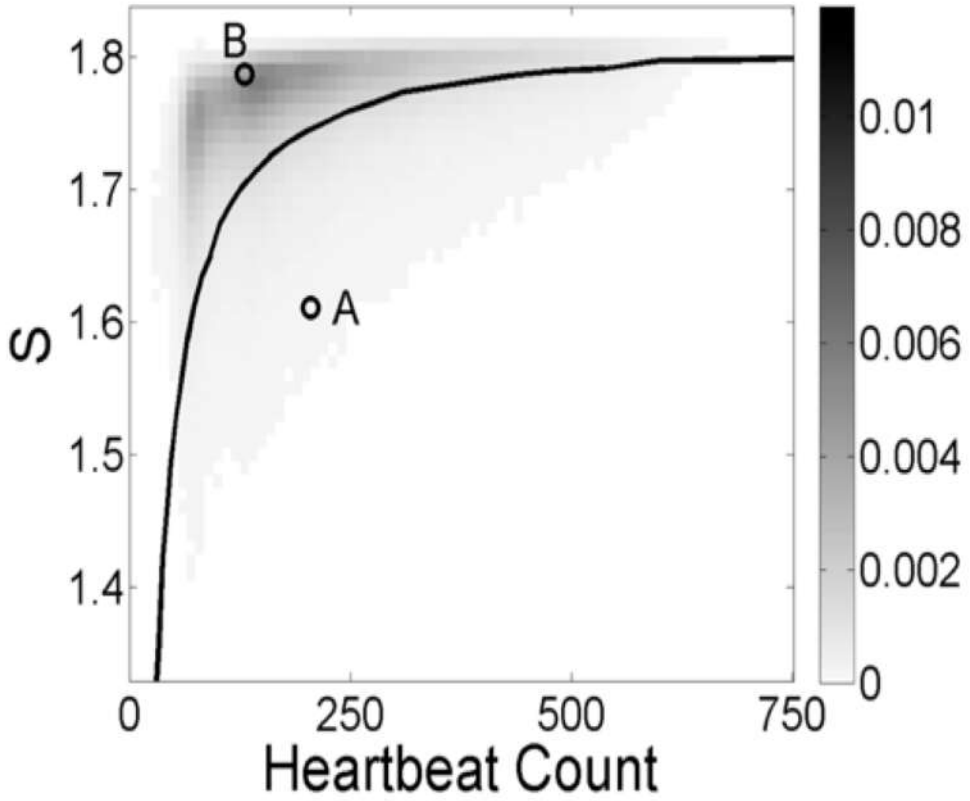




2012

Non-random beats during breaths





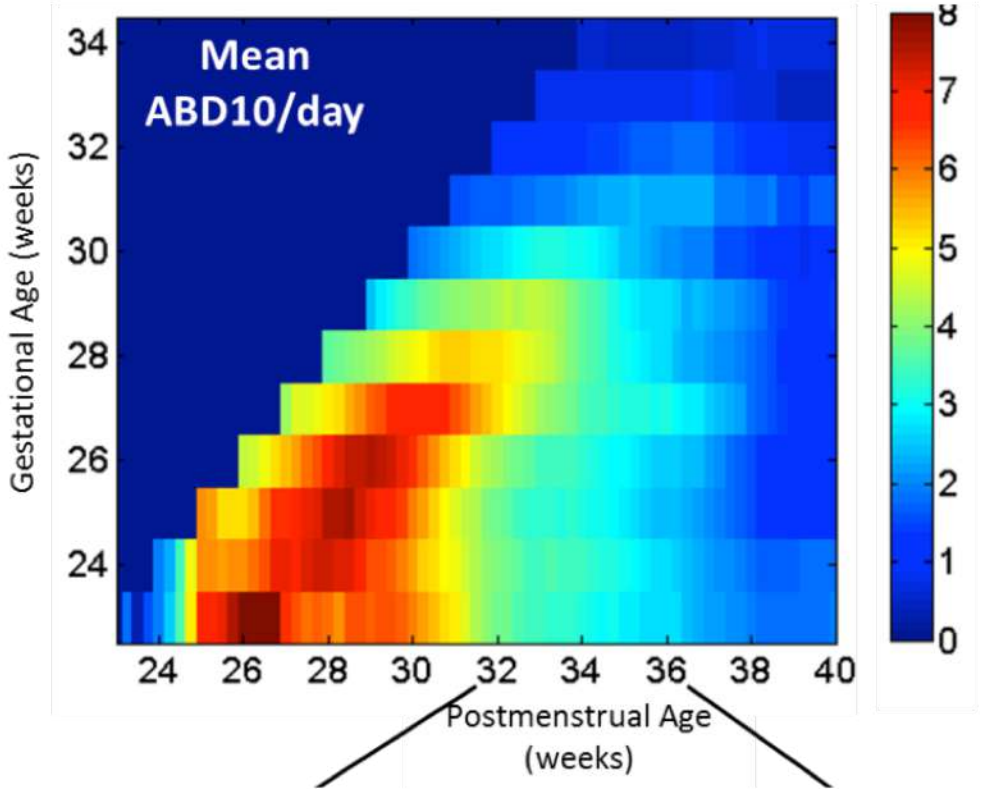
2012

- Yesterday we spoke of how the lungs entrain the heartbeat in healthy adults as RSA.
- Today we talk about premature infants, and other forms of cardiorespiratory entrainment
- Like yesterday, we will talk about an example that makes sense, and another one that does not – but it is only the latter that has been put to use to save babies

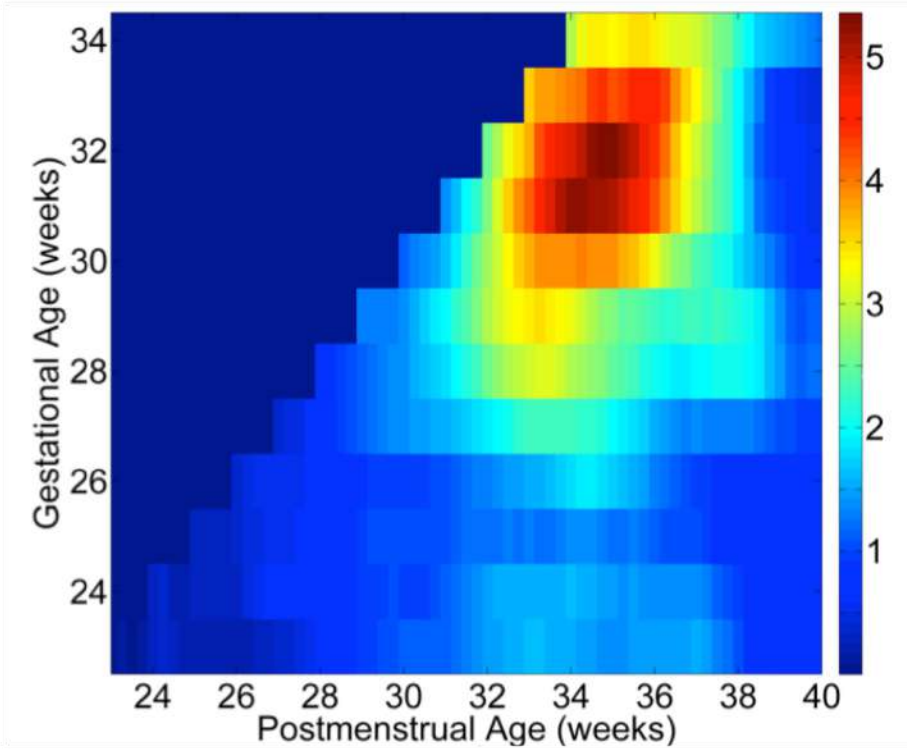
Network Physiology examples that make sense: Common disorders of breathing in premature infants

- **Central apnea** – generally, troublesome
- **Periodic breathing** - generally, not
- Heat maps show the natural histories

Apnea



Periodic breathing

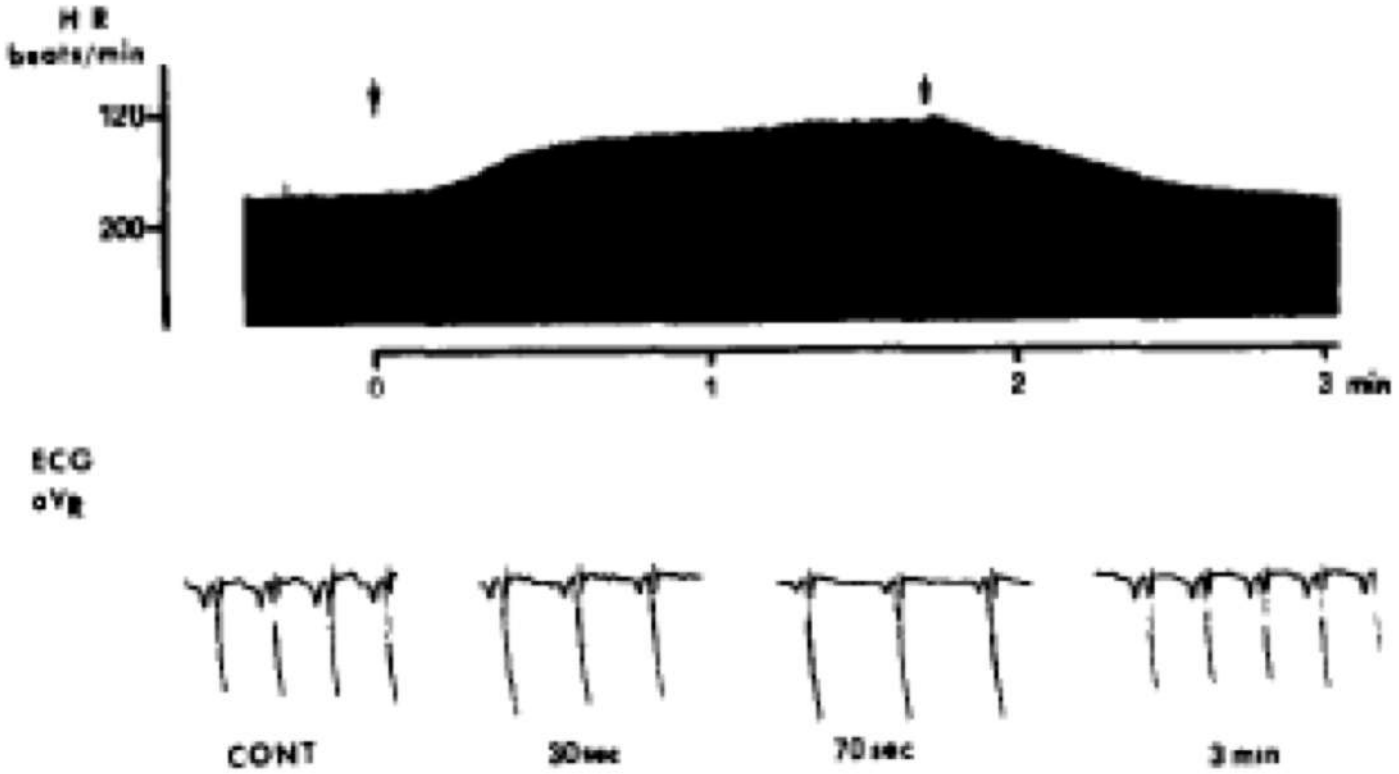


2017

Disorders of breathing in premature infants

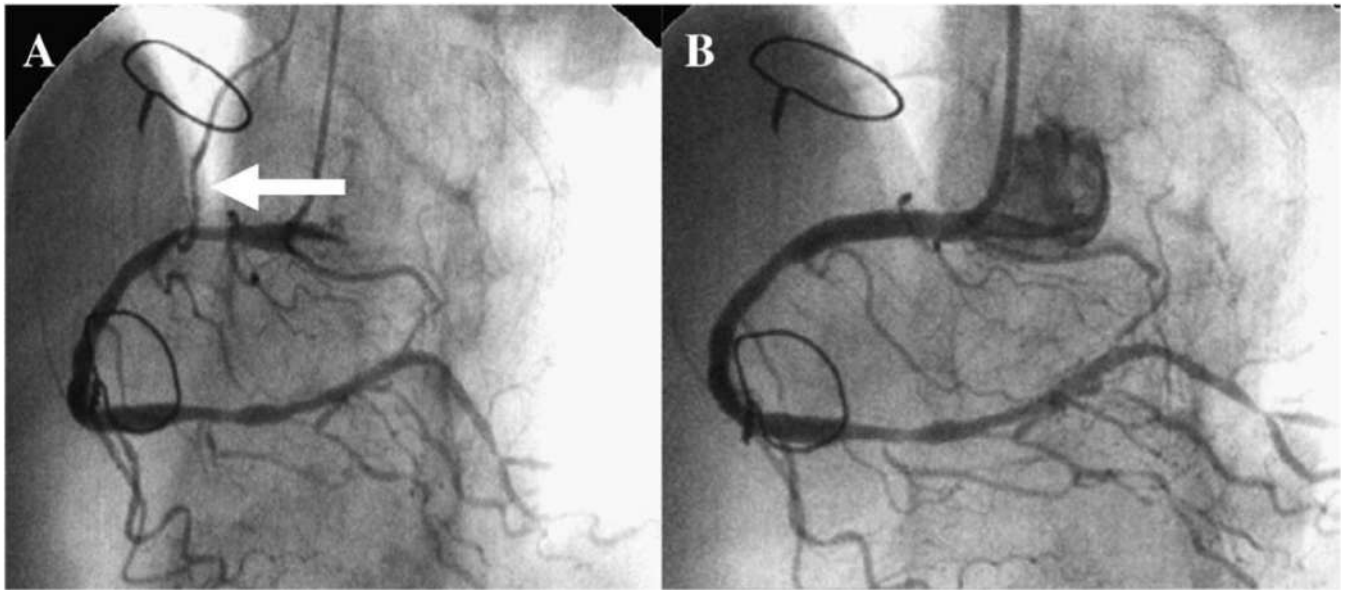
- **Central apnea** – generally, troublesome
- **Periodic breathing** - generally, not
- Heat maps show the natural histories
- ***Entrainment*** takes the form of apnea leading to bradycardia and oxygen desaturation
- If I tell you that hypoxemia makes sinus node cells slow their beating rate, then this makes sense.

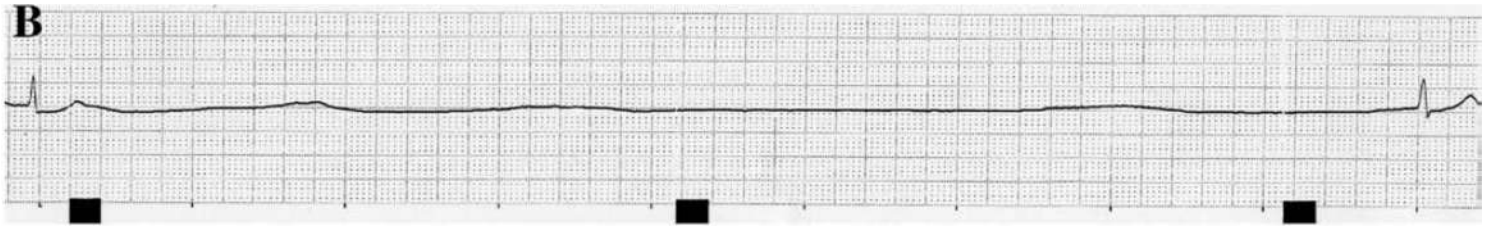
SA node hypoxemia slows the heart



Billette 1973

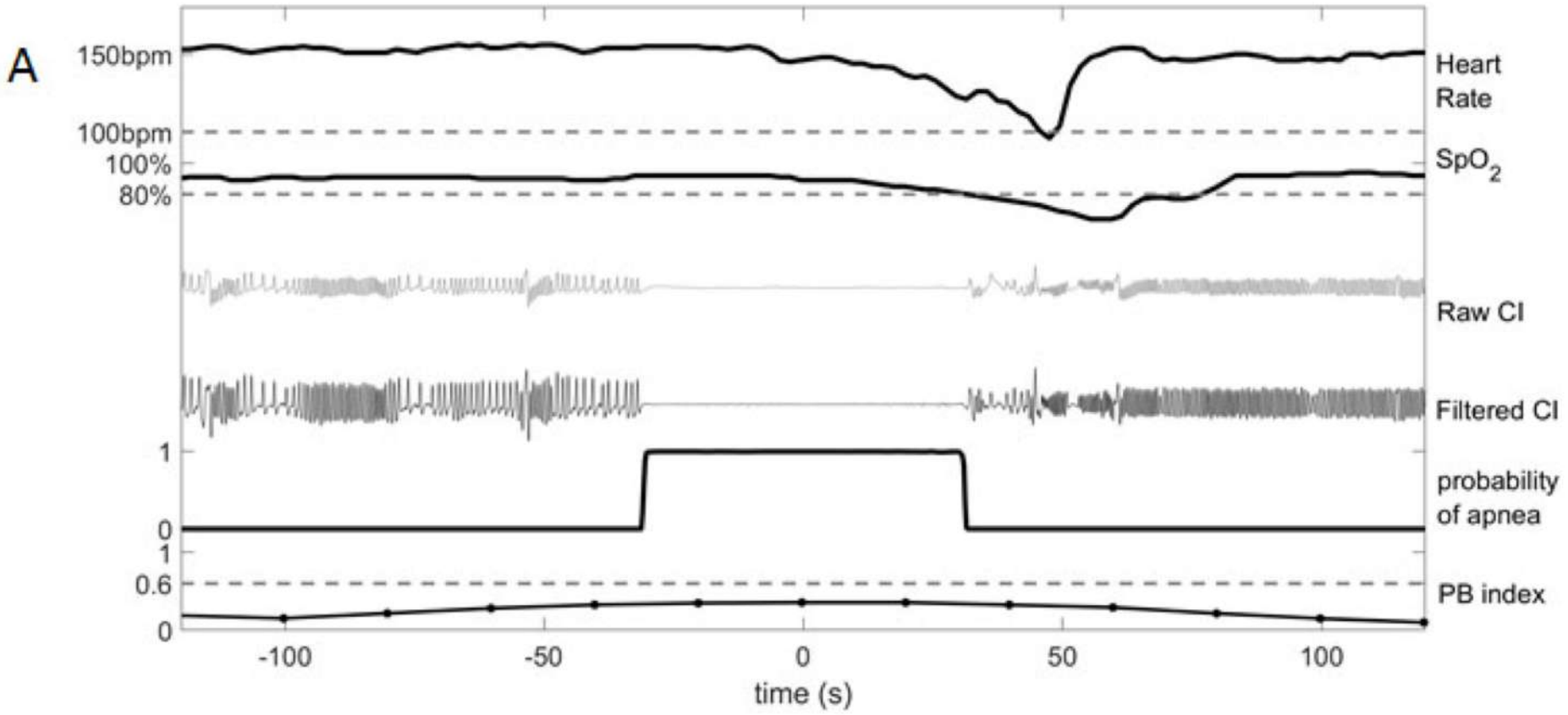
Local factors:
SA node ischemia slows the heart(!!)





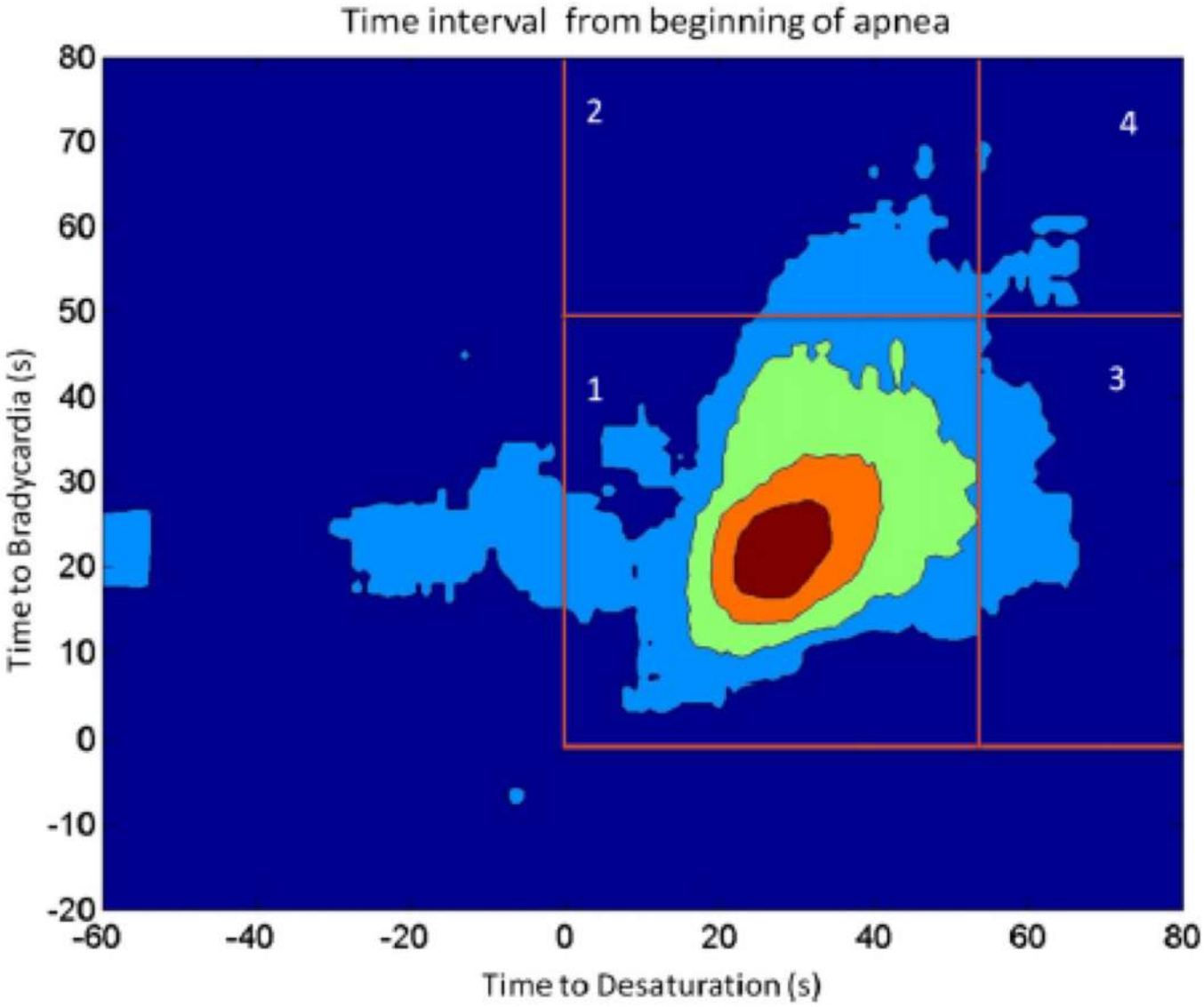
Abe 2008

Quantitative breathing record: central apnea



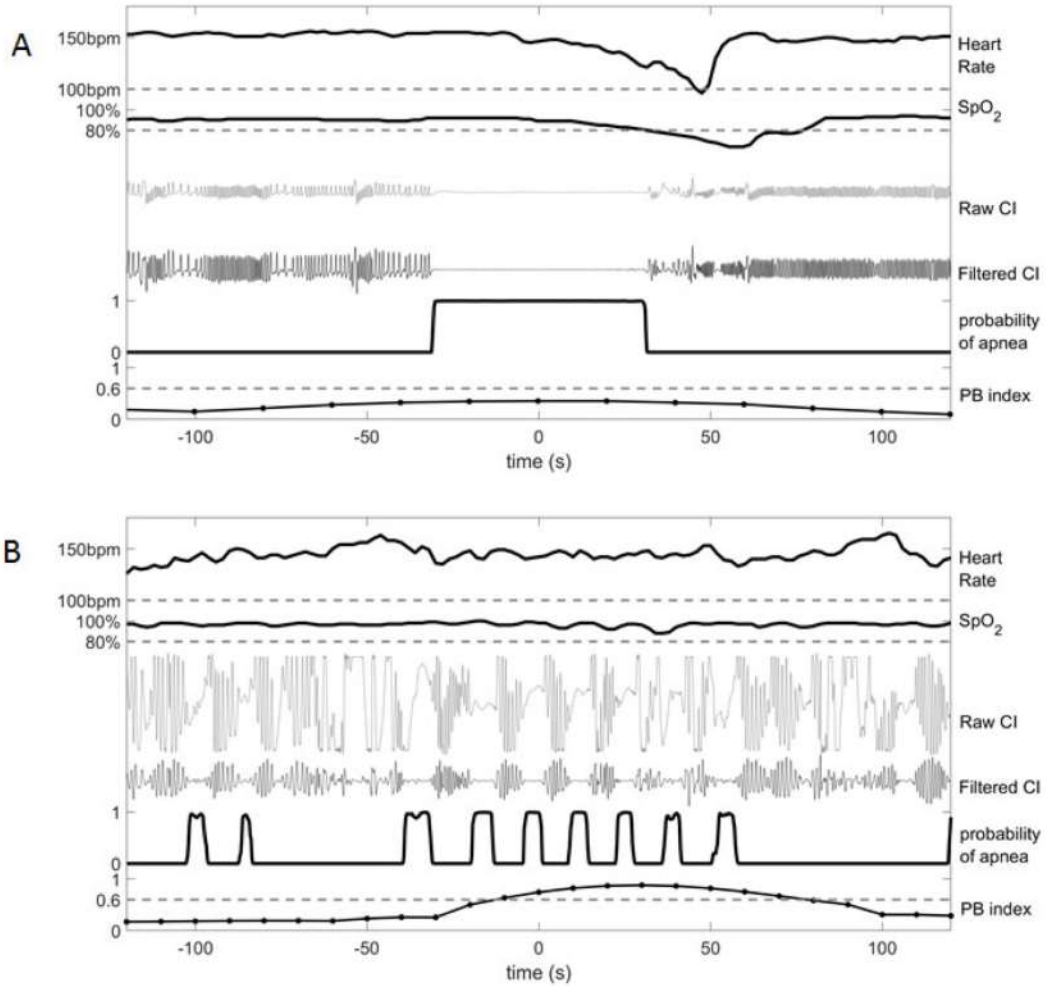
2012 -

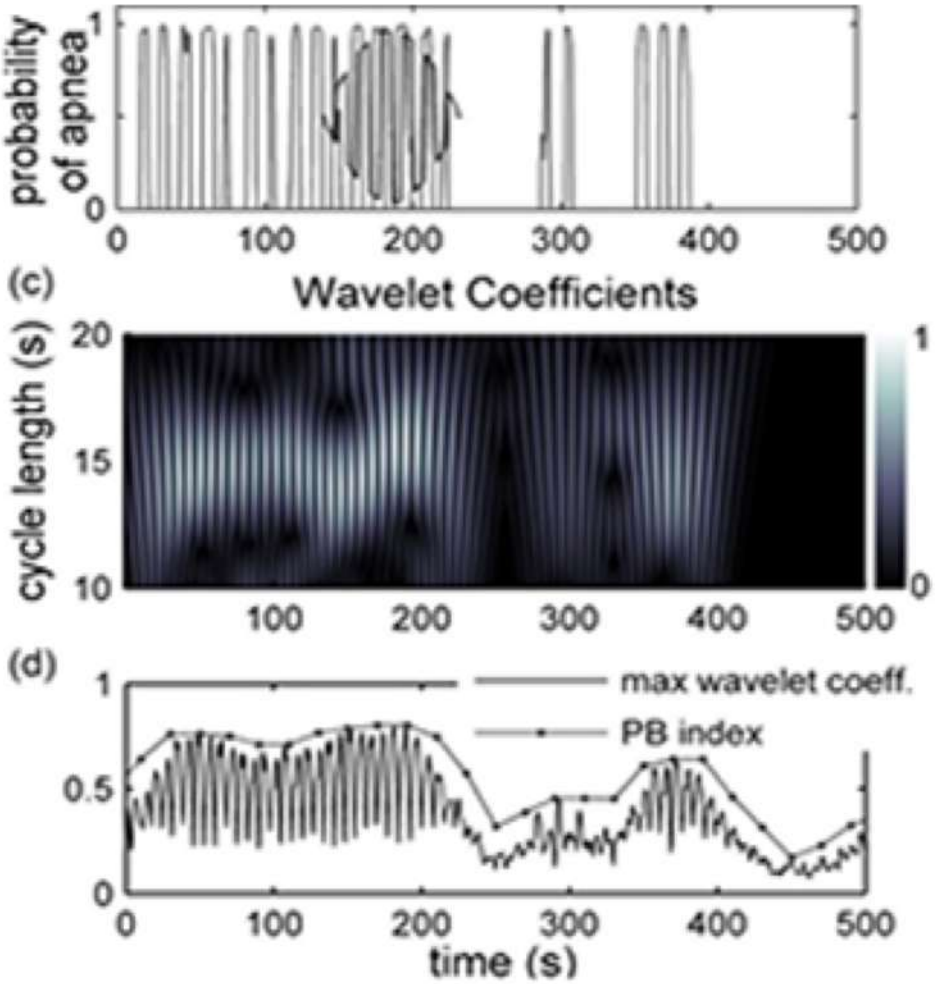
Time lags: beware thresholds!



2014

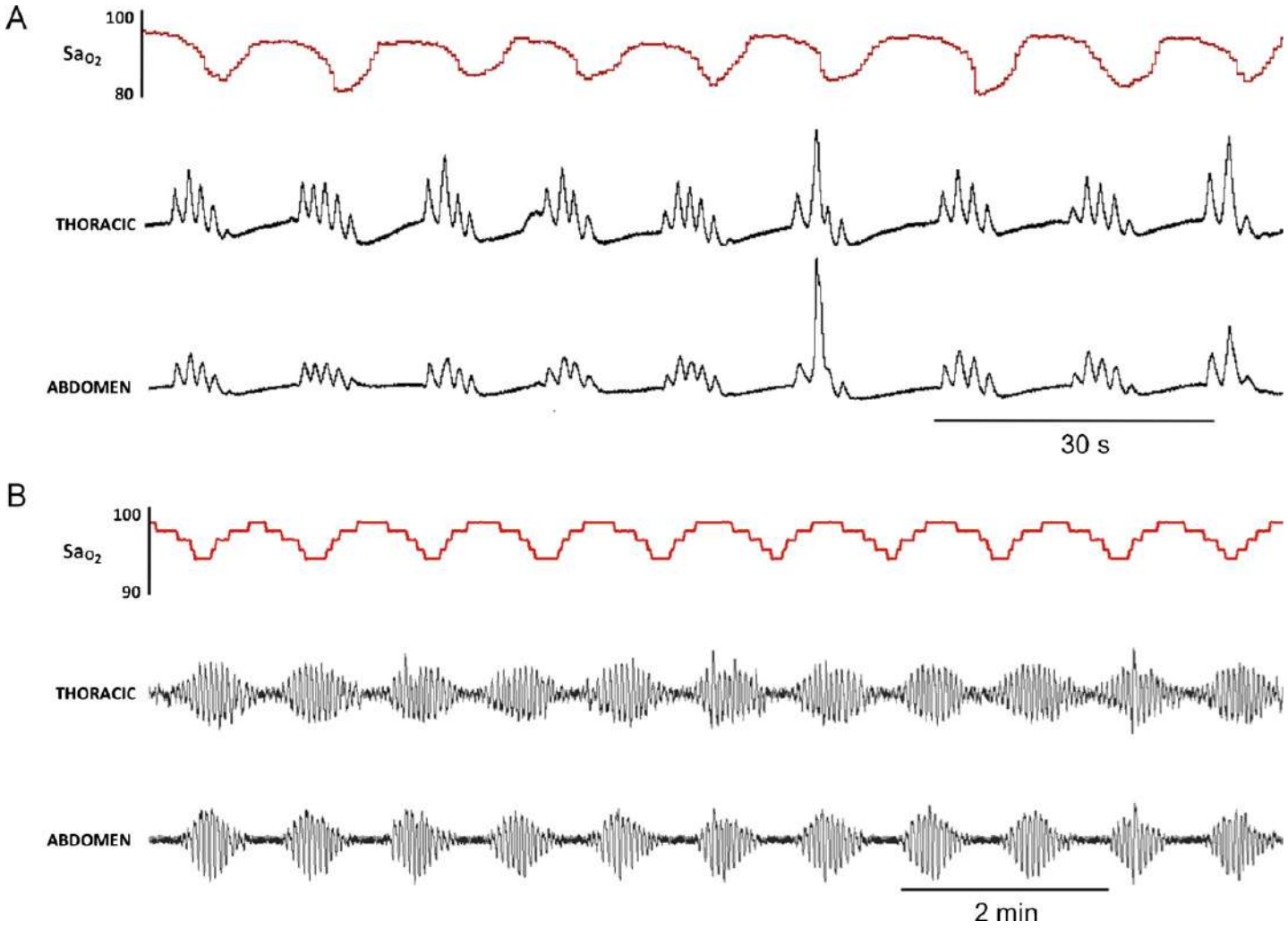
Quantitative breathing record: apnea and periodic breathing





2014-16

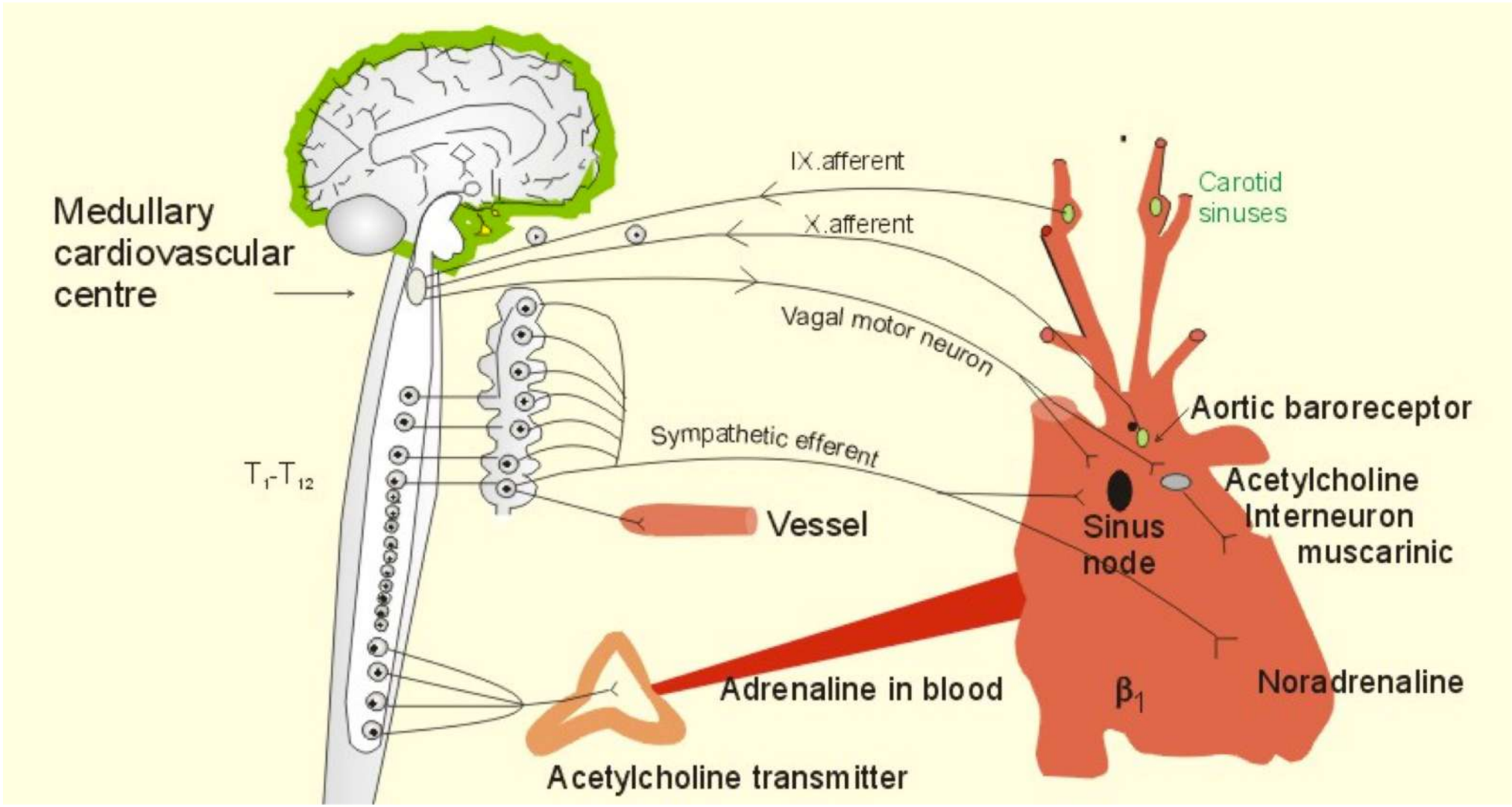
Periodic breathing in infant (top)
Cheyne Stokes respiration in adult (bottom)



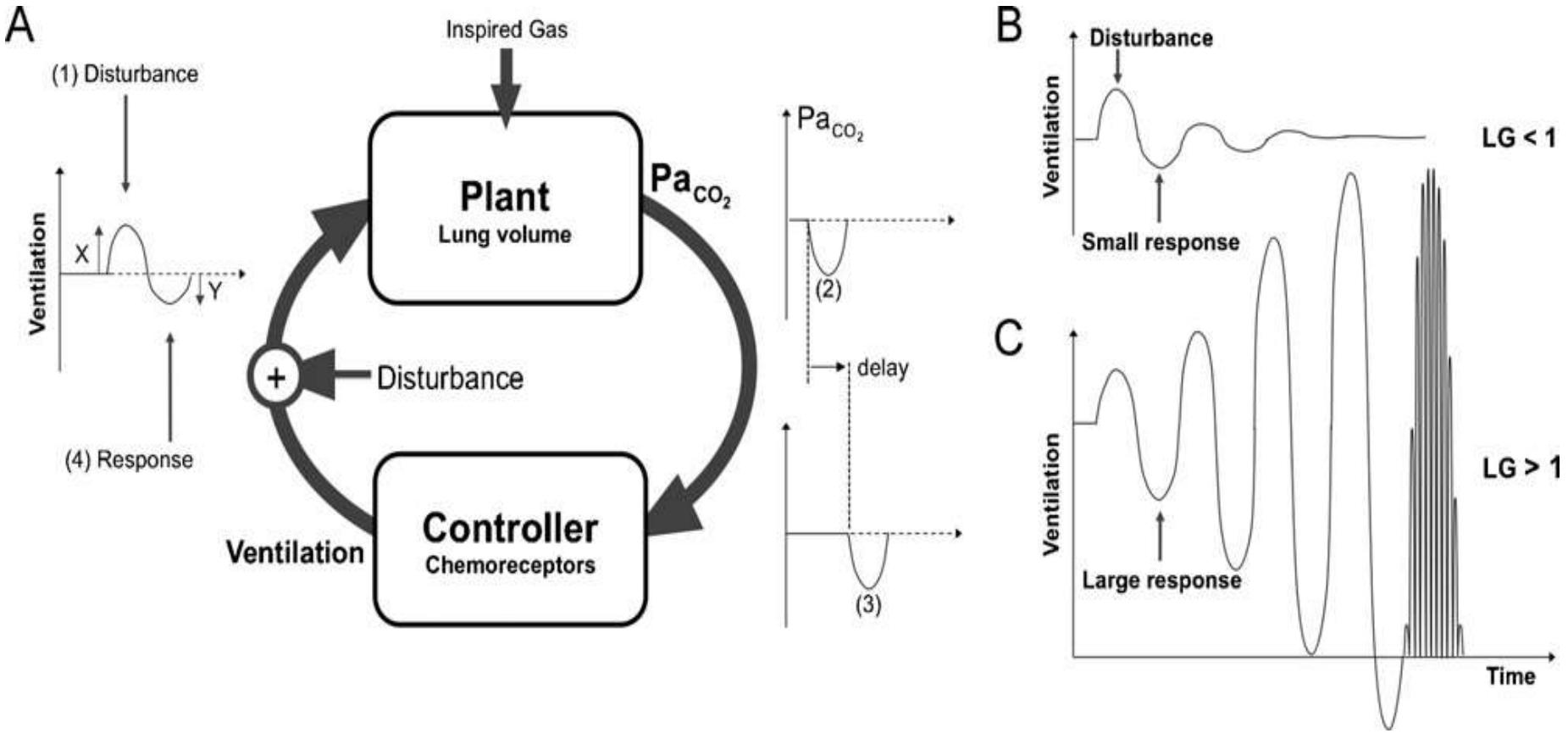
15 sec/cycle

60 sec/cycle

The lungs couple to the heart via the brainstem



A mechanical model for periodic breathing



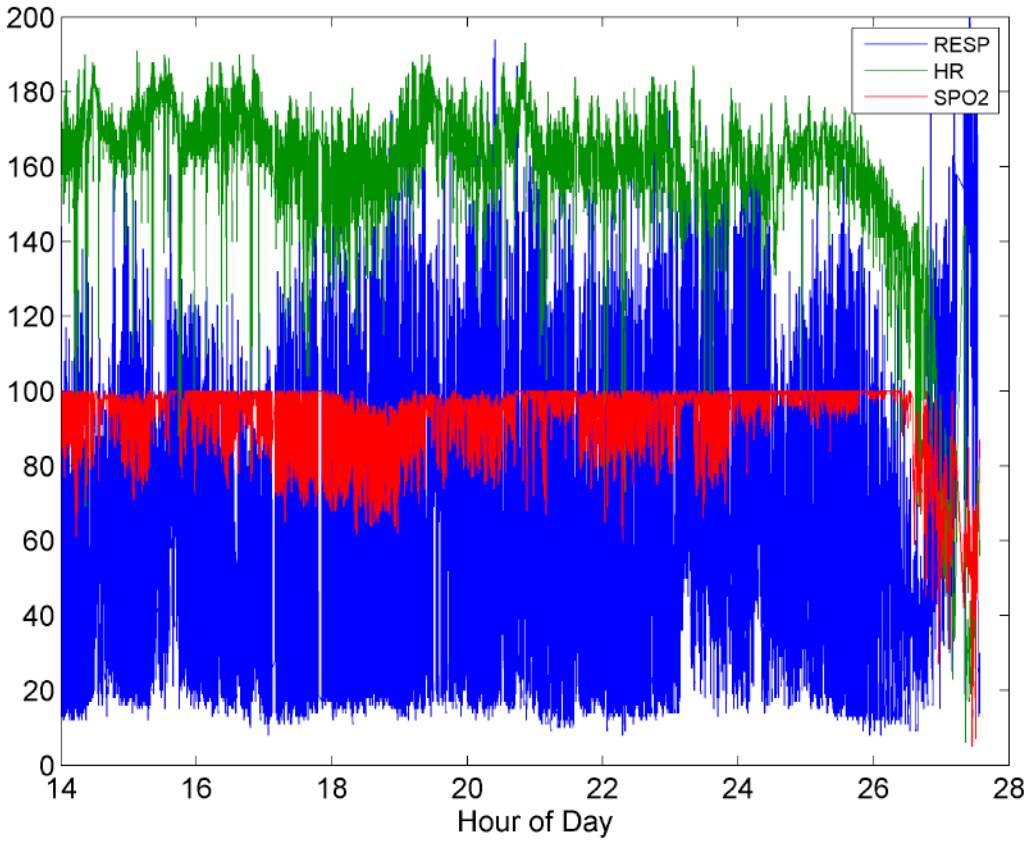
$$\text{Loop gain} = G\frac{P_I - P_a}{V_L}T$$

Edwards, Berger 2012

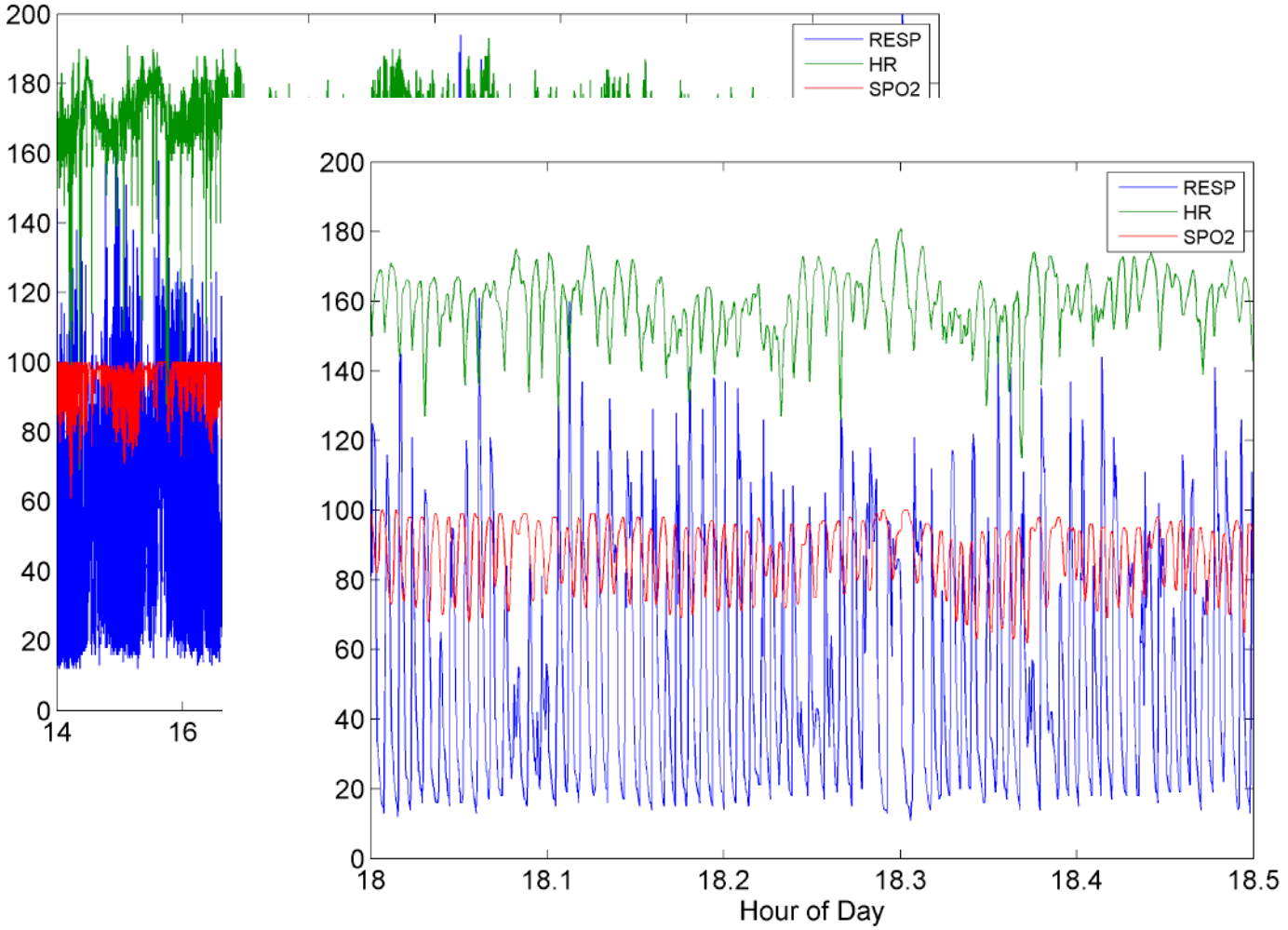
Periodic breathing in infants

- Clinicians consider it to be benign
- Accounts for up to 10% of the time
- We have found rare cases of pathological periodic breathing: a few per 1000
- This is an instance of how Network Physiology can be normal at one dose and abnormal in another

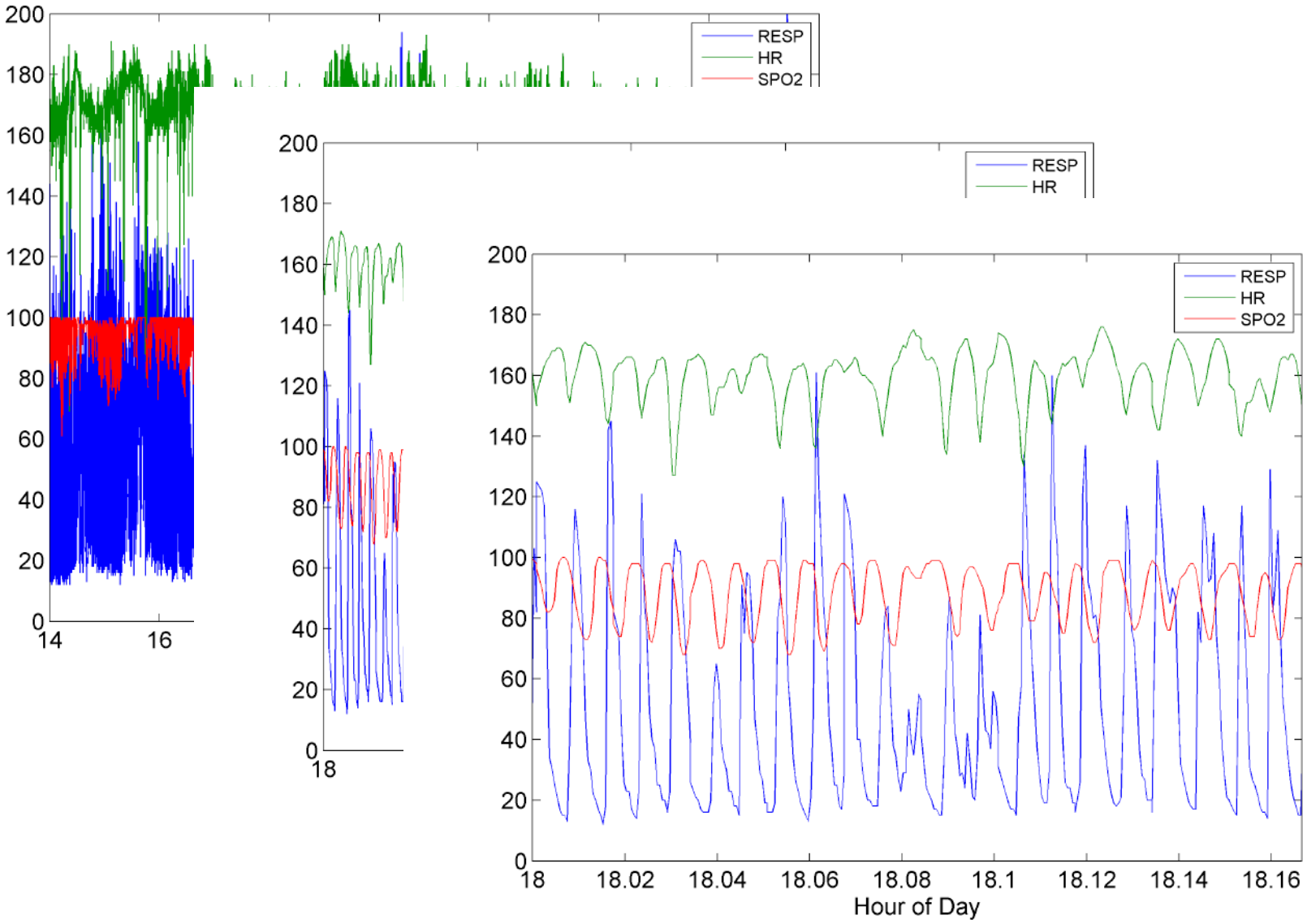
Sudden death in the NICU



Sudden death in the NICU

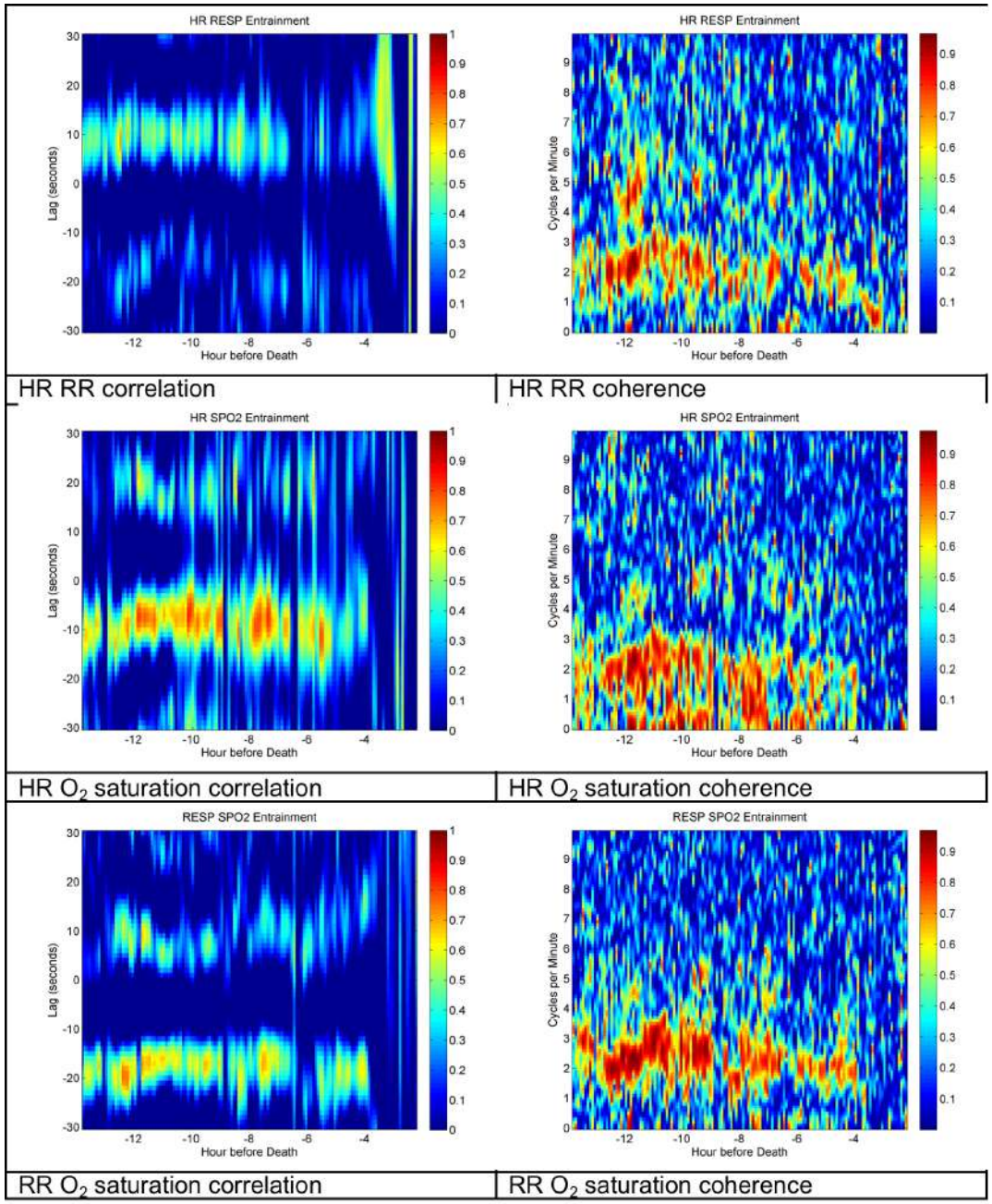


Sudden death in the NICU

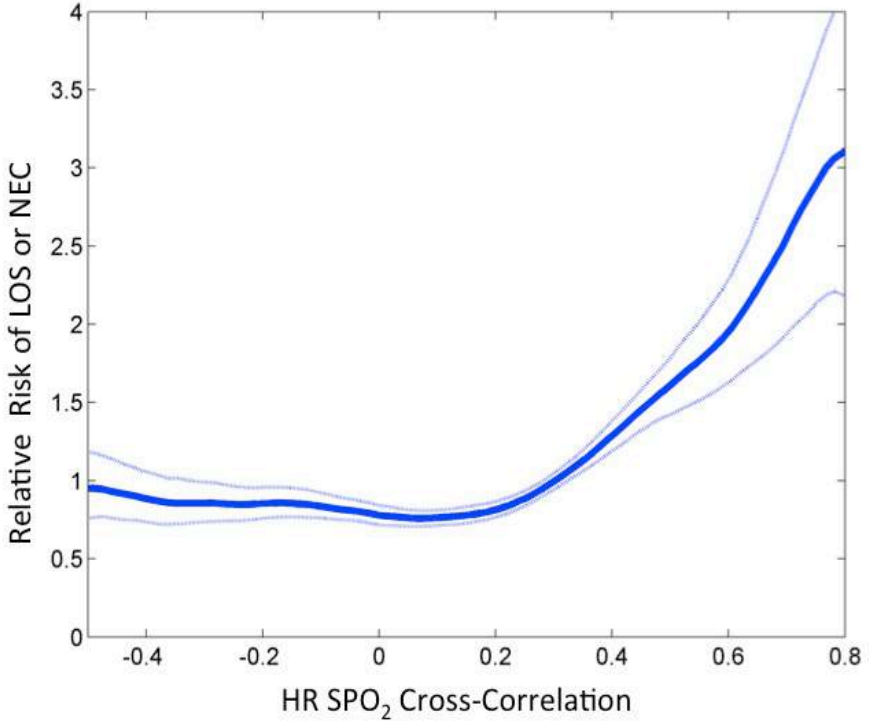


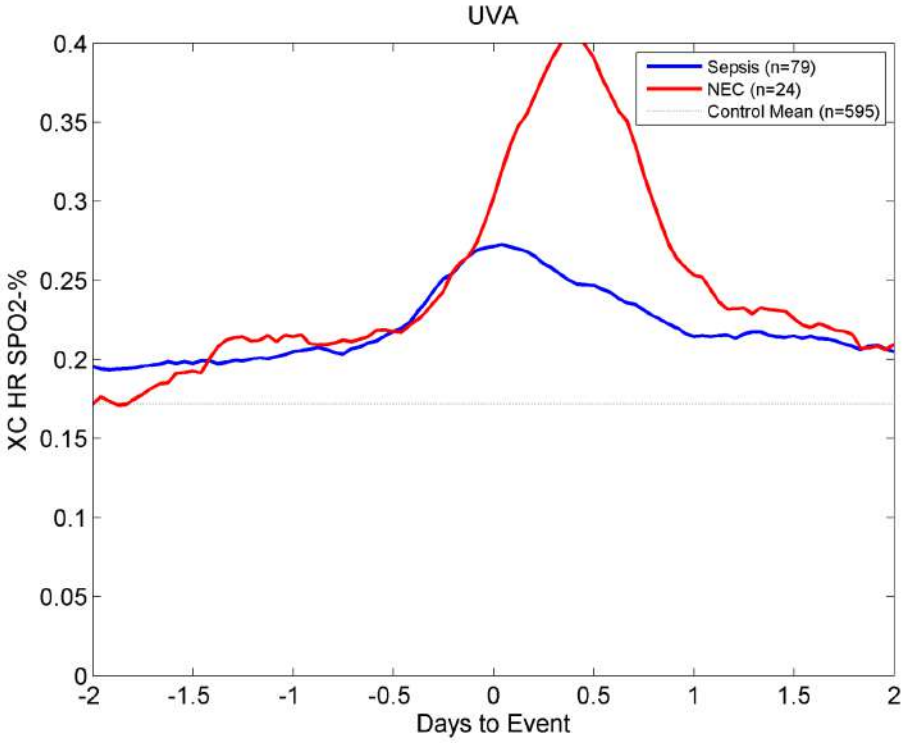
Multidimensional entrainment

- All 3 vital signs are changing together in time
- The frequency is about 2 per minute
- The changes are offset by 10 to 20 seconds
- Note the very prolonged duration of the entrainments – most of the 14 hour period displayed leading up to death.



Entrainment increases prior to illness

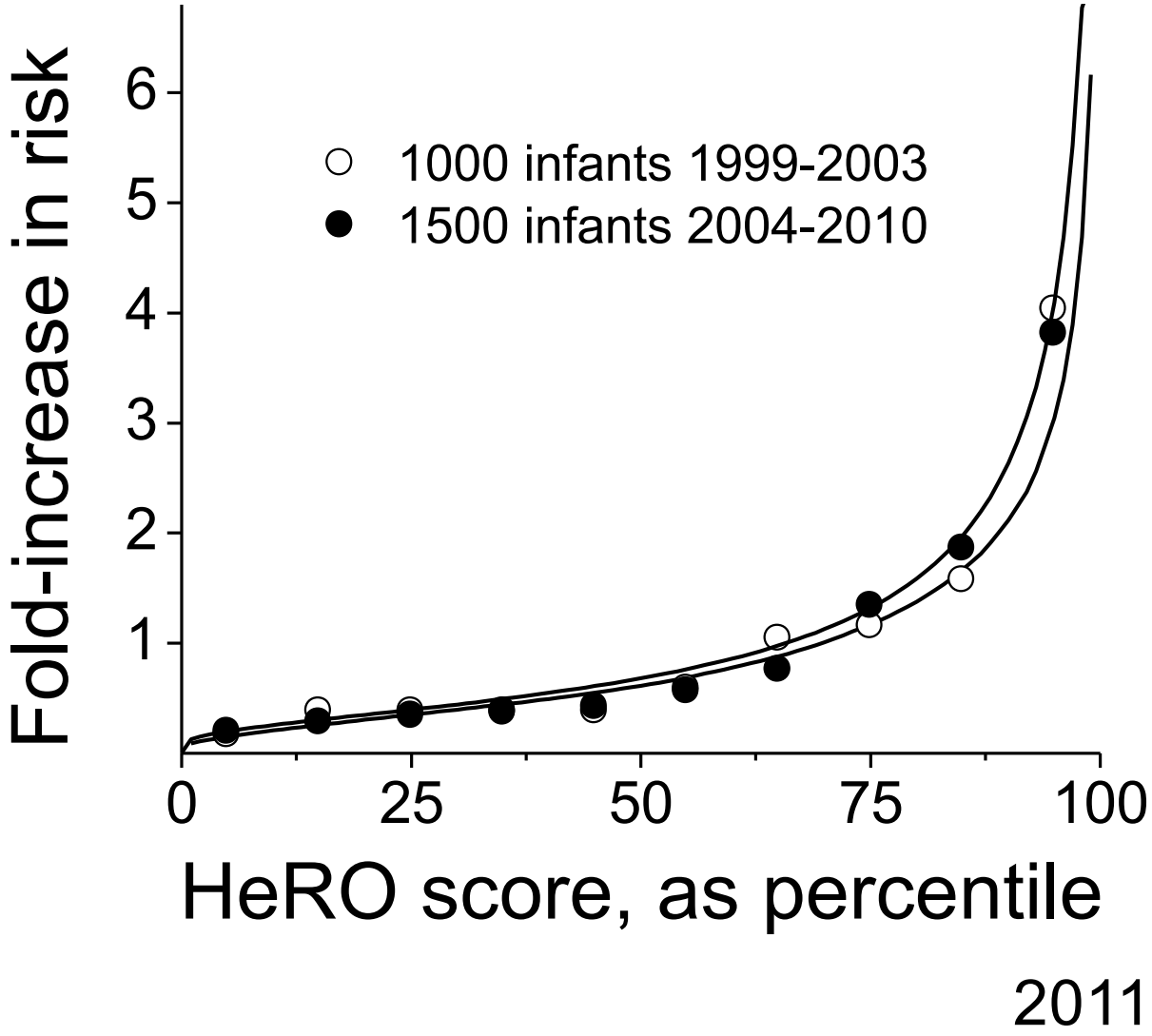


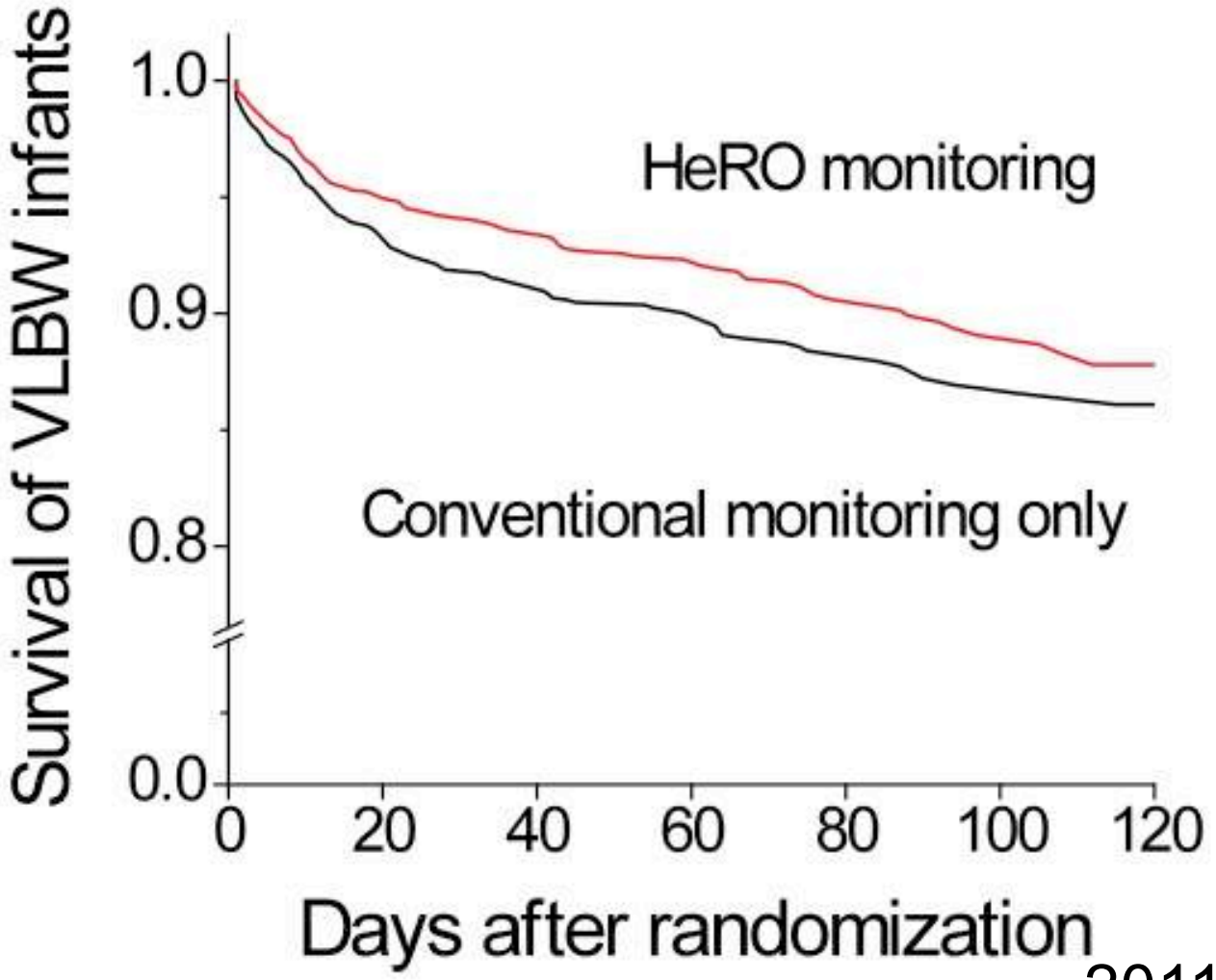


2017

A counter-example: abnormal heart rate characteristics prior to neonatal sepsis

2003


Fold-increase in risk
6
5
4
3
2
1
1000 infants 1999-2003
1500 infants 2004-2010
0
25
50
75
100
HeRO score, as percentile
2011

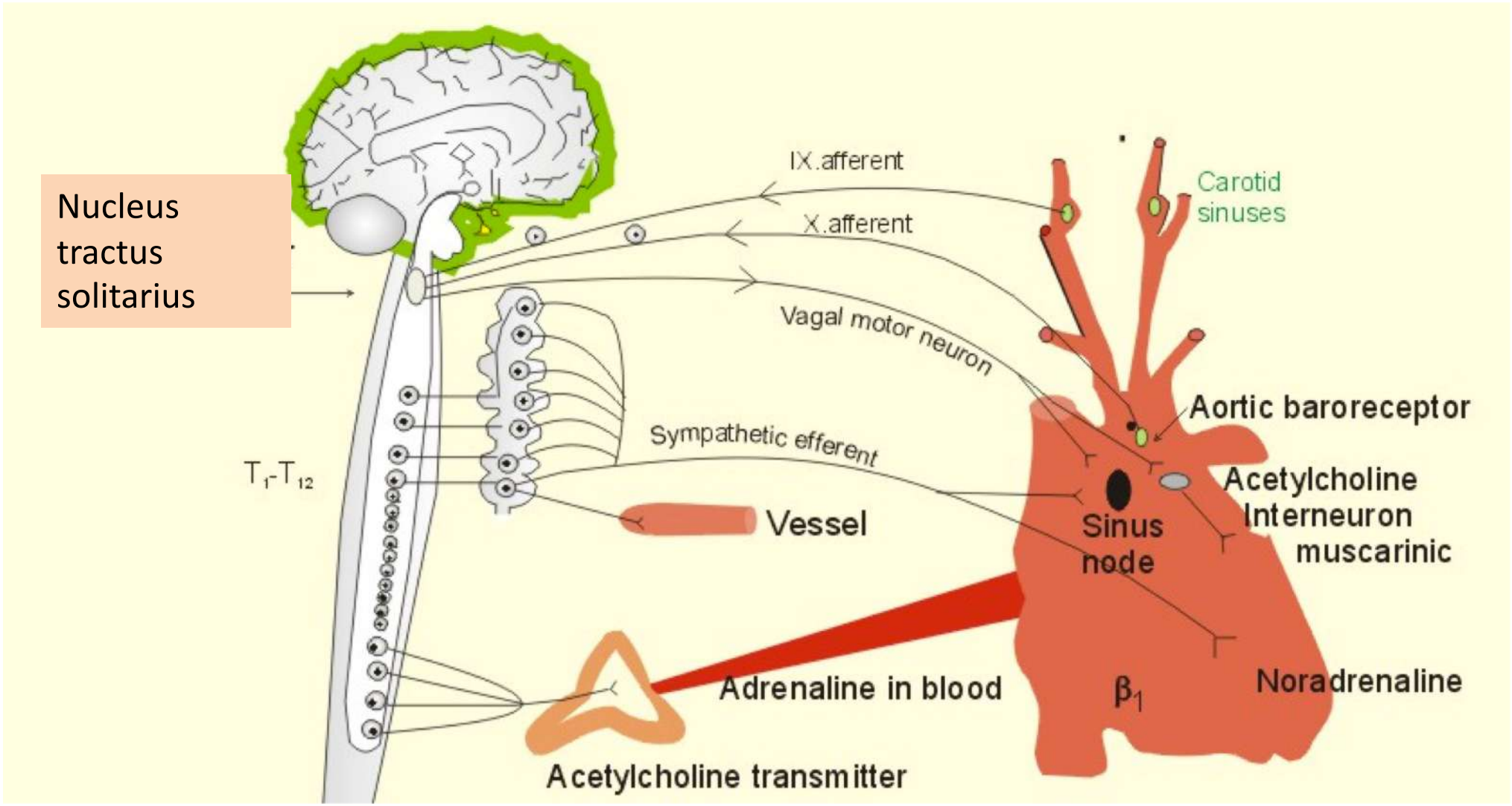

Survival of VLBW infants
1.0
0.9
0.8
0.0
HeRO monitoring
Conventional monitoring only
0
20
40
60
80
100
120
Days after randomization

2011

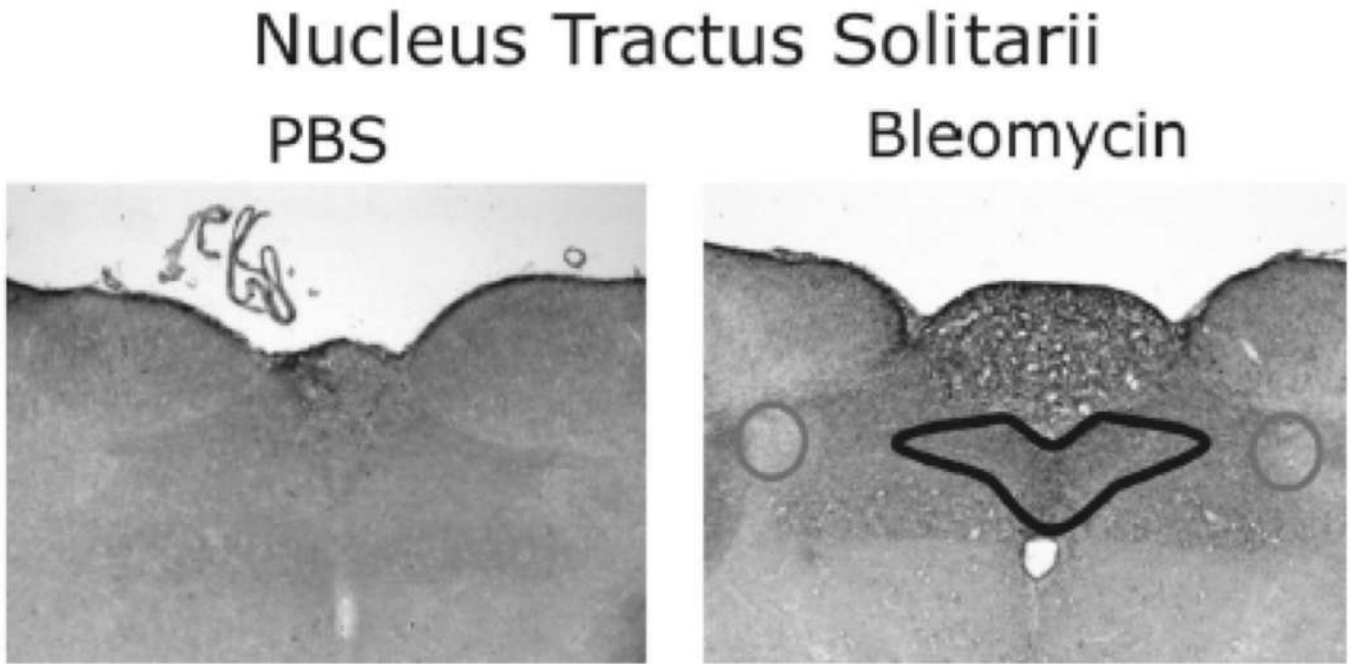
What's wrong with this picture?

- There is a paradox
- ***Low*** vagal activity is suggested by the low heart rate variability
- ***High*** vagal activity is suggested by the decelerations
- Is there another mechanism for the decelerations?
  - A different vagal activation pathway
  - Local factors that affect the sinus node
  - One that is lost with maturation – as more connections develop?

The lungs couple to the heart via the brainstem

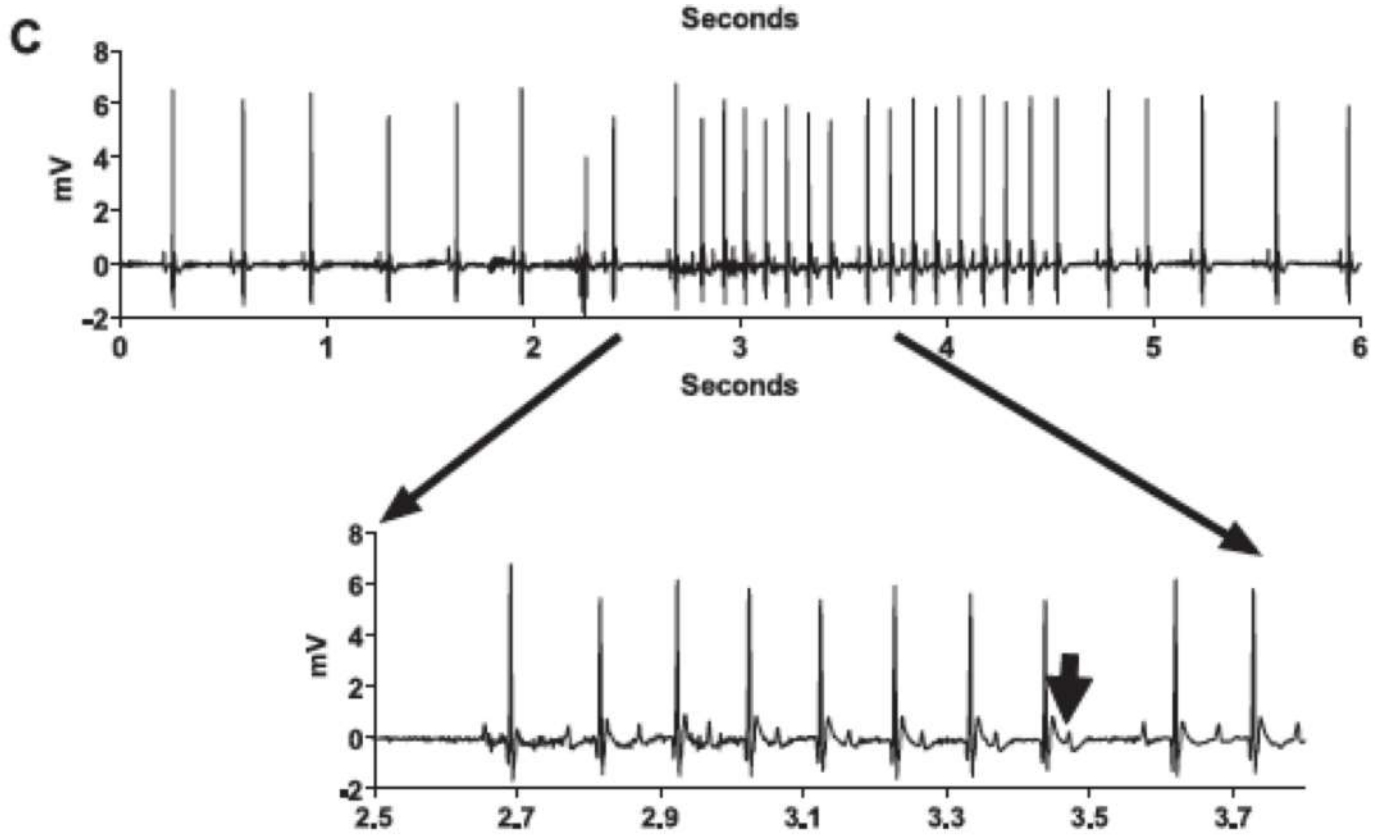


Inflammation at a distance affects brainstem function



Jacono 2011

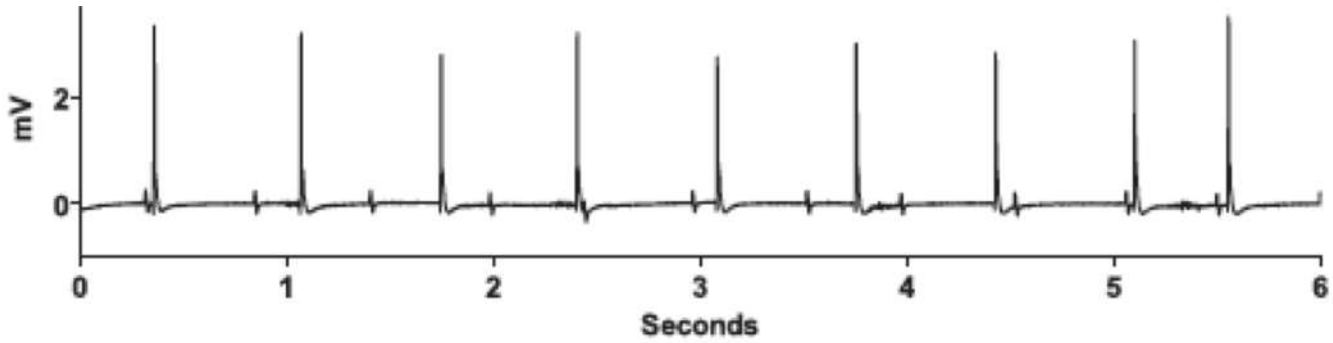
A direct vagal reflex between abdominal microorganism and heart



Sinus node exit block (top, beginning and end of tracing)
Type II 2nd degree atrioventricular block (Wenckebach phenomenon)(top middle and inset)

2009

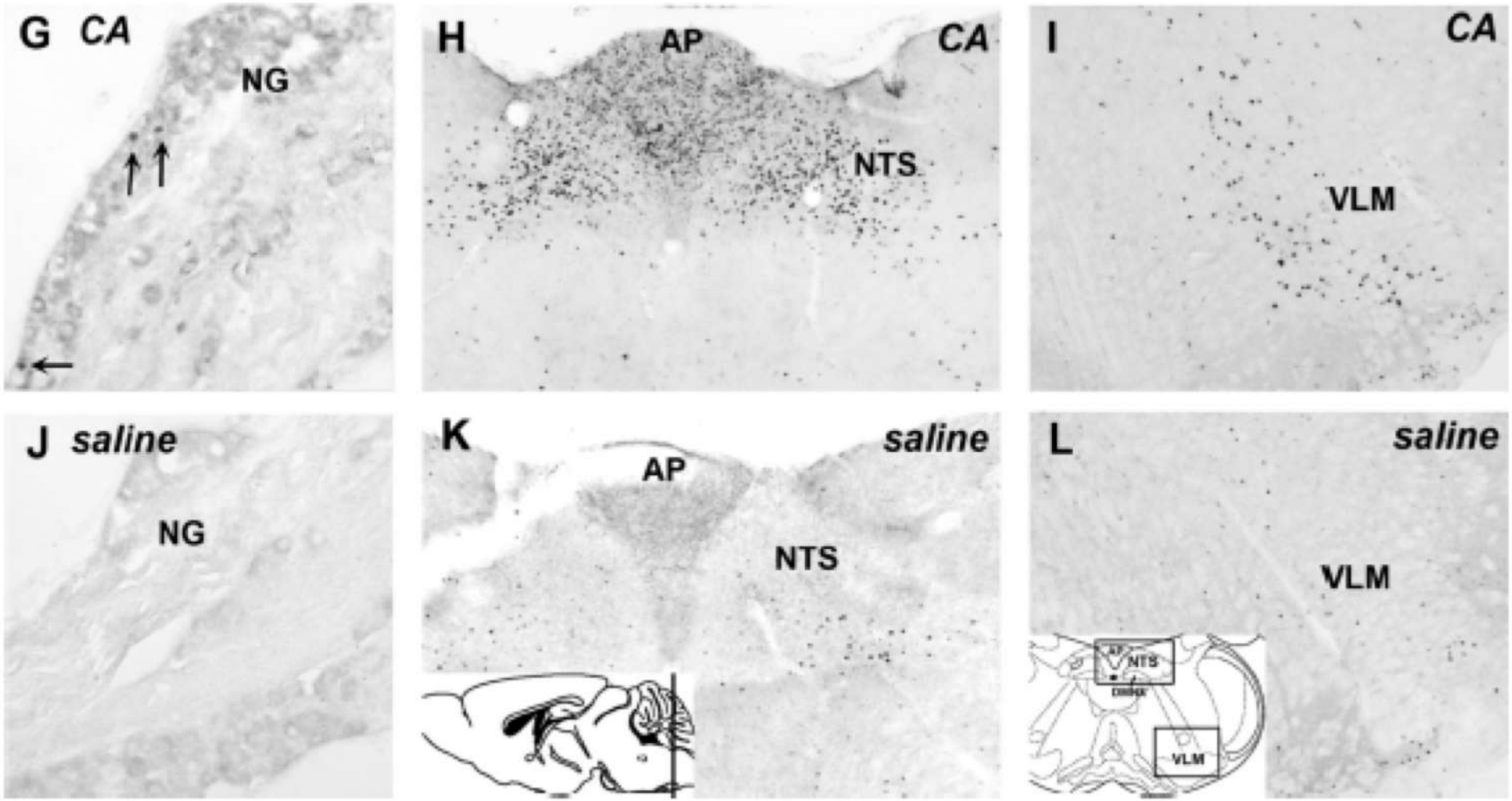
A vagal reflex between abdominal microorganism and heart



Complete AV nodal heart block

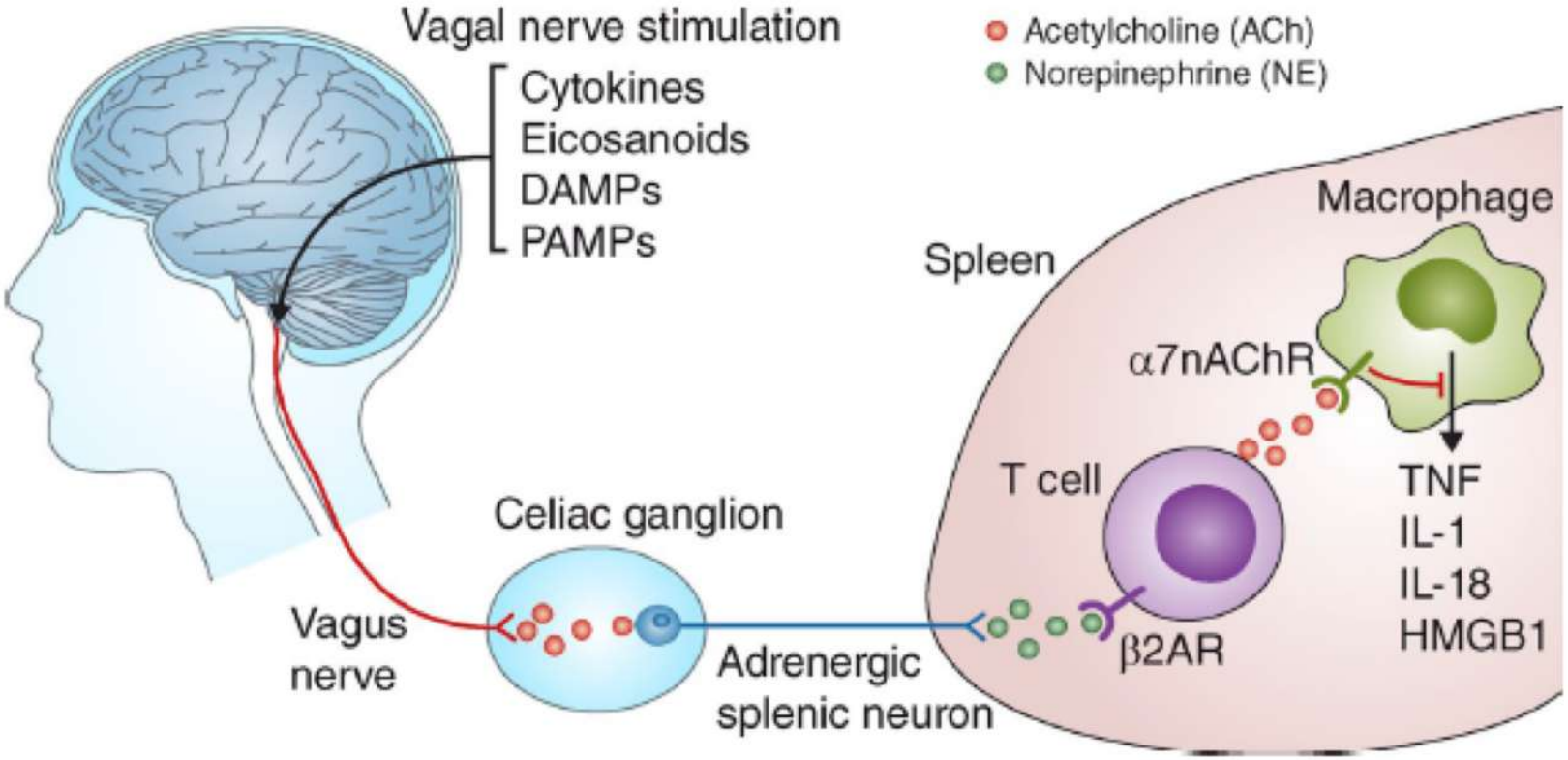
2009

A direct vagal reflex between abdominal microorganism and heart



2009

The cholinergic anti-inflammatory pathway



Tracey 2000

Summary

- In infants:
  - hypoxemia slows the heart rate
  - heart and lungs are coupled by the brainstem
- One understandable sign of Network Physiology – periodic breathing – is normal nearly all of the time
- Sepsis is preceded by reduced variability and transient decelerations of the heart rate
- This is not easily explained by the known coupling mechanisms
  - is the reduced HRV due to brainstem inflammation?
  - are the decels due to vagal bursts via the cholinergic anti-inflammatory pathway?

Questions for the field of Network Physiology

- What is normal and what is abnormal?
- What are the mechanisms? Autonomic nervous system, cholinergic anti-inflammatory pathway, local factors…
- What data can be examined?
- What patients can be studied?
- What time series methods can be used?
- What Network Physiology-based diagnostic tests can be fashioned?
- What Network Physiology-based therapies can be conceived?