Cardiorespiratory Networking is Altered Early in Subacute Potentially Catastrophic Illness

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Editor-in-chief, *Physiological Measurement*

Overview

- The purpose of the cardiac electrical system is to provide heartbeats exactly when you need them.
- For this, the sinus node is in constant communication with other organs, principally the brain and lungs.
- Until you get sick.
- Take a deep breath….

Although science may seem to proceed at a breathless pace, with one exciting discovery after another, the concepts we work with are frequently old ones that scientists have been refining for generations. The current excitement, then, is over the new clarity with which old concepts are revealed. Indeed, reading old books gives one humility in the clarity of our predecessors' thinking and in the continuity and apparent slowness of subsequent discovery.

Bertil Hille, *Ionic Channels of Excitable Membranes*

Rev. Hales 1744

HÆMASTATIQUE,
Ou
LA STATIQUE
DES ANIMAUX:
EXPE'RIENCES HYDRAULIQUES
Faites ſur des Animaux vivans.

Avec un RECUEIL de quelques EXPE'RIENCES ſur les PIERRES que l'on trouve dans les reins & dans la veſſie; & des recherches ſur la nature de ces Concrétions irréguliéres.

Par Mr. ETIENNE HALES, *de la Societé Royale des Sciences, Miniſtre de Teddington, dans le Comté de Middleſex, & Recteur de Faringdon.*

OUVRAGE TRE'S UTILE AUX MEDECINS:

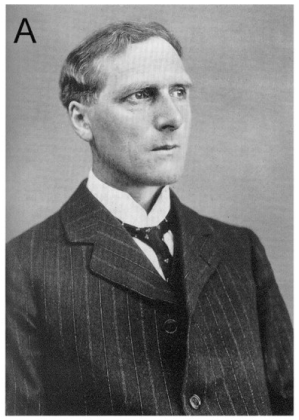
Traduit de l'Anglois, & augmenté de pluſieurs REMARQUES *& de deux* DISSERTATIONS DE MEDECINE, SUR LA THEORIE DE L'INFLAMMATION, ET SUR LA CAUSE DE LA FIEVRE;

Par Mr. DE SAUVAGES, Conſeiller Médecin du Roy, Profeſſeur Royal de Médecine en l'Univerſité de Montpellier, & Membre de la Societé Royale de Suéde.

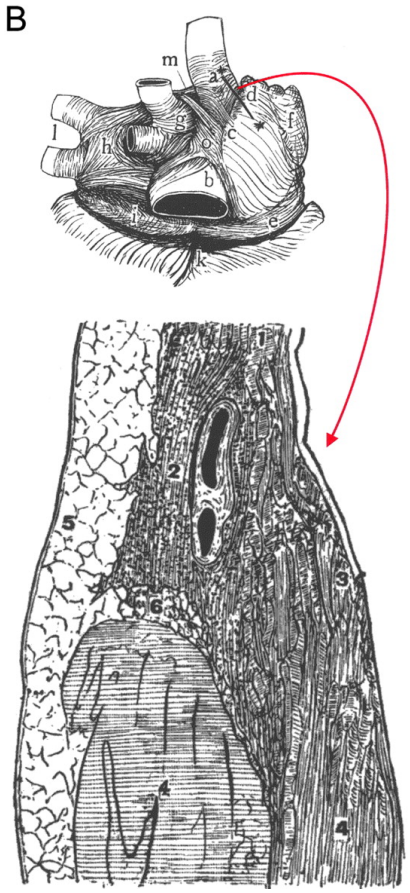
A GENEVE,
Chez les Hérit. CRAMER & Fréres PHILIBERT.
M DCC XLIV.

“In December I caused a mare to be tied down alive on her back ... having laid open the left crural artery about three inches from her belly, I inserted into a brass pipe whose bore was one-sixth of an inch in diameter and to that by means of another brass pipe which was fitly adapted to it, I fixed a glass tube of nearly the same diameter which was nine feet in length. Then , untying the ligature on the artery, the blood rose in the tube to eight feet three inches … at its full height, it would rise and fall at and after each pulse 2, 3 or 4 inches.”

Keith and Flack 1906



a, superior caval vein
b, inferior caval vein
c, terminal crest
i, coronary sinus
k, base of ventricles
l, left pulmonary veins
**, line of section below
1, muscle of superior caval vein
2, sinus node artery surrounded by sinus node tissue
4, terminal crest
5, sub-epicardial tissue
6, connective tissue beween sinus node and terminal crest



By the summer of 1906, Keith had enlisted the help of a young medical student, Martin Flack, the son of the local grocer and butcher. Together, Keith and Flack studied the hearts of smaller animals, such as the mole.

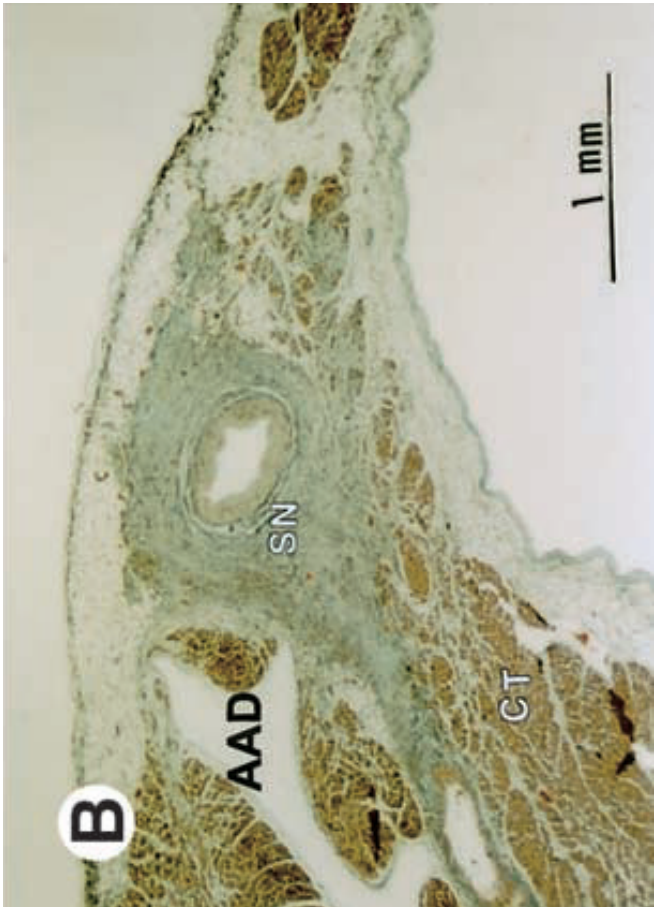
On a hot summer day in 1906, Flack was studying microscopic sections of the heart of a mole while Arthur Keith and his wife were bicycling through the beautiful cherry orchards near their cottage in Kent . Upon their return, Flack excitedly showed Keith a ‘‘wonderful structure he had discovered in the right auricle of the mole, just where the superior vena cava enters that chamber.’’

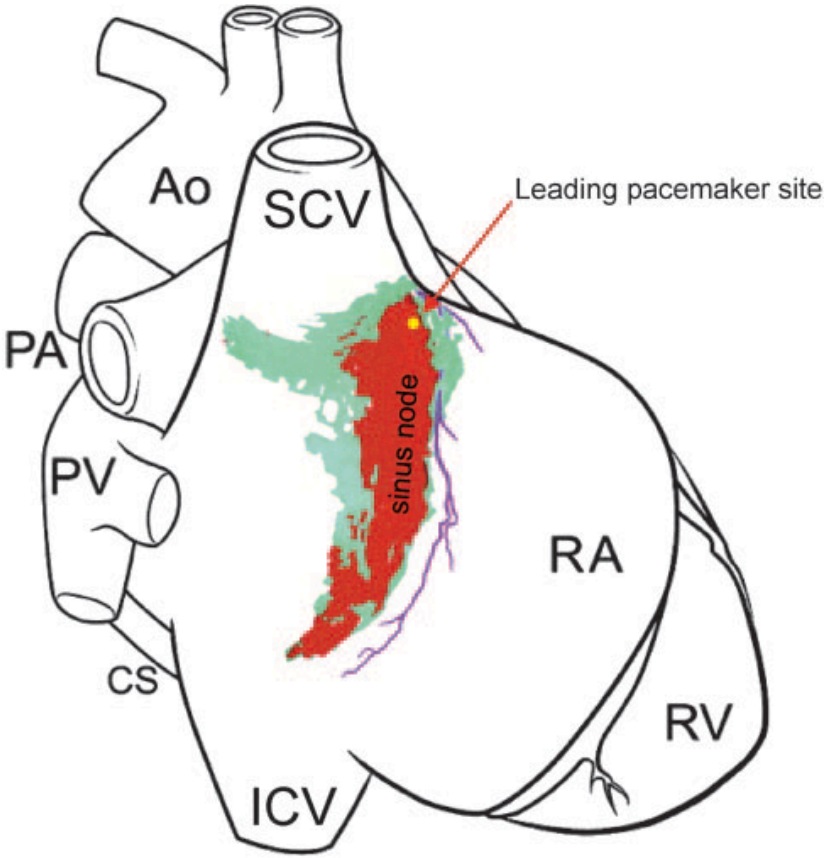
Keith quickly realised that this structure closely resembled the atrioventricular node as described by Sunao Tawara earlier that year. Further anatomical studies confirmed the same structure in other hearts, which they named ‘‘the sino-auricular node.’’ The long sought-after site of origin of the heartbeat had finally been discovered.

For Flack’s work, Keith was knighted.

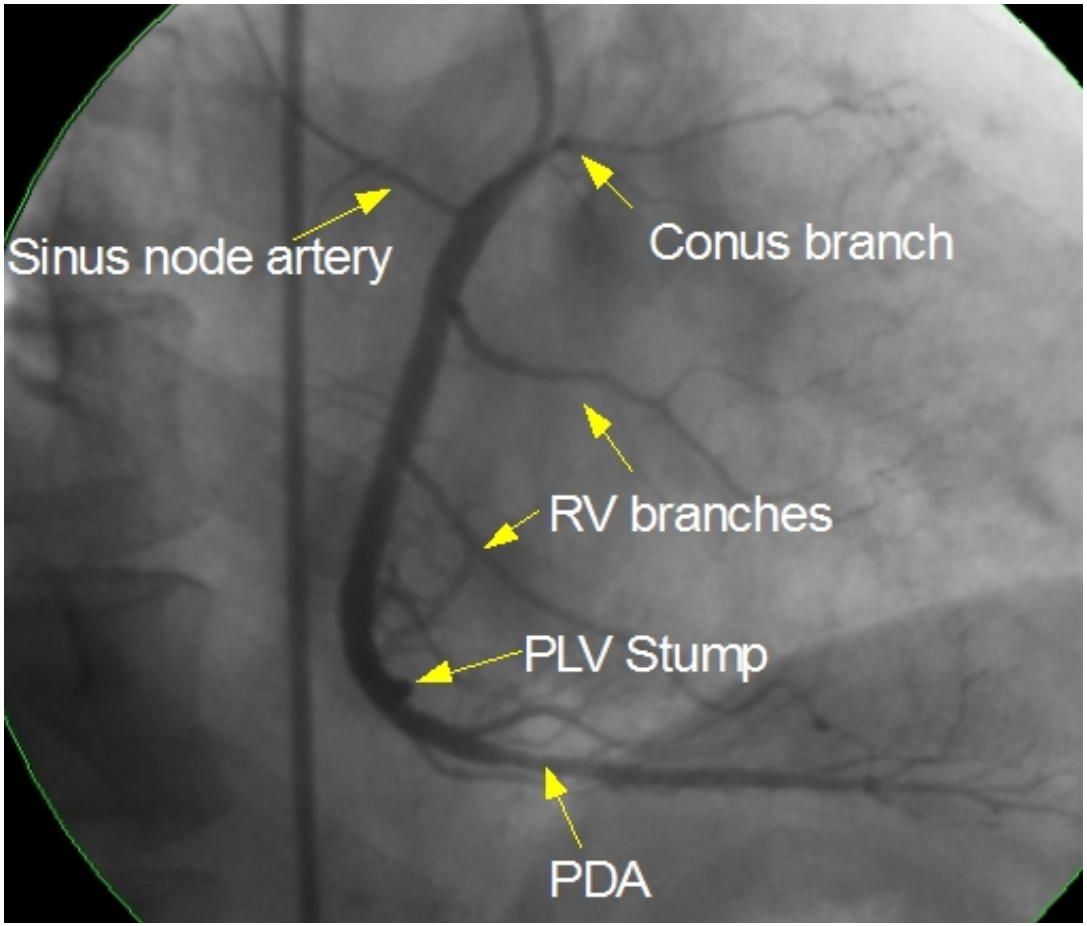
Keith A, Flack M. The form and nature of the muscular connections between the primary divisions of the vertebrate heart. J Anat Physiol 1907;41:172–89.

The sinus node began as the adventitia of the sinus node artery





The sinus node artery arises from the proximal RCA in man



Regulation of the heart rate

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Topical Review

An introduction into autonomic nervous function

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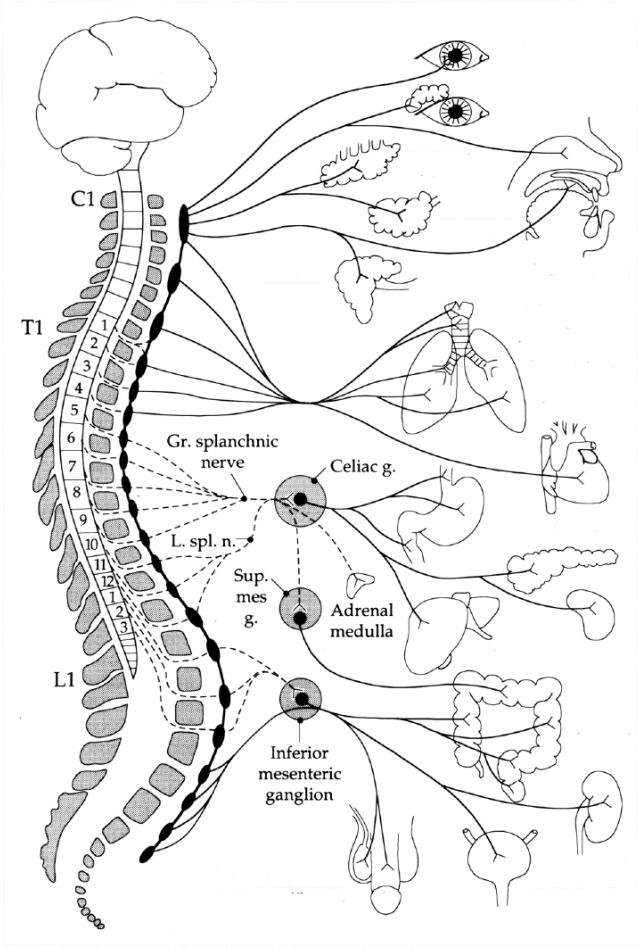
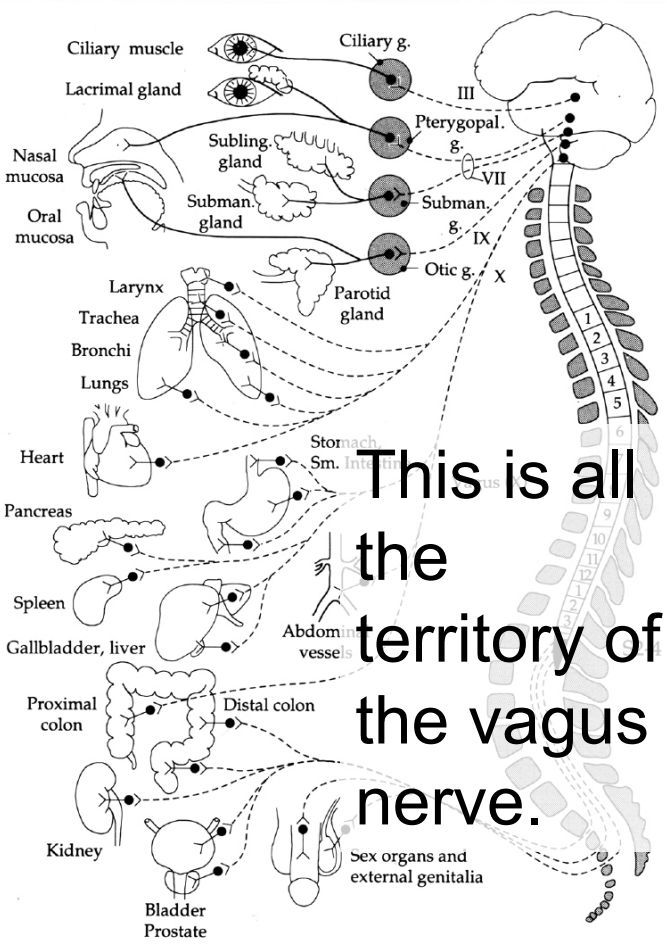
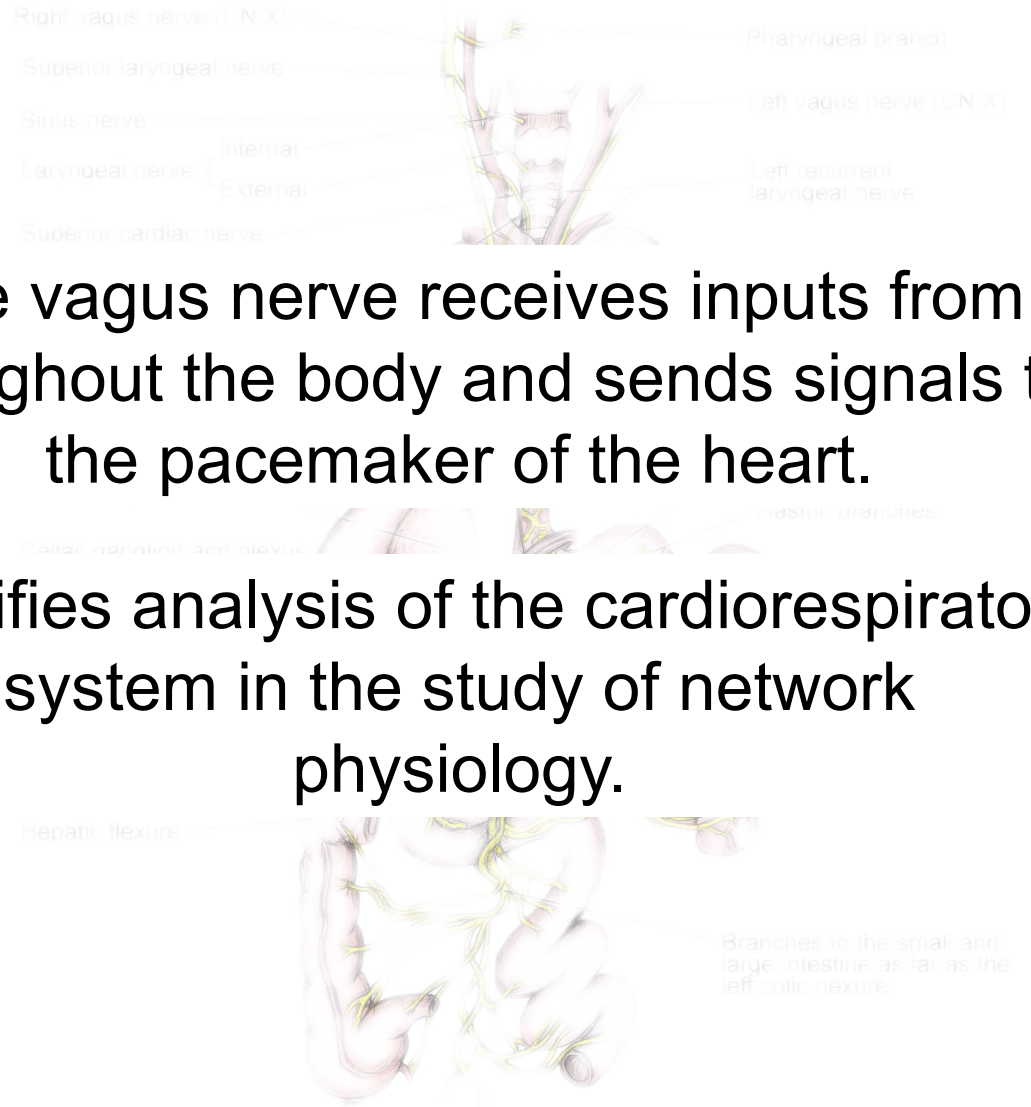
Sympathetic



Parasympathetic



This is all the territory of the vagus nerve.



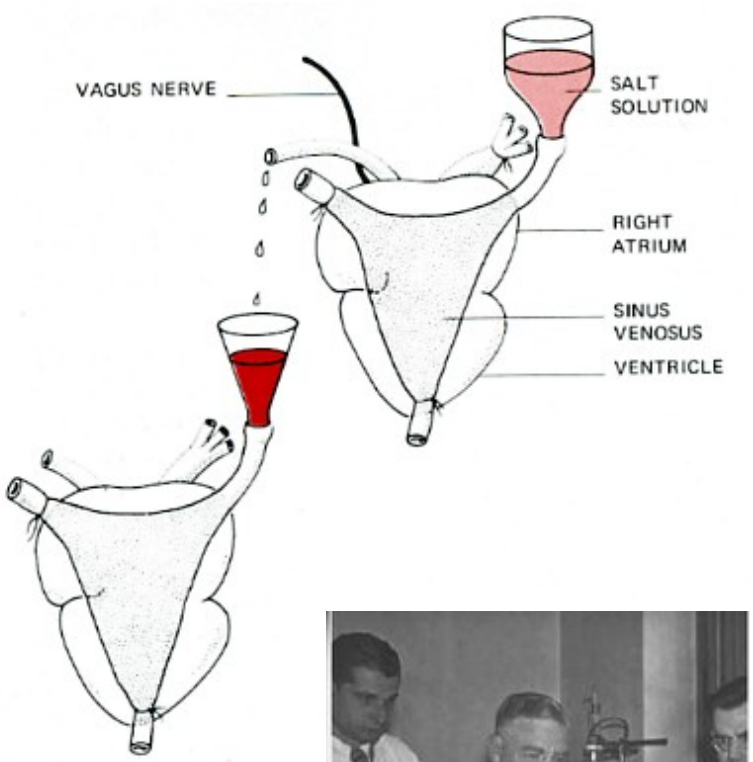
The vagus nerve receives inputs from throughout the body and sends signals to the pacemaker of the heart.

It justifies analysis of the cardiorespiratory system in the study of network physiology.

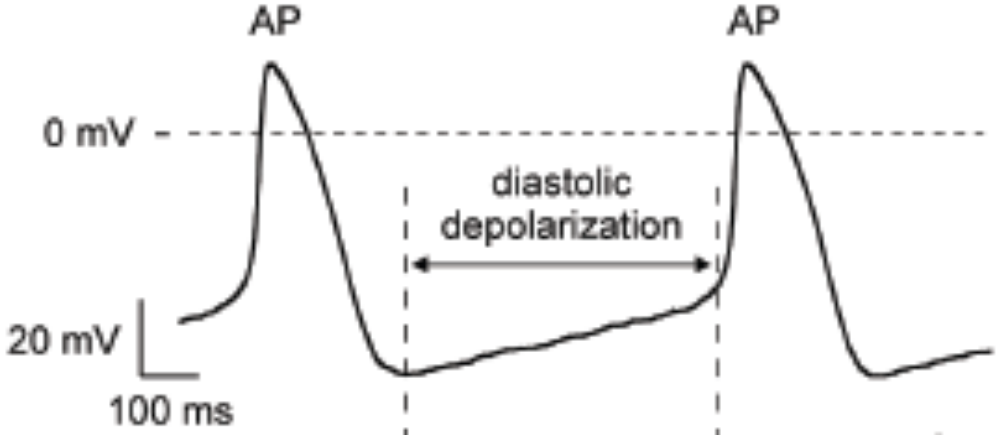
In 1920, following a dream on Easter Sunday, future Nobel laureate Otto Loewi isolated the hearts of two frogs. Into the cavity of one heart he put a salt solution - and stimulated the vagus. The expected immediate slowing of the heart rate occurred.

He transferred some of the salt solution to the second heart, and its beat was immediately slowed.

Later, he showed that this “Vagusstoff” was ACh.

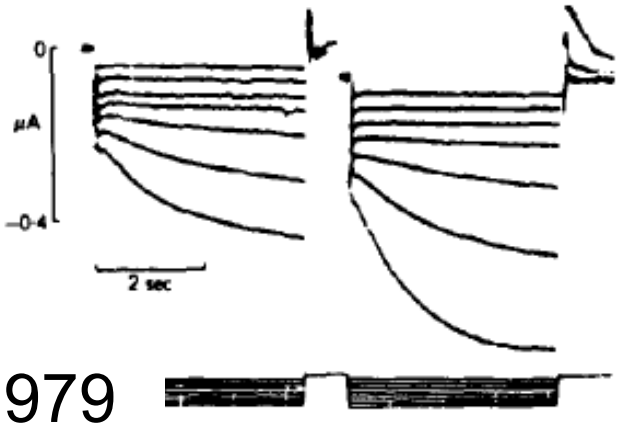


The sinus node is self-starting…



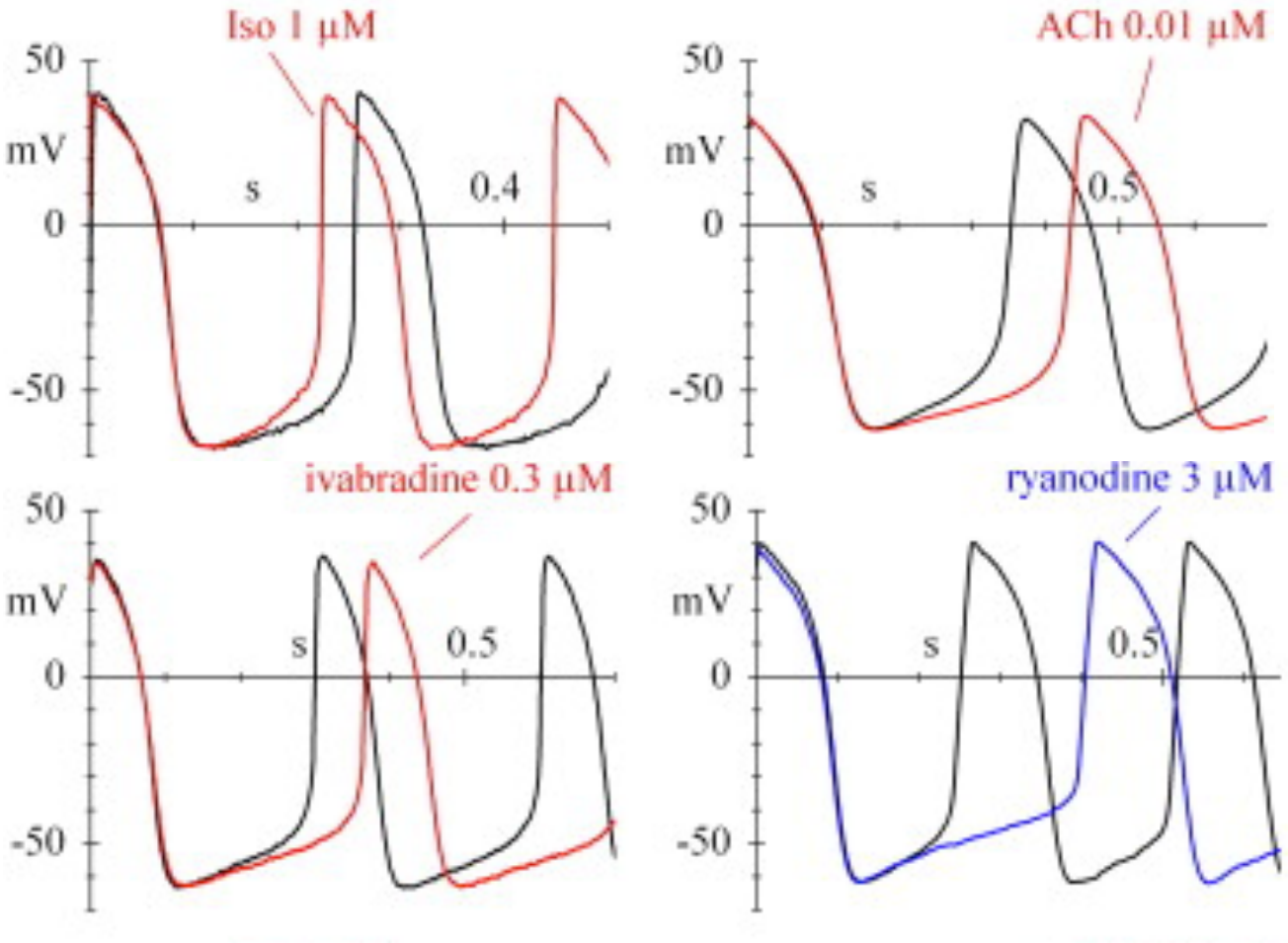
Human SN action potentials

DiFrancesco 1979



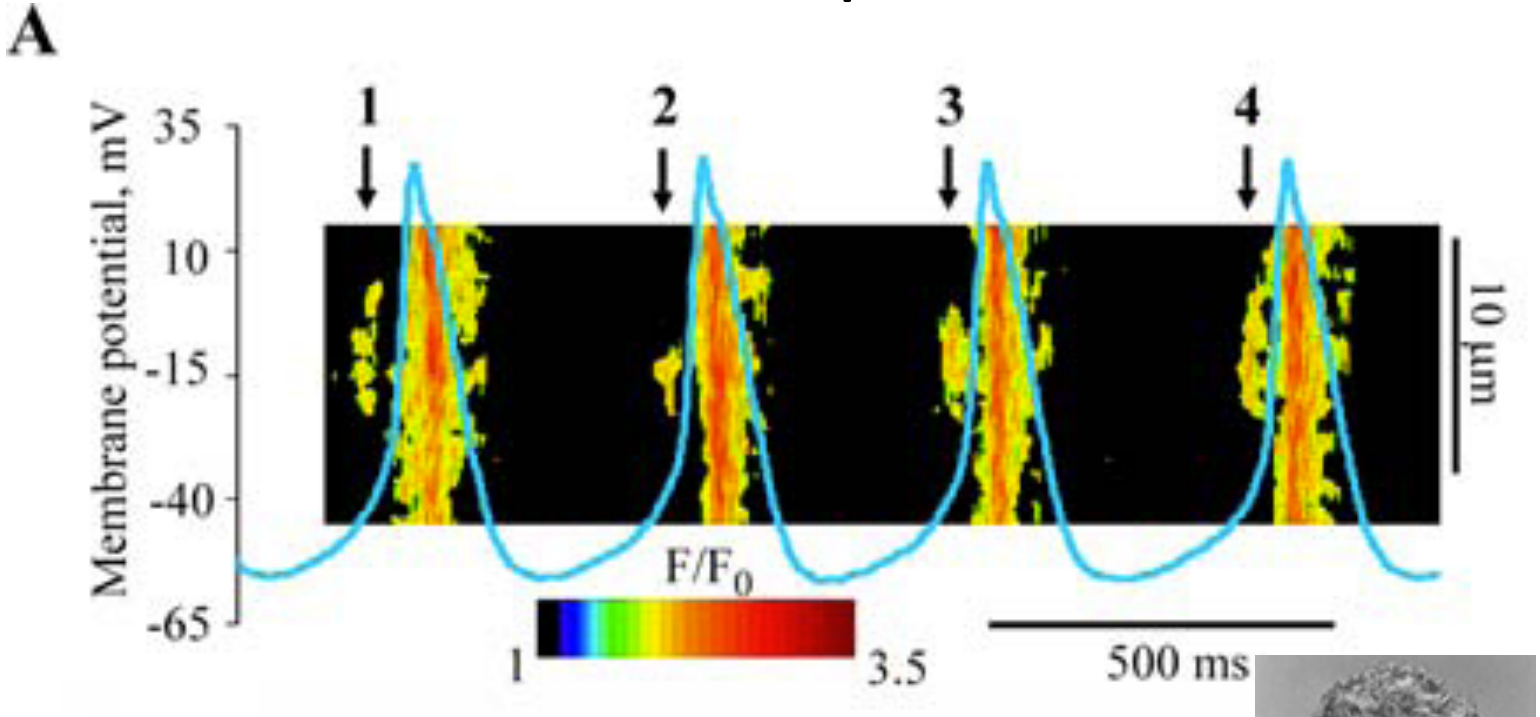
Funny current, HCN channels

… at different rates...

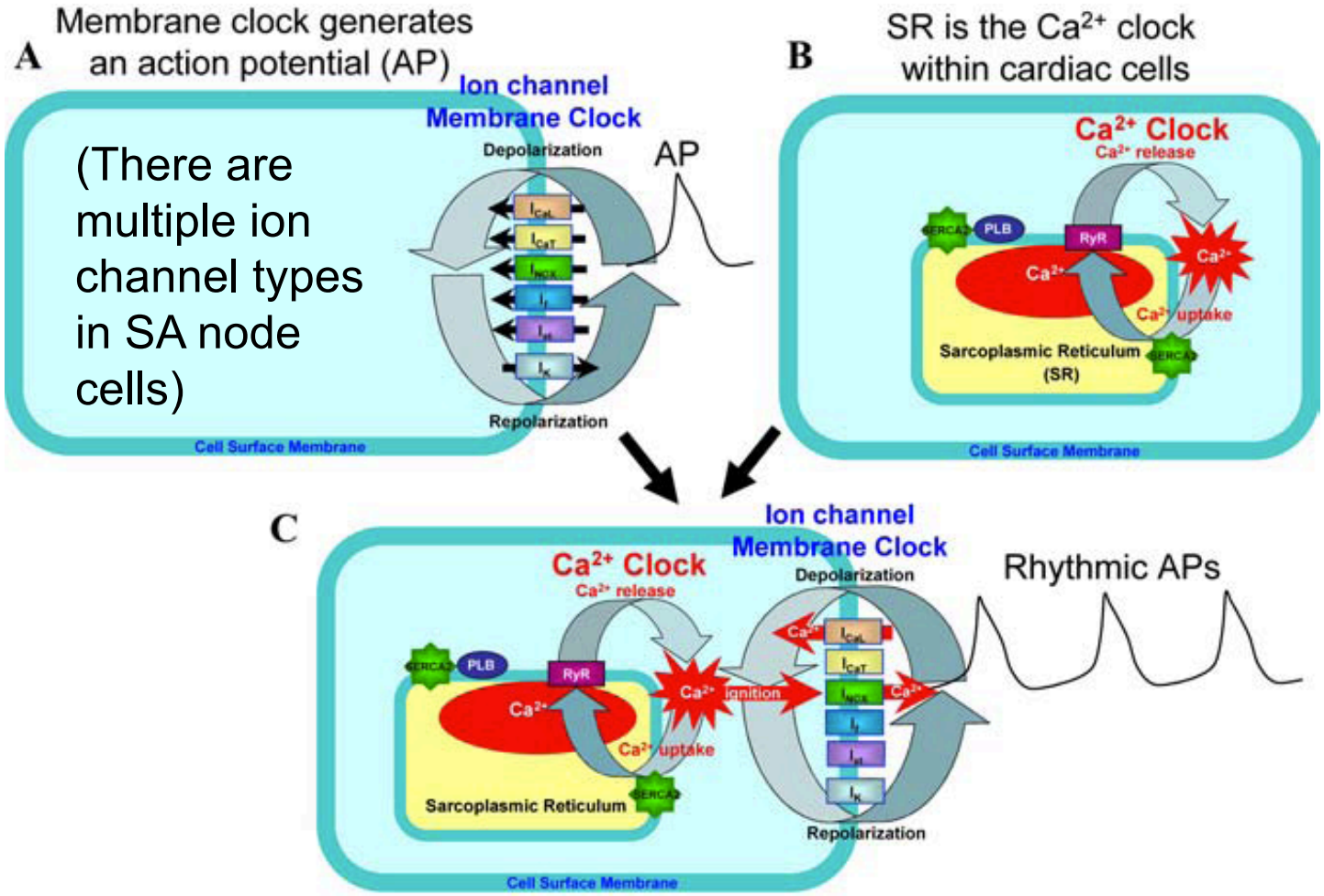


!!!!

… and with a complicated clock.



Lakatta 2006



Ca^{2+} clock rhythmically ignites M-clock
resulting in robust automaticity of cardiac pacemaker cells

The story so far

- There is good anatomical and physiological basis for using the vagus nerve to regulate the heart rate.
- Since the vagus nerve receives inputs from many places, this could be a useful system to make sure there are heartbeats exactly when you need them.
- Next: a demonstration that this is so.

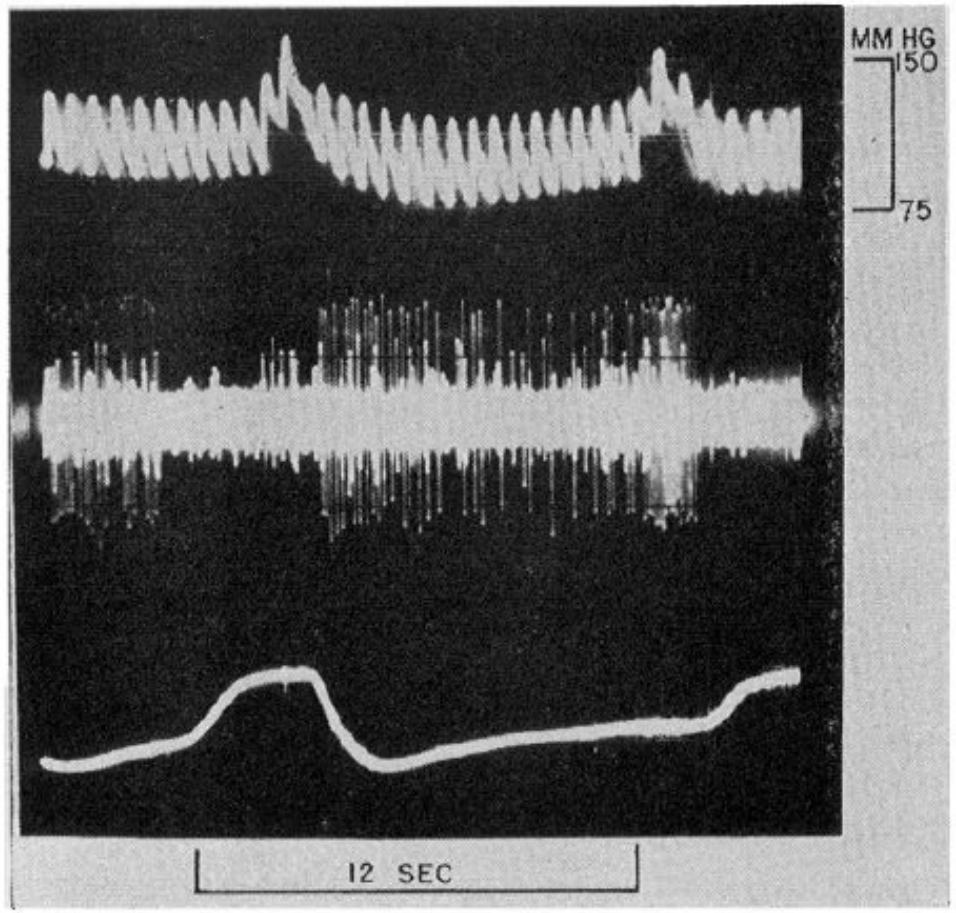
A vagal reflex between lungs and heart

Blood pressure

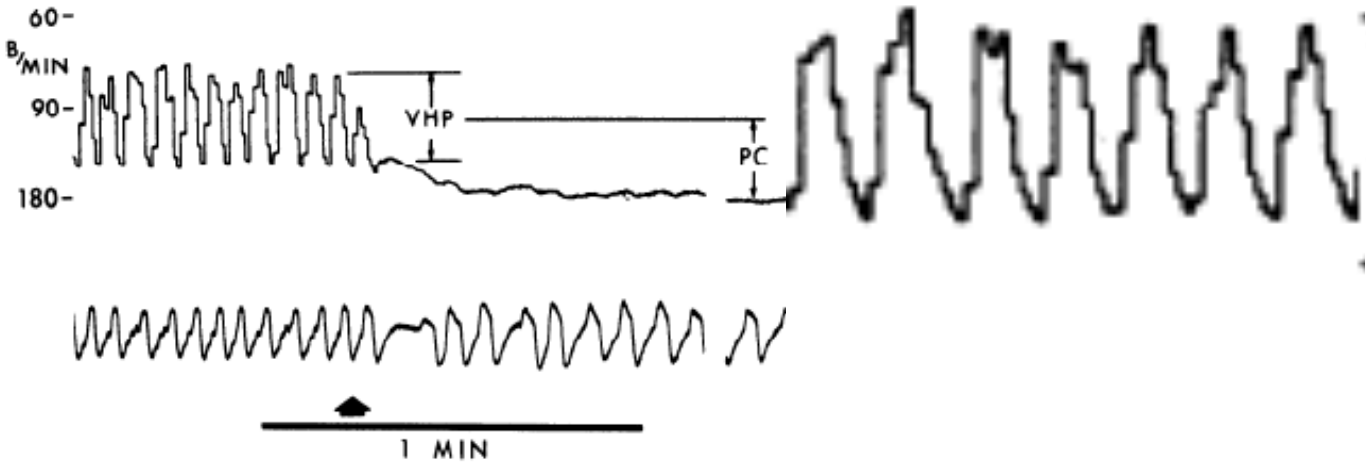
Vagus nerve

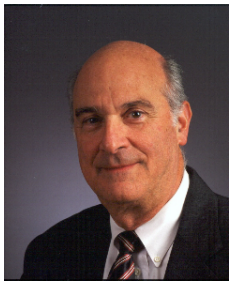
Inspiration ↑

Katona 1970



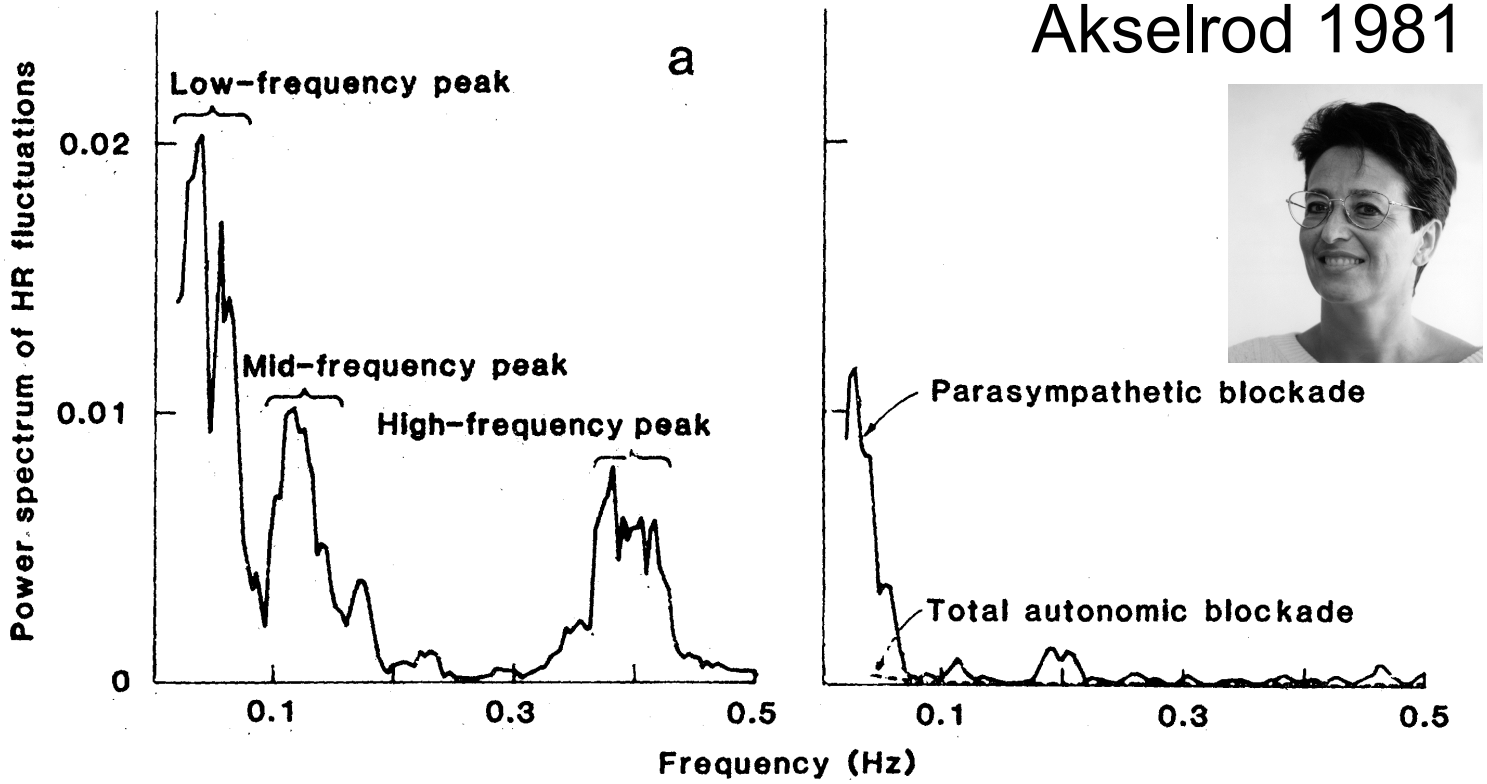
This explains respiratory sinus arrhythmia



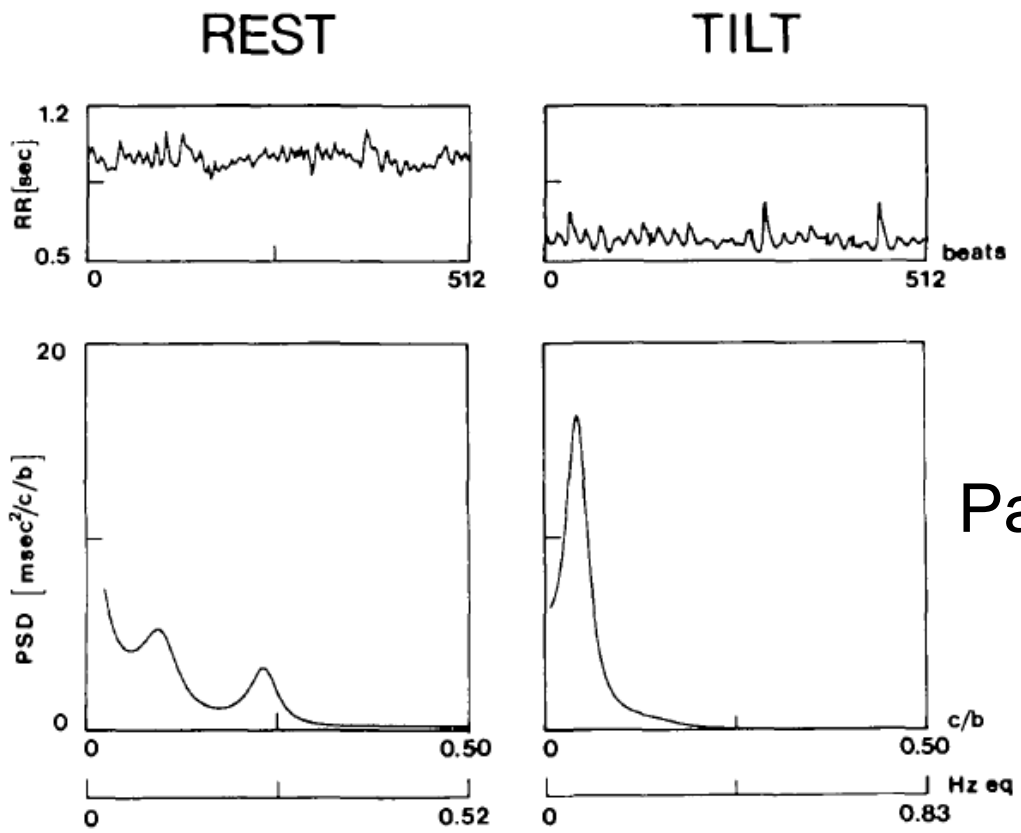


Katona 1970, 1975

Frequency domain analysis of heart rate time series

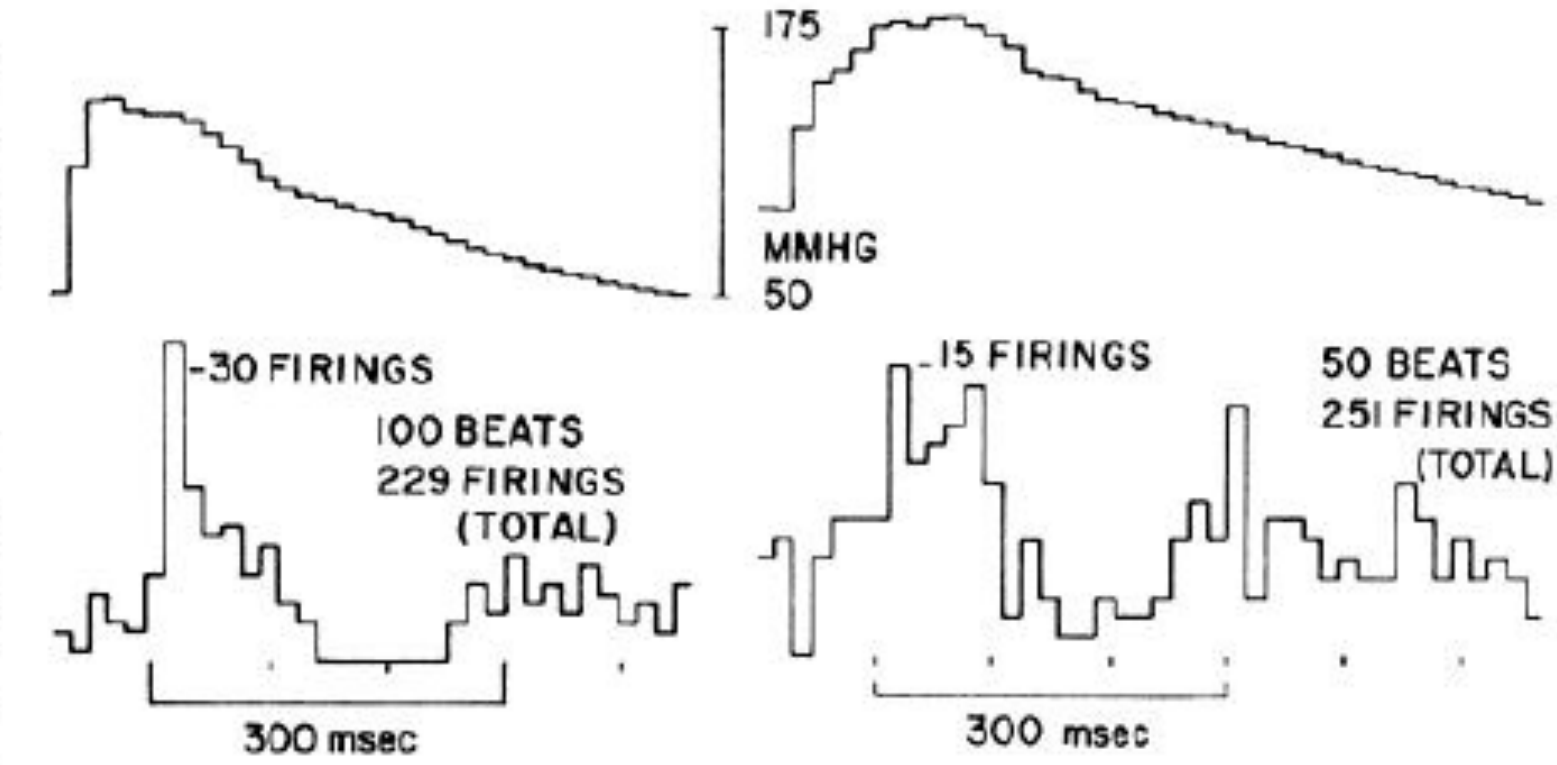


Frequency domain analysis of heart rate time series

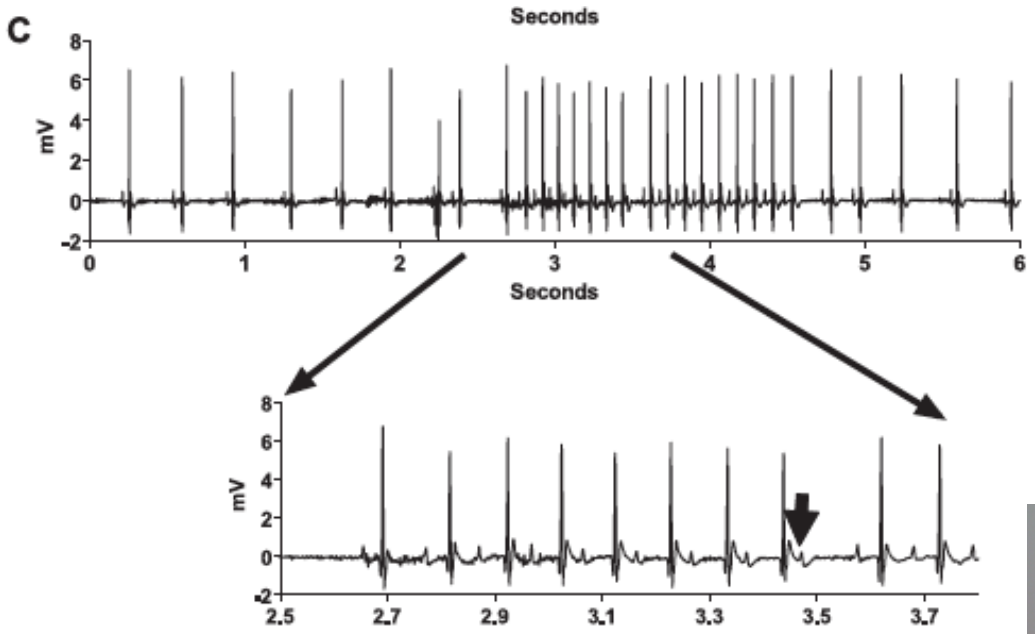


Pagani 1986

A vagal reflex between arterial pulse and heart



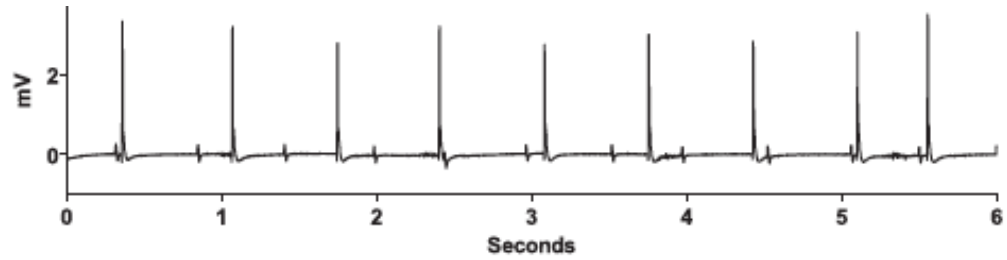
A vagal reflex between immune system and heart



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

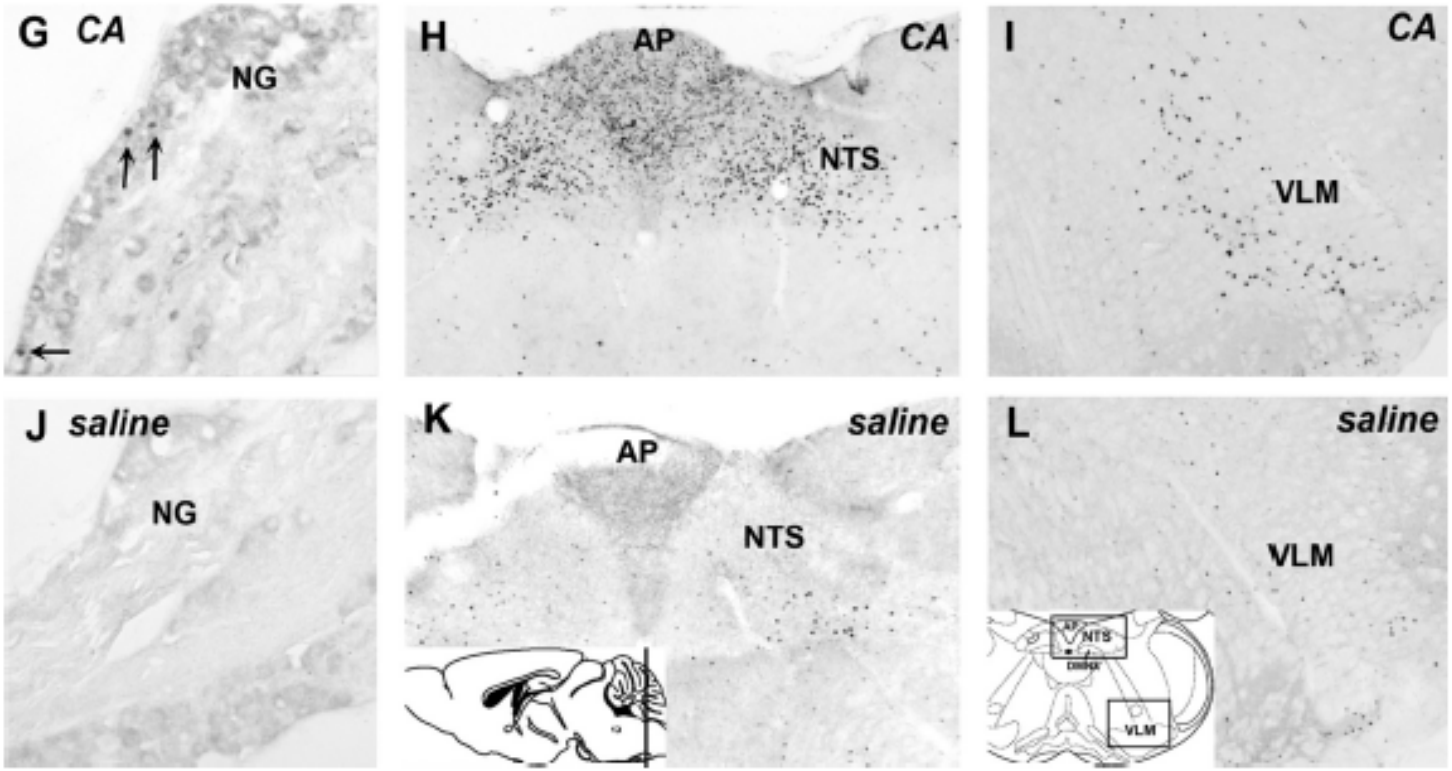
Fairchild 2009

A vagal reflex between immune system and heart

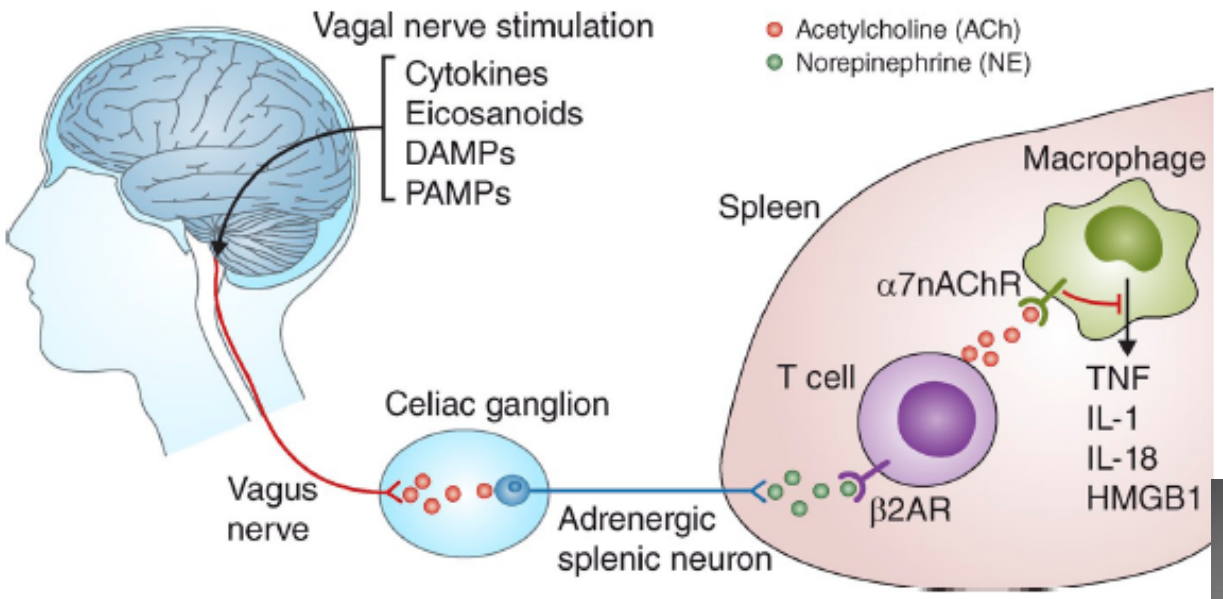


Complete heart block

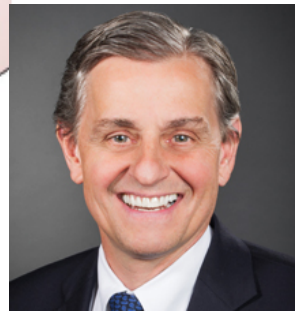
A vagal reflex between immune system and heart



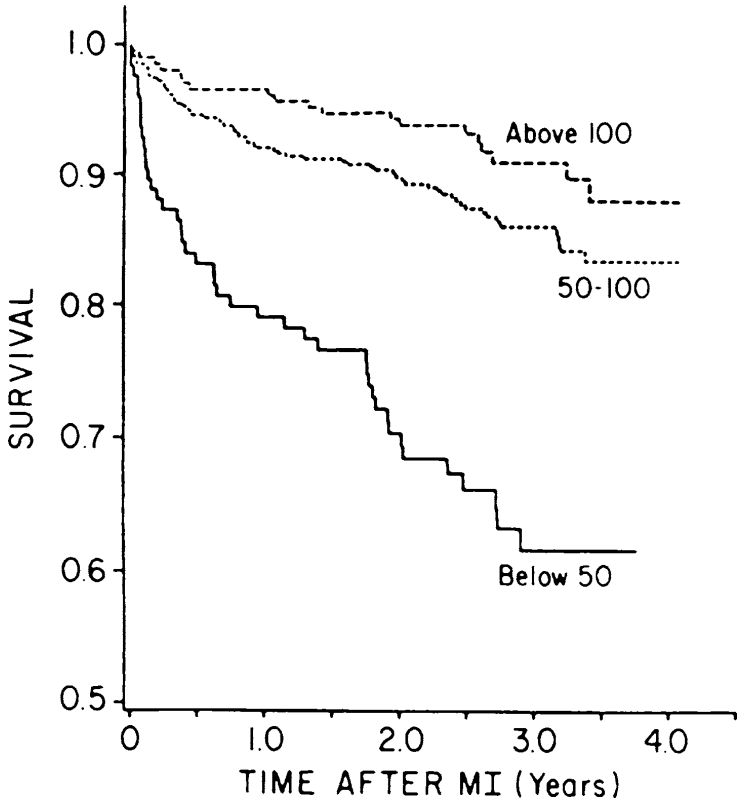
The cholinergic anti-inflammatory pathway



Tracey 2000

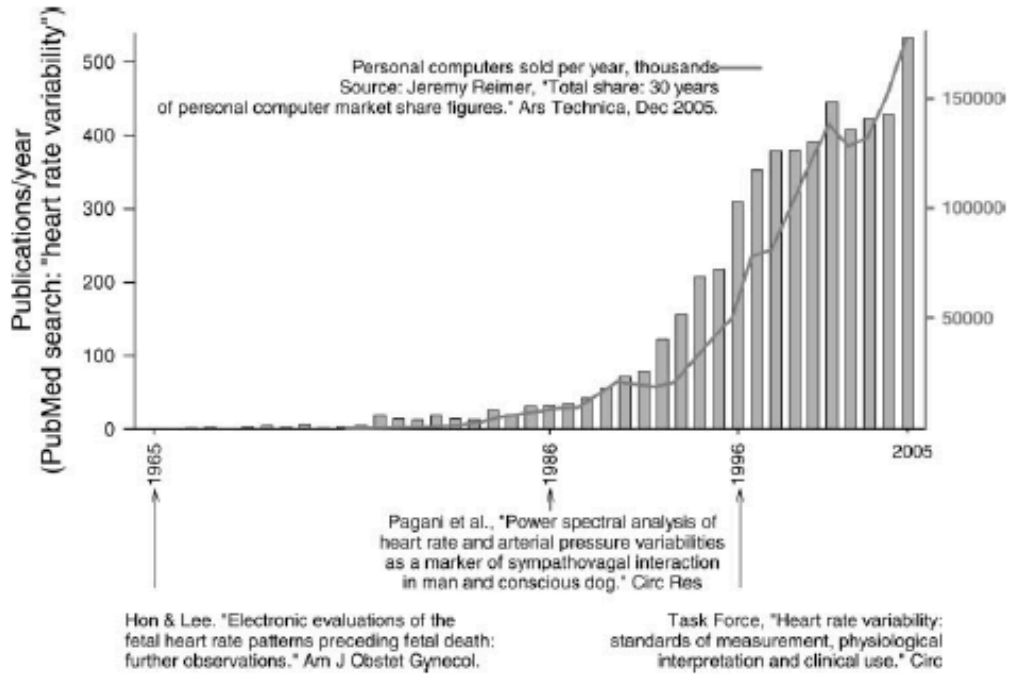


A clinical use for HRV measures



Kleiger 1987

Boom cycle in HRV papers



By 2005, an average of 10 scientific articles on heart rate variability were published each week and cardiovascular variabilities had achieved amazingly wide application as indexes of autonomic outflow from dinosaurs (1) to dinghy sailors (26), from sex (5) to religion (4).

Sympathovagal balance: a critical appraisal

"This review calls attention to major problems with the construct of sympathovagal balance."

Eckberg 1997

Correspondence followed.

A letter is inadequate to rebut fully Eckberg's destructive and selectively referenced polemic against sympathovagal balance,[1] which ignored many prior contributions constructively addressing the same points now raised.

The article by D.L. Eckberg[1] will surely promote a florid discussion. Its structure is based on a number of arguments about which our disagreement is substantial.

Finally, I find it difficult to understand why Dr Eckberg (for whom I have a high regard) proposes that the study by Pagani et al was not conducted properly. Such an approach to criticism will not help us obtain a consensus between research groups that is badly needed.

I thank my friends for their thoughtful responses to my article.

I disagree that it is wrong to criticize science; debate of scientific issues is integral to the process of doing science. Scientific debate has intrinsic merit, independent of outcome. Authors who advance new ideas deserve great credit; the ideas themselves deserve close scrutiny.

J Appl Physiol 101: 676–682, 2006;
doi:10.1152/japplphysiol.00446.2006.

Point:Counterpoint: Cardiovascular variability is/is not an index of autonomic control of circulation

Despite the limitations mentioned above, cardiovascular variabilities are thought to be valid indices of autonomic outflows by many, because they

- are simple and cheap methods (Piepoli) that represent the only non-invasive window into autonomic control (Evans)
- provide some physiological interpretation (Cerutti), based on significant although not perfect correlations (Bernardi)
- have possible clinical application (Cerutti), and provide valuable prognostic information (Piepoli, Laude, Evans, Julien)

Non-invasiveness, price and availability are advantageous, yet have no bearing on validity.

Taylor and Studinger 2006

Another point of view: Godin and Buchman 1996

We suggest … that recovery of individual organ function is necessary but, by itself, may be insufficient to restore physiologic mechanisms essential to homeostasis in the system of multiple organs.

We believe that (sepsis) changes the functional relationships among organs, and that restoration of these … is necessary to recovery.

In this alternative view, the collected organs function as a complex adaptive system, where the ability to adapt depends on the adequate function of both the complex adaptive system's interconnections and its constituents

We therefore offer a new hypothesis … that progression (of sepsis) erodes necessary interconnections among organs.

(We view) the vital organs (and their cells) as collections of biological oscillators that are coupled to one another and that the stability of the system resides as much in the couplings as in the oscillators themselves.

The story so far

- The heart and lungs and other organs are networked by the autonomic nervous system, in particular the vagus nerve
- Heart rates change as a result of signals from the vagus nerve, which reflect the activity of other organs
- Measurement of HRV, though, is not sufficient.
- Or can it be?

Cardiorespiratory Networking is Altered Early in Subacute Potentially Catastrophic Illness

A proof of principle.

METHOD

- Pick the right problem.

Little babies are dying.

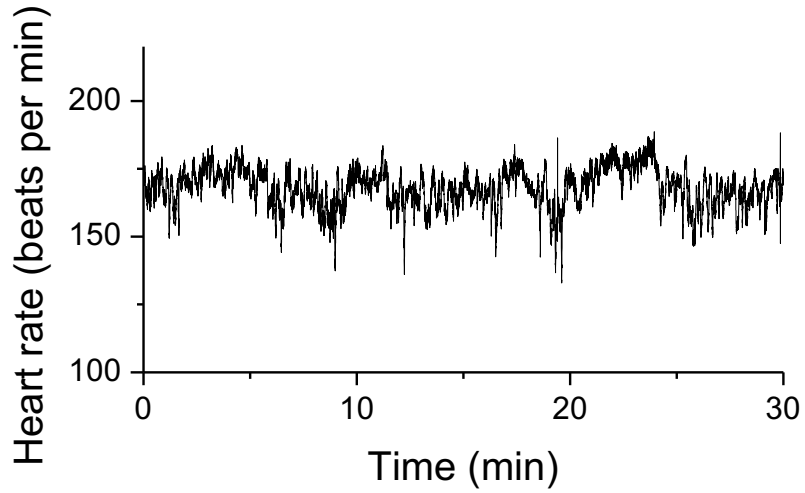
Is this baby septic?

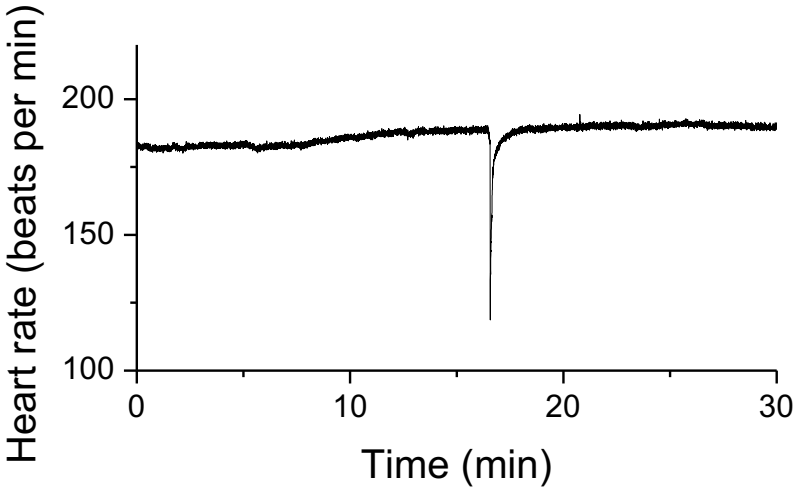
- The diagnosis of neonatal sepsis is difficult
- The outcome of sepsis is potentially catastrophic
- Leading physicians to:
  - obtain lab tests
  - administer antibiotics early and often

METHOD

- Pick the right problem.
- Inspect the data

We observed *reduced variability and transient decelerations* prior to clinical illness and death.





Hours prior to death

>150

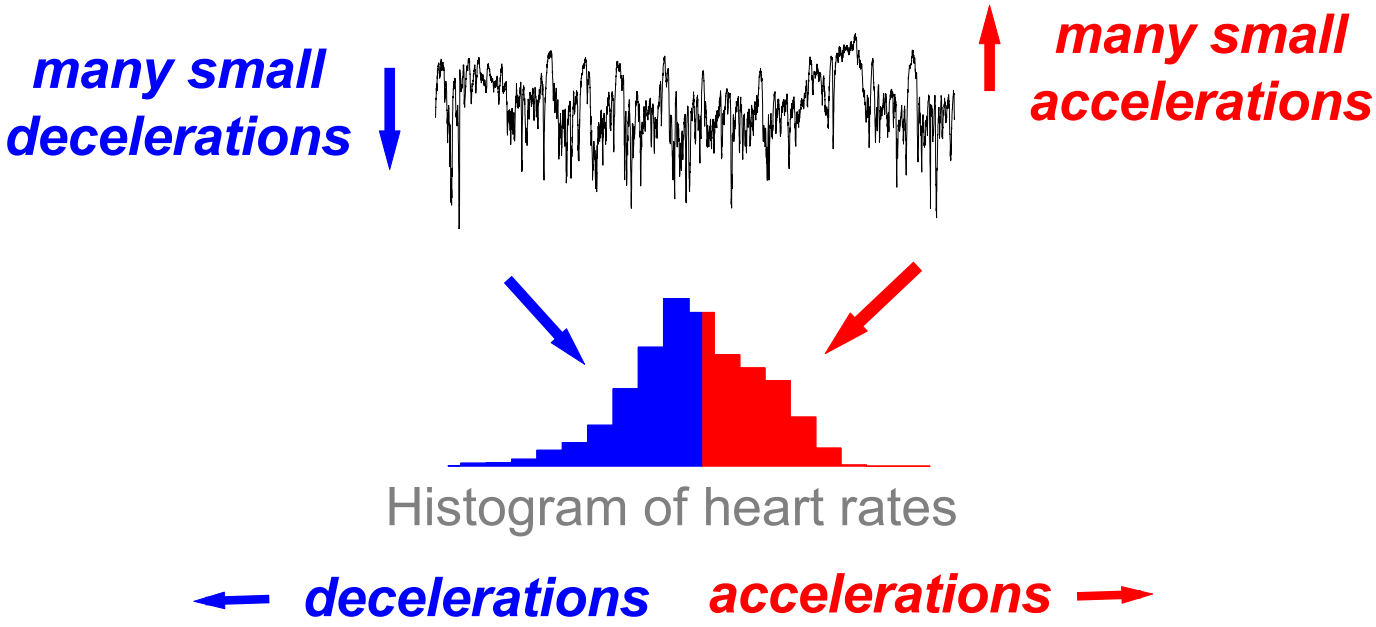
<24

METHOD

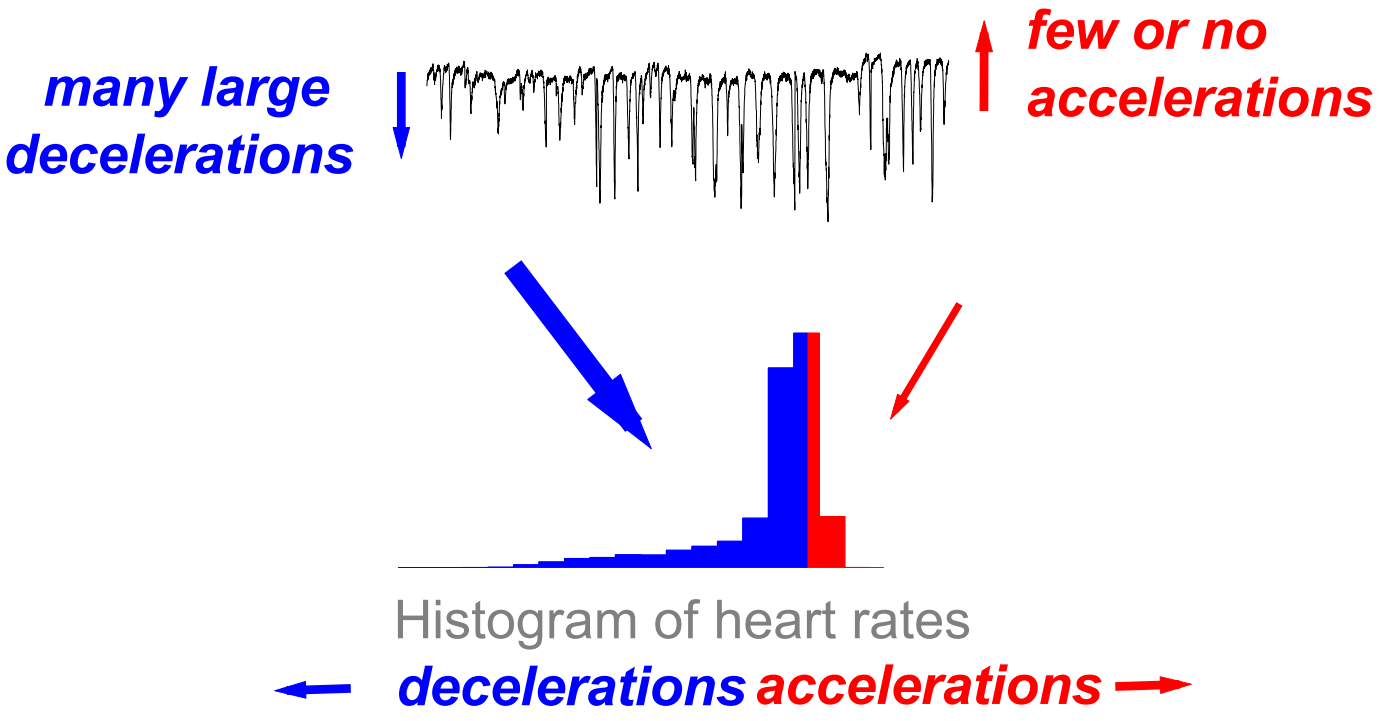
- Pick the right problem.
- Inspect the data.
- Assume 0.

Conventional HRV measures do not detect reduced variability and transient decelerations, so we made some up.

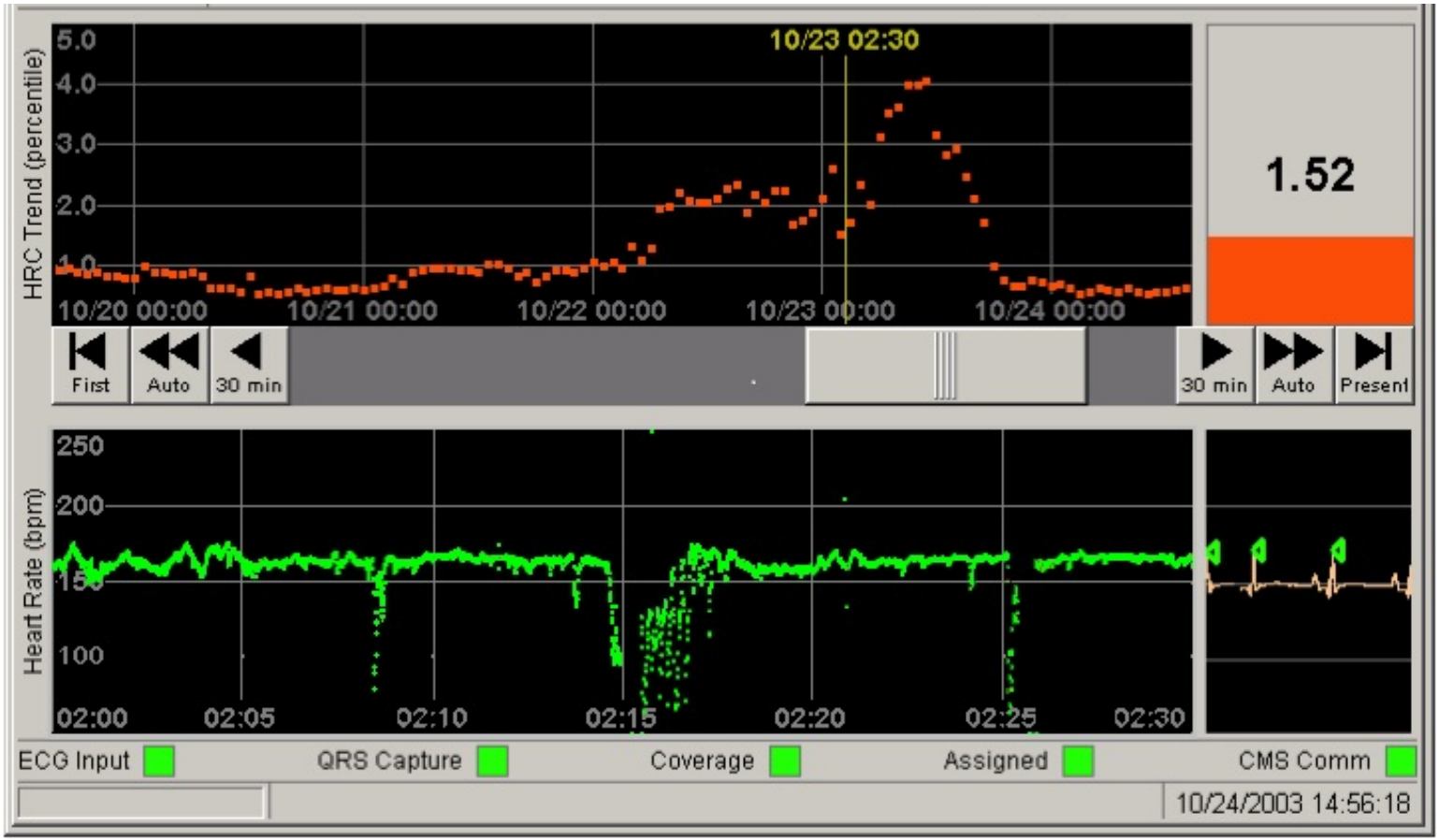
Normal heart rate characteristics



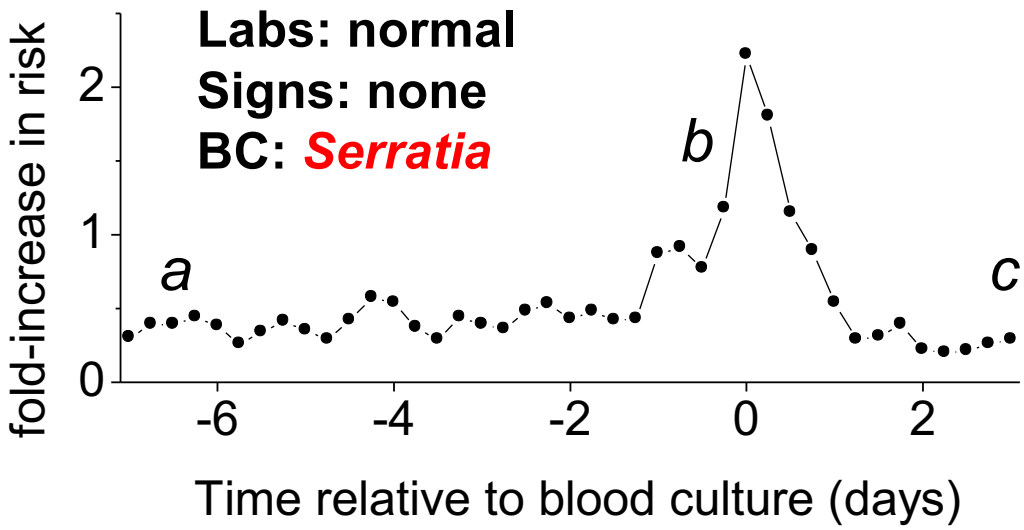
Abnormal heart rate characteristics

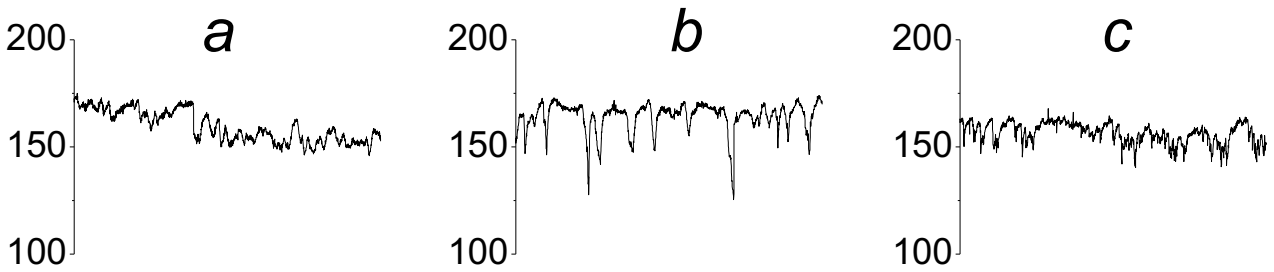


Predictive analytics at the bedside



Very, very early diagnosis of sepsis





METHOD

- Pick the right problem.
- Inspect the data.
- Assume 0.
- Randomize.

1 R01-HD 048562-01
"Impact of neonatal heart rate characteristics"
ClinicalTrials.gov identifier NCT 00307333

Study design

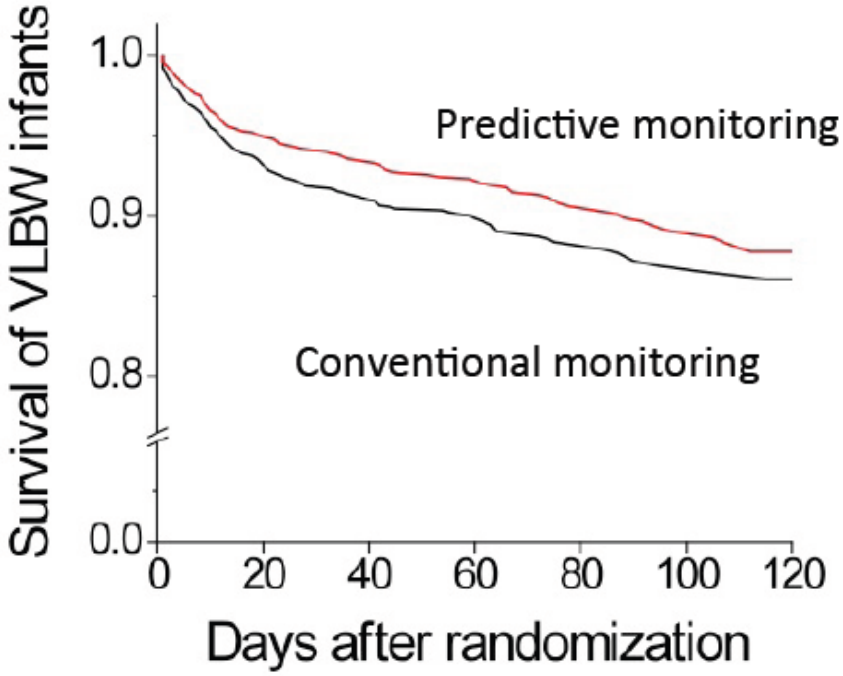
3000 VLBW infants admitted to NICU

randomize

HRC monitor display

no *HRC monitor display*

Predictive monitoring saves lives



One extra survivor per 48 VLBW or 23 ELBW infants monitored

Conclusion

- The anatomical, physiological and molecular components of networks such as the heart and lungs is well understood enough to get started.
- Some potentially catastrophic illnesses alter network physiology prior to clinical signs
- Quantitative analysis of signatures of illness in physiological time series data can improve patient outcomes.
- In my view, this is a job for teams of clinicians and quantitative scientists.