Air Pollutants: Cardiovascular Effects and Mechanisms

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Objectives

1. Common theme from human literature
2. What is reduced HRV?
3. Hypothesis and preliminary data from indoor air pollutants.
4. Proposed studies and what we hope to accomplish with real world outdoor air pollutants

What do we know from human literature?

Proposed mechanisms for arrhythmias, sudden cardiac death, stroke, and heart failure

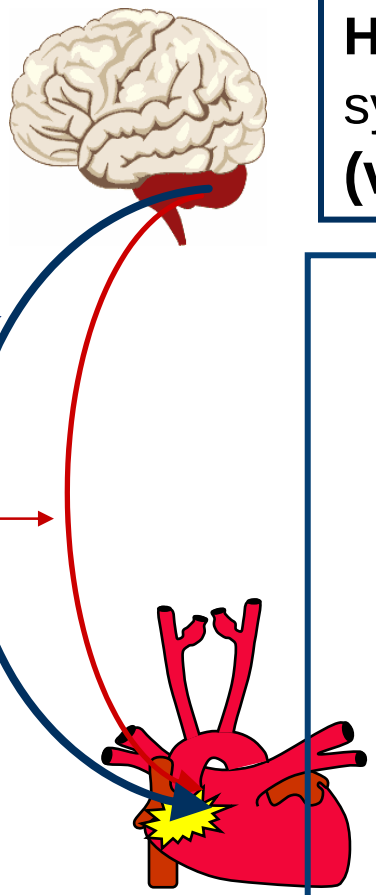
1. Pulmonary/systemic oxidative stress
2. Systemic inflammatory responses
3. Impaired cardiac autonomic function
4. √ Susceptible populations

Pope, NEJM
Sept 9,2004

- *Decreased heart rate variability (HRV)*
- *Increased susceptibility to ventricular arrhythmias and sudden cardiac death*

Regulation of HRV vs HR

HRV: set by dual regulation of sympathetic and **parasympathetic (vagal)** innervation of the SA node



Parasympathetic innervation "cardio-inhibitory"

Sympathetic innervation "cardio-excitatory"

Intrinsic HR
set by SA node pacemaker cells

Brainstem "vagal" neurons:

- *tonic* activity ⇒ low HR
- *dynamic* activity ⇒ rapidly return HR to normal

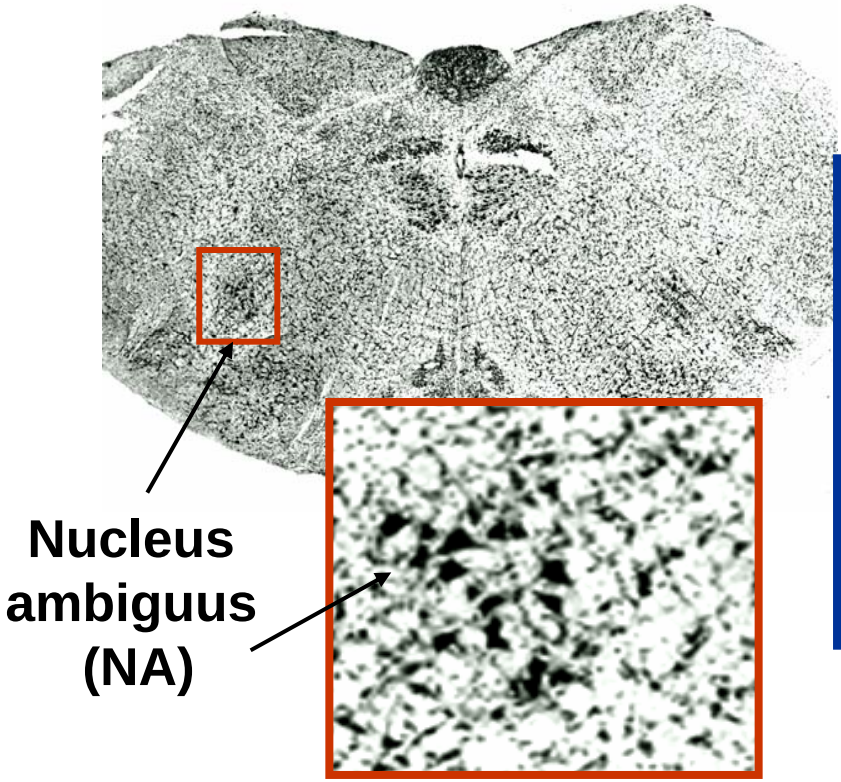
⇩

- loss of vagal input to SA node

⇩

↓HRV

Neurons in discrete brainstem nucleus determines vagal cardiac tone



If the behavior of these NA neurons changes, (↓)

↓

cardiac vagal tone changes (↓)

↓

HRV changes (↓)

Overall Hypotheses

1. Short-term exposure to ambient air pollutants in the form of concentrated ambient particles (CAPs) $PM_{2.5}$ reduces HRV.

2. One underlying mechanism is *neuroplasticity* in ***brainstem*** neurons that regulate HRV.

3. Seasonal composition of the CAPs will affect the degree of reduced HRV and neuroplasticity.

4. The decreased HRV and neuroplasticity will be exaggerated in the elderly.

First Hypothesis

Short-term exposure to ambient air pollutants reduces HRV.

Approach

1. Establish a mouse model that:
   - displays phenotype.
   - allows us to determine mechanisms.

2. Develop protocols for short-term exposure to *real world* pollutants (CAPs).

Approach

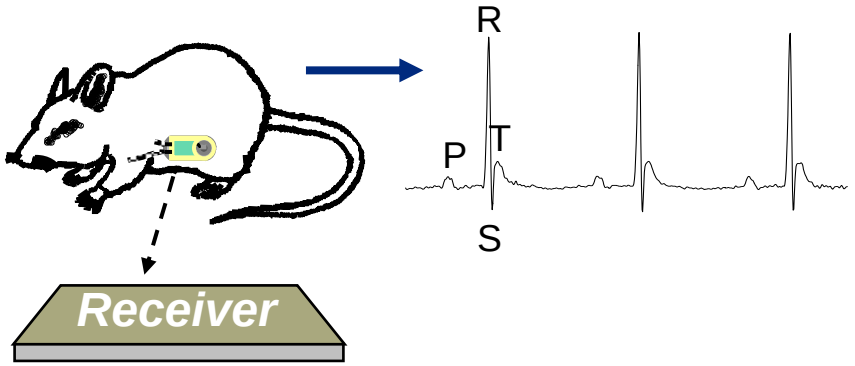
Exposure Protocol
Surrogate for CAPS

Sidestream Smoke (1° source of indoor air $PM_{2.5}$) or filtered air (FA)

Expose 6 hrs/day for 3 days

Total suspended particulates 30 mcg/m^3

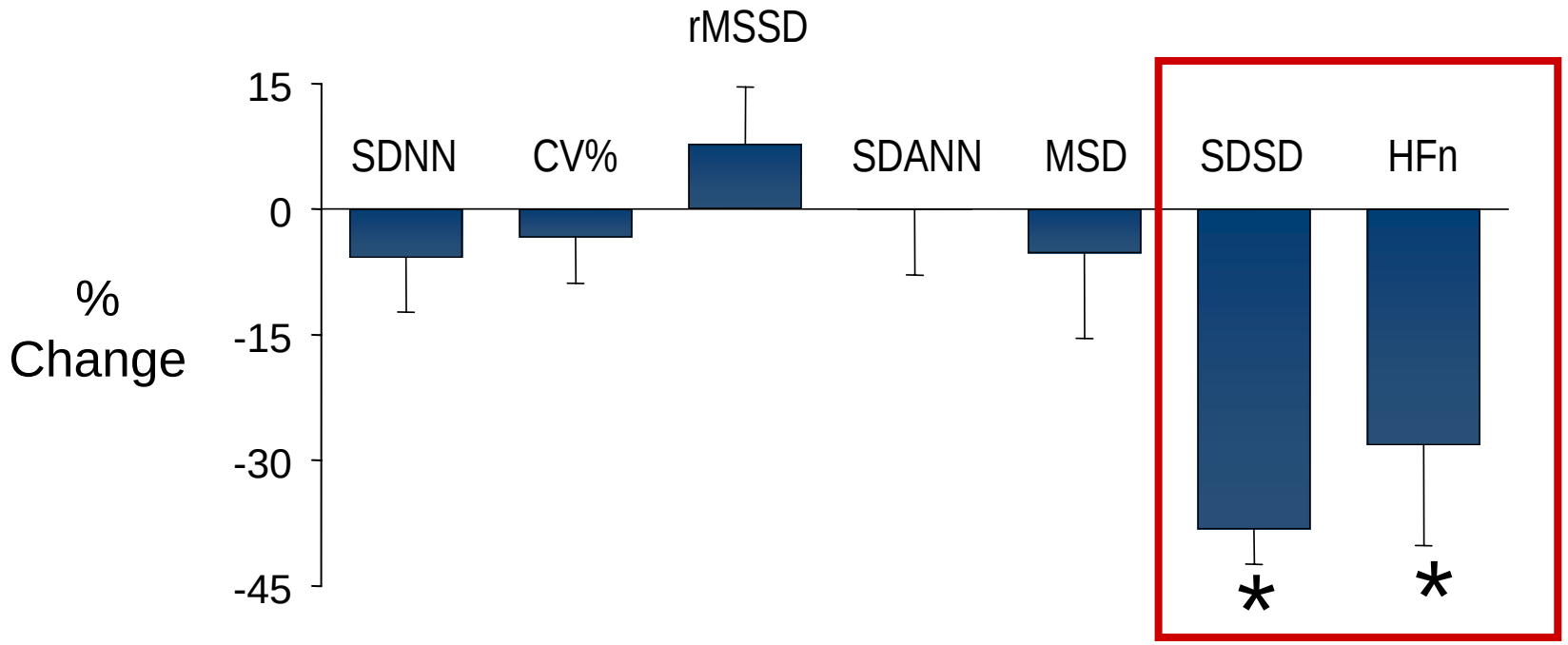
Telemetry



Analyze HRV in time and frequency domains:

- 24 hr HRV
- Day-night difference
- Acute stresses: Exercise stress test

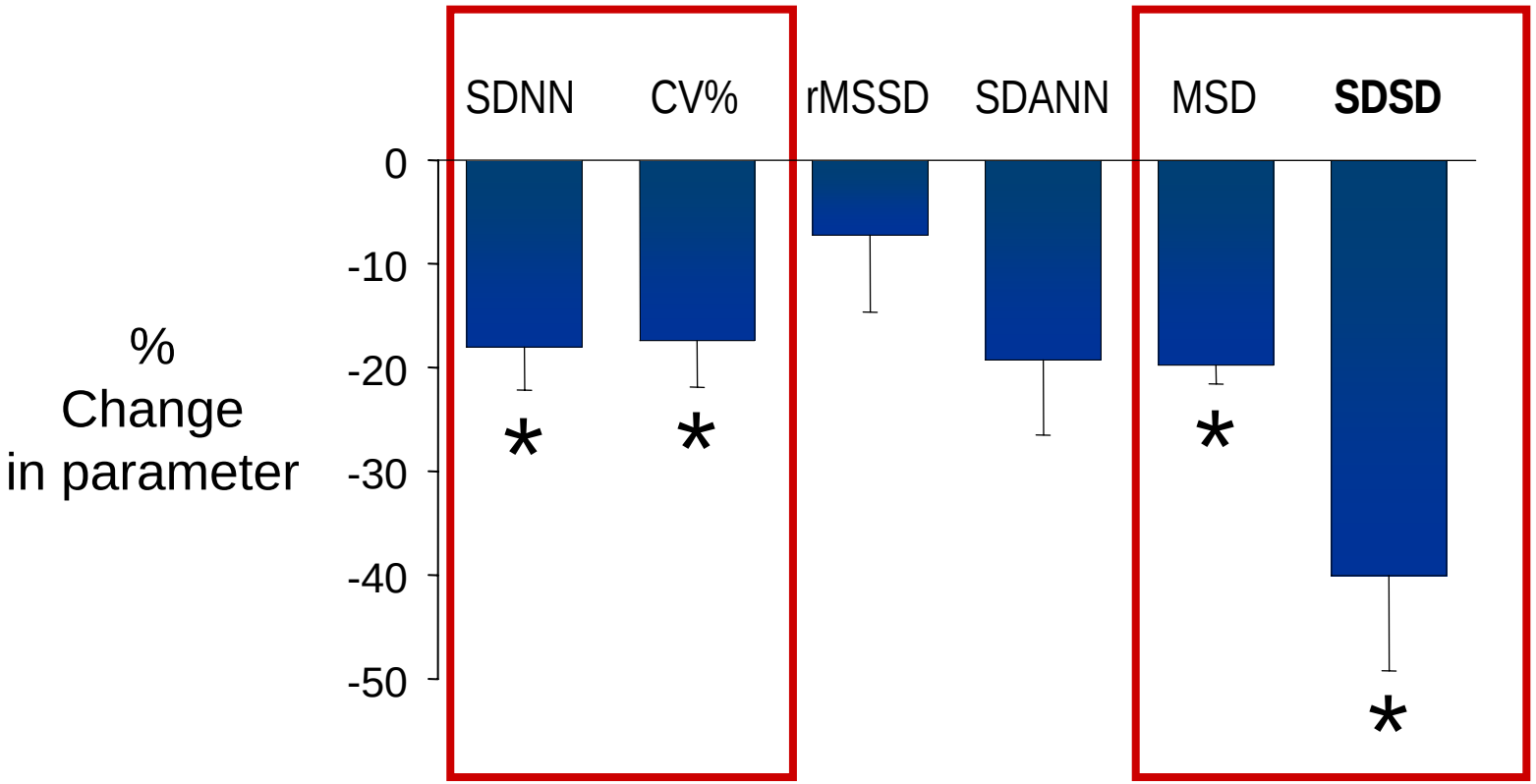
Preliminary Results:
Sidestream smoke decreased 24 hr HRV



SDSD: SD of SD of normal RR intervals in all 5min segments (measure of overall HRV)

HFn: index of vagal activity

Preliminary Results: Sidestream smoke decreased day-night difference



What did we learn from our preliminary studies?

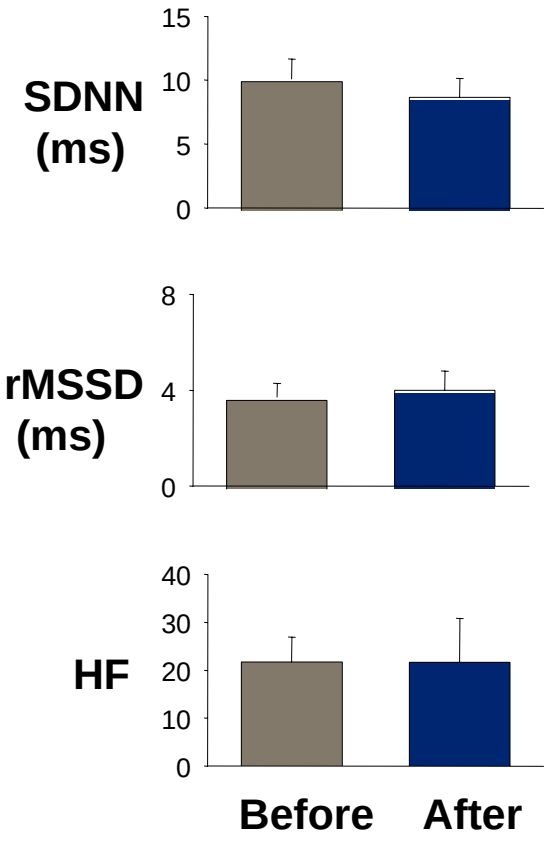
- The mouse displays the phenotype.
- We can explore the mechanisms.

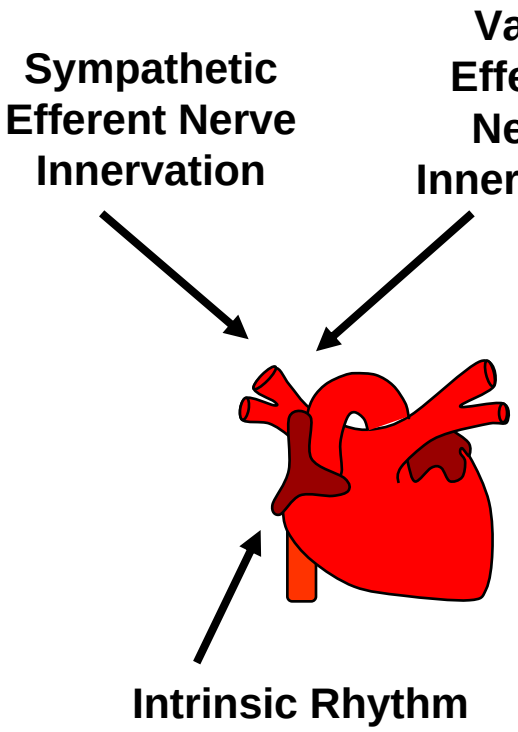
First Question:

Is autonomic regulation of HRV in mouse like human

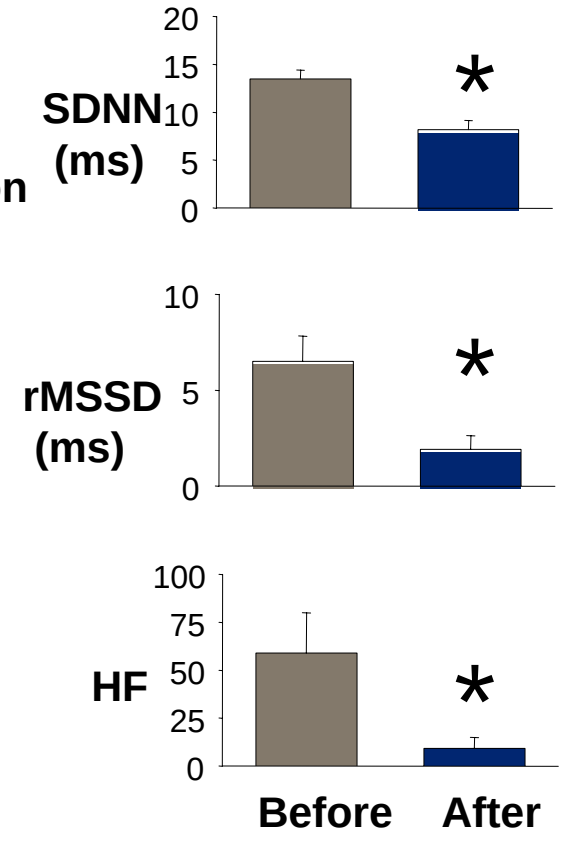
Preliminary Results:
Mouse HRV is regulated like human HRV

Sympathetic blockade





Vagal blockade



Second Hypothesis

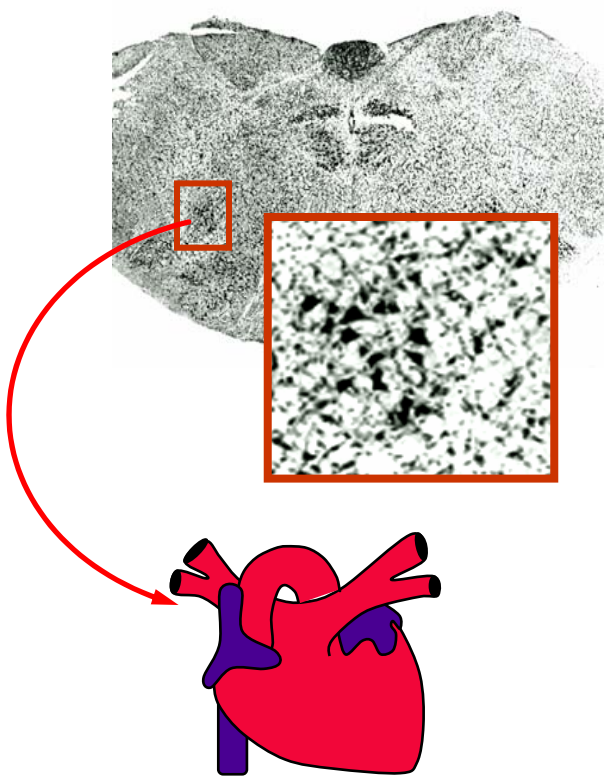
1. Short-term exposure to ambient air pollutants reduces HRV.

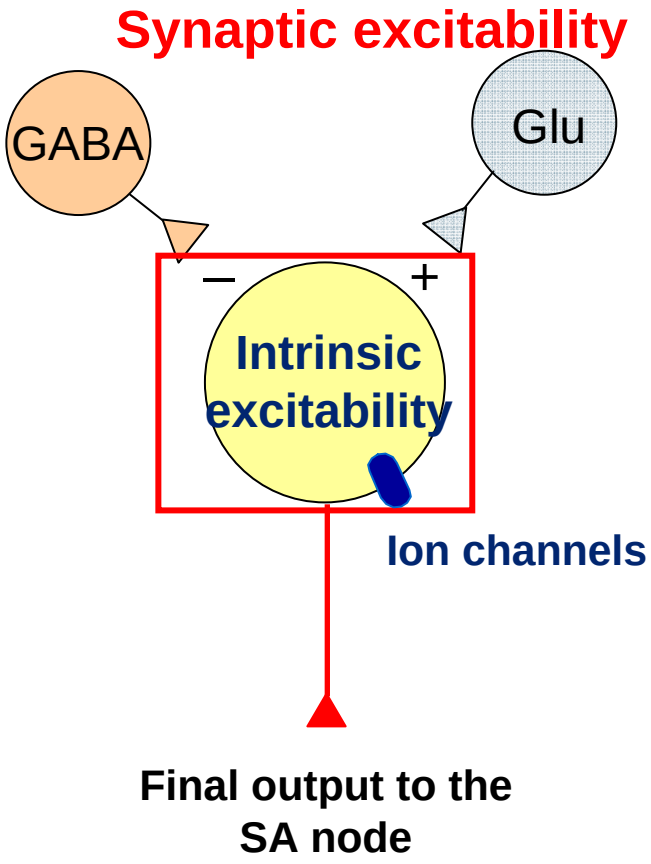
2. One underlying mechanism is *neuroplasticity* in brainstem neurons (nucleus ambiguus, NA) that regulate HRV.

3. Seasonal composition of the ambient air pollutants will affect the degree of reduced HRV and neuroplasticity.

4. The decreased HRV and neuroplasticity will be exaggerated in the elderly.

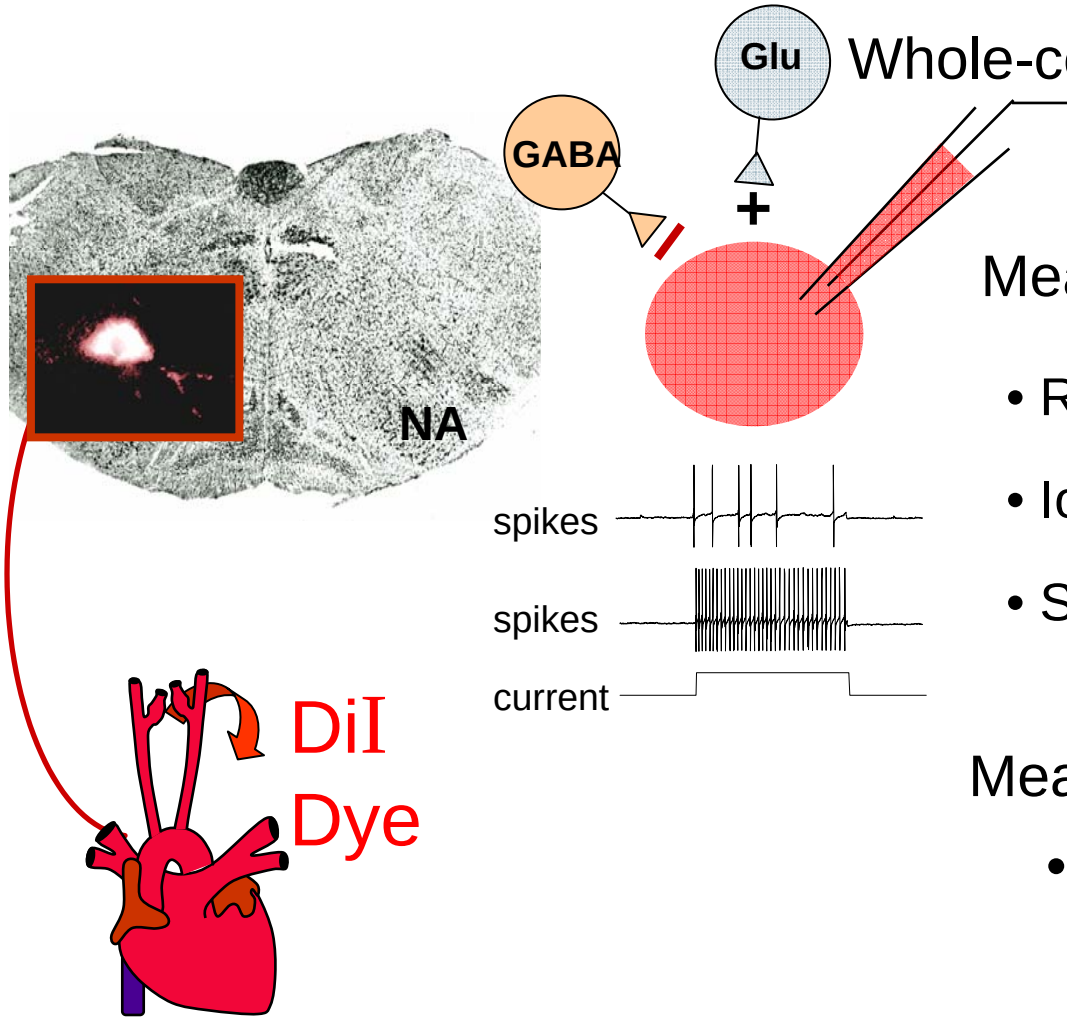
What do we know about NA cardiac vagal neurons ?





So.. changes in synaptic or intrinsic excitability will change neuron behavior and hence vagal control of HRV

Identify the neurons: Test the hypothesis



Whole-cell patch clamping

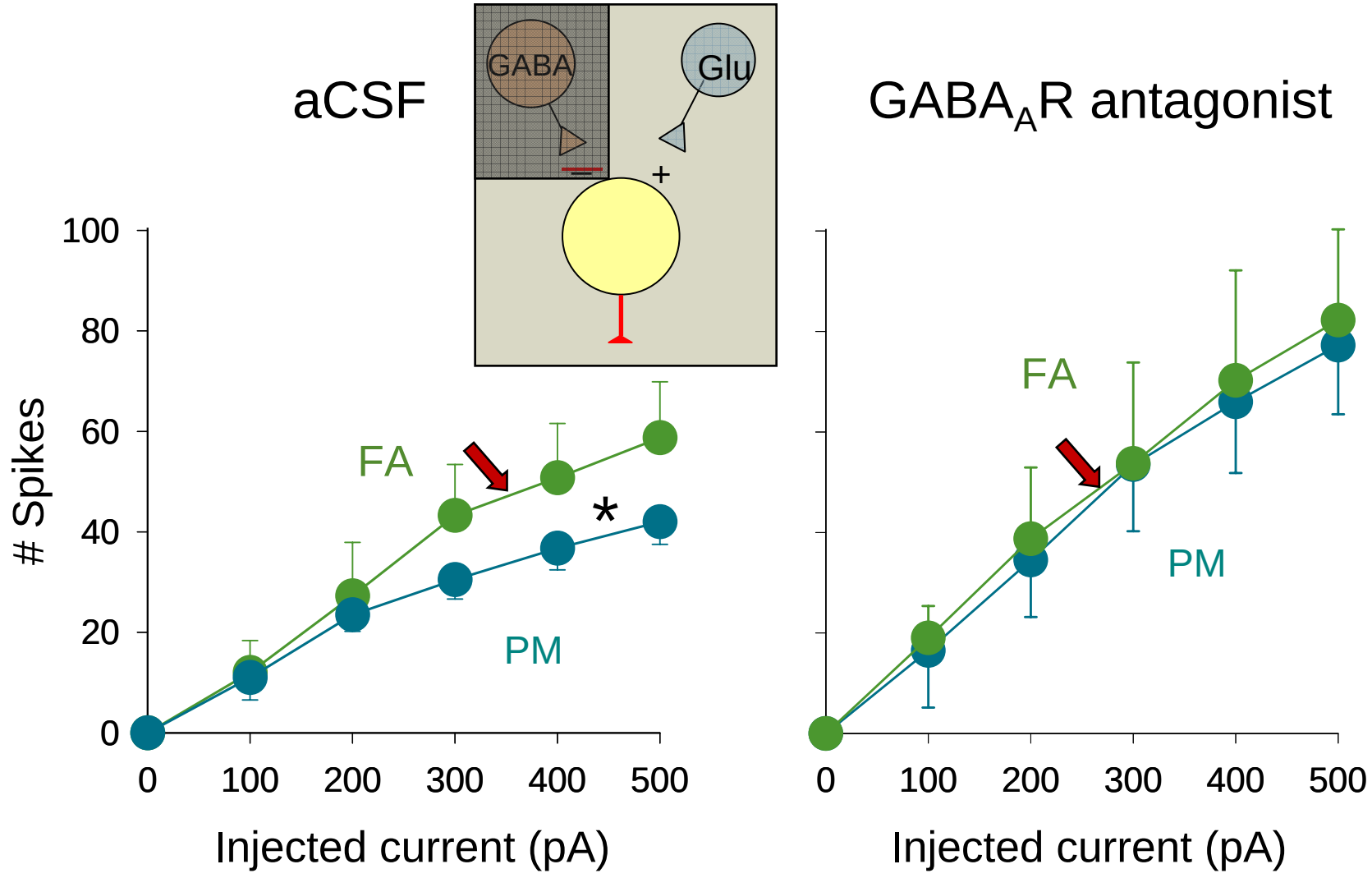
Measure intrinsic properties

- Resting membrane potential
- Ion channel function
- Spiking behavior

Measure synaptic properties

- Spiking behavior with blockade of GLU and GABA synaptic inputs

Results: Indoor PM decreased spiking *by enhanced $GABA_A$-R mechanism*



Summary:
What we learned from preliminary studies

- Indoor PM exposure results in neuroplasticity - decreases the spiking behavior of the cardiac vagal neurons
- The decreased spiking is mediated by ***enhanced*** GABA mechanism

Proposed Studies with CAPs

CAPs exposures

Versatile Aerosol Concentration Enrichment Systems to generate ***CAPs in the $PM_{2.5}$*** fraction (which also includes their UF component).

Winter and summer exposures
when particle size and composition are different in the Central California Valley.

Susceptible (elderly) population:
presenescent mice

Characteristics of $PM_{2.5}$ in the Davis-Sacramento, CA Area

Source-Component	**Summer (% Contribution to total $PM_{2.5}$)**	**Winter (% Contribution to total $PM_{2.5}$)**
Motor Vehicle*	43	22
Wood Smoke*	1	21
Nitrate, Sulfate, Dust, Other	8, 21, 16, 11	37, 5, 1,14

Expansion: HRV measures

Time domain measures – overall HRV

RRmean (ms)
SDNN (ms)
CV%
r-MSSD
SDANN (ms)
MSD (ms)

Time domain measures – range of vagal influence

Day-Night Difference in HRV between day and night
SDSD (ms)

Frequency domain measures

TP (ms2)
LF (ms2)
HF (ms2) (vagal)
LFn (nu)
HFn (nu) (vagal)
LF/HF Ratio of LF to HF

Expansion:
Overall and acute-stress related HRV

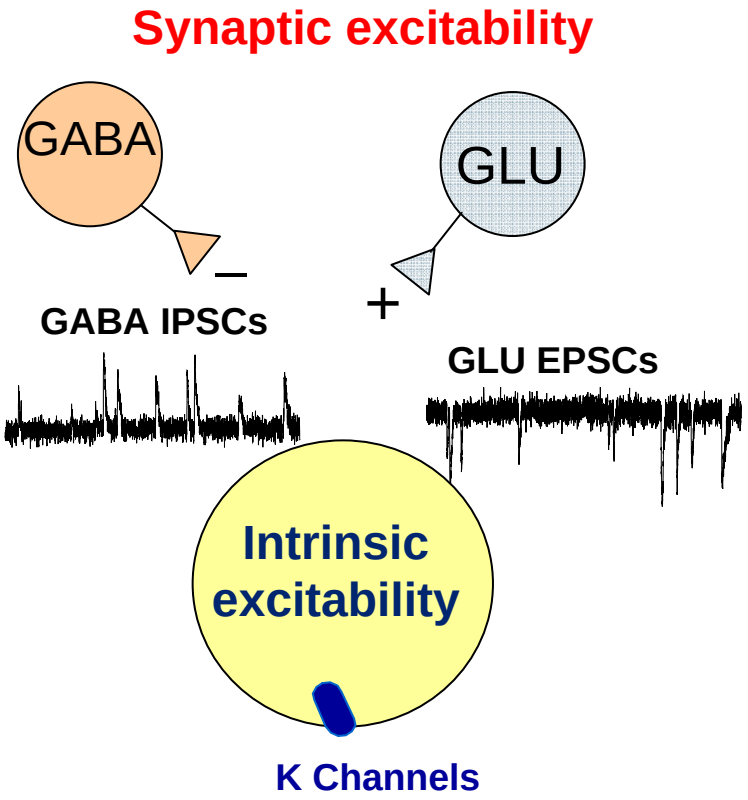
24 hour HRV

Day night differences

HR recovery from acute stresses:

Exercise stress
Restraint stress
Susceptibility to arrhythmias

Expansion of protocols: *Intrinsic and synaptic excitability*



Decreased intrinsic excitability

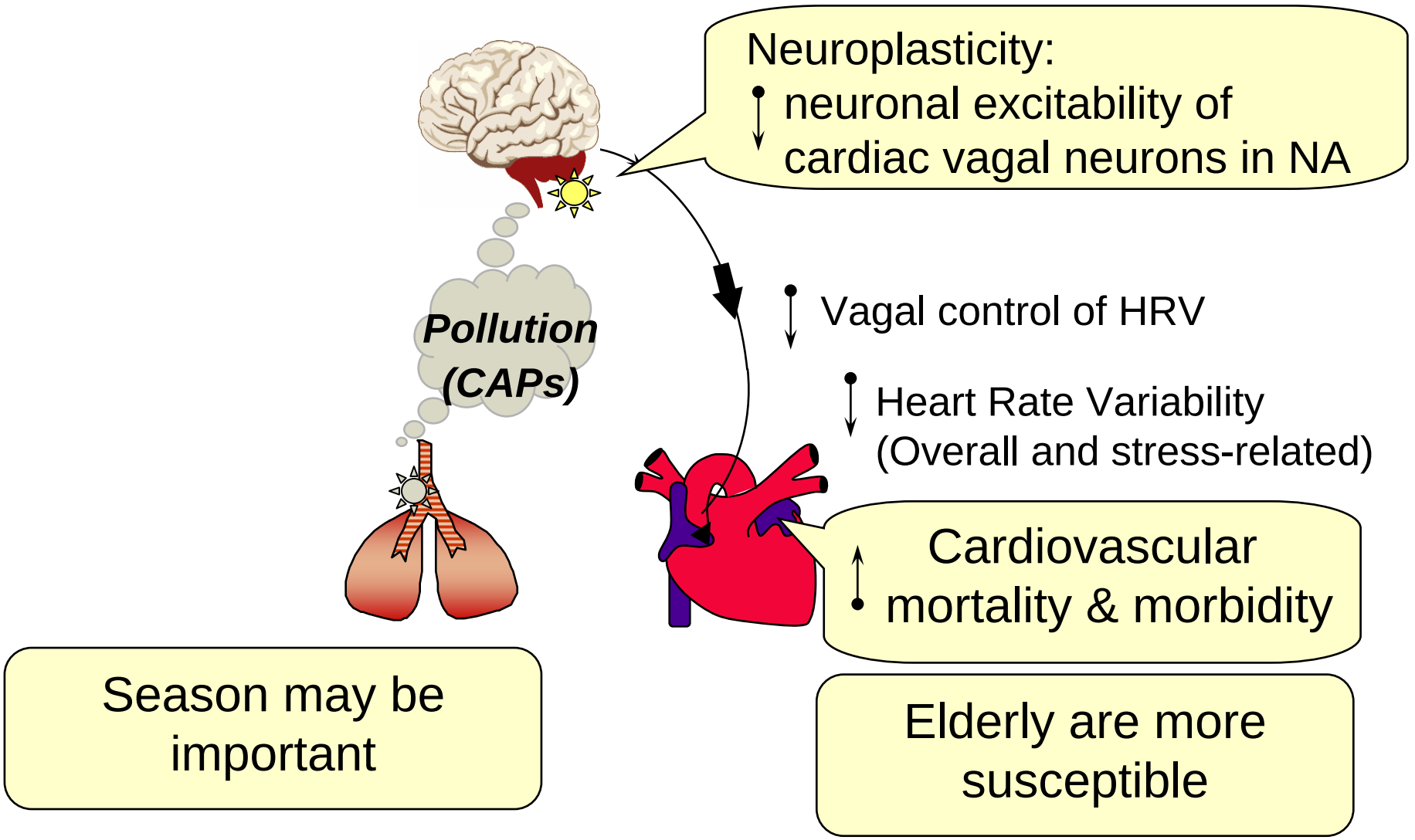
Are there specific changes in K channel function:
(conductances and kinetics)

Decreased synaptic excitability:

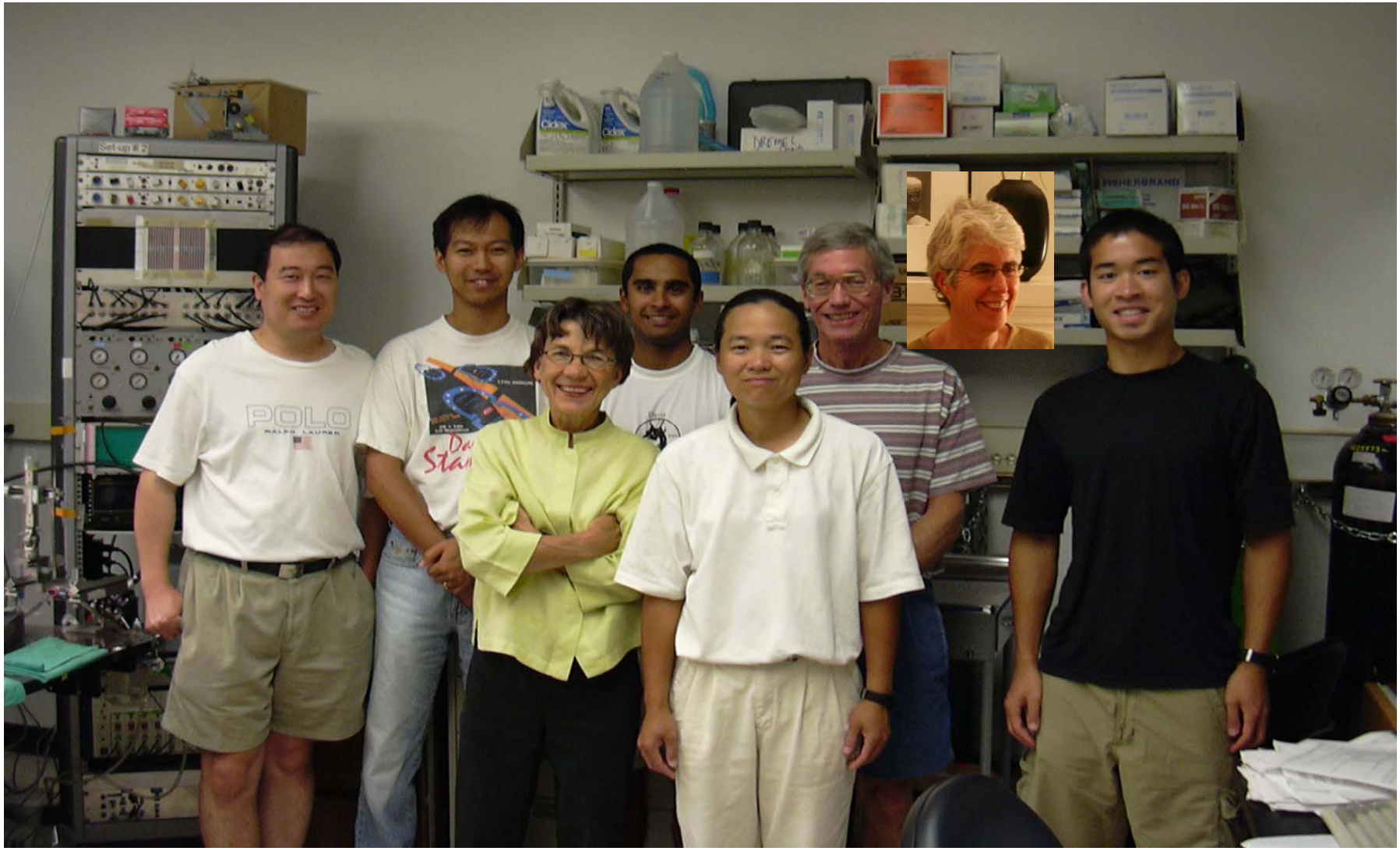
upregulated inhibitory GABA mechanisms (GABA IPSCs)

downregulated excitatory glutamatergic (GLU) mechanisms (GLU EPSCs)

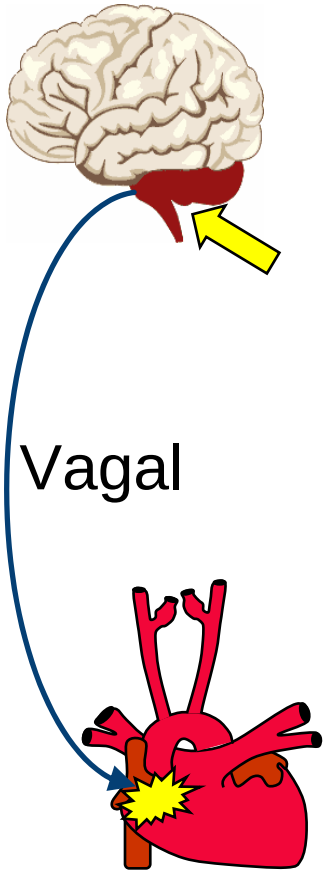
What gaps do we hope to fill?

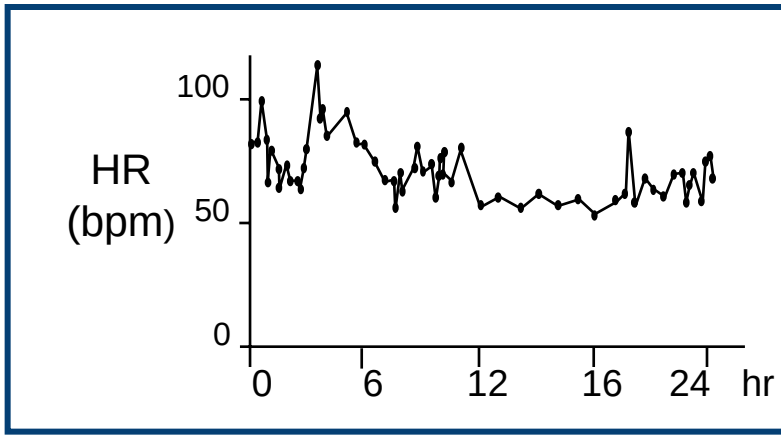


The people who made this possible…

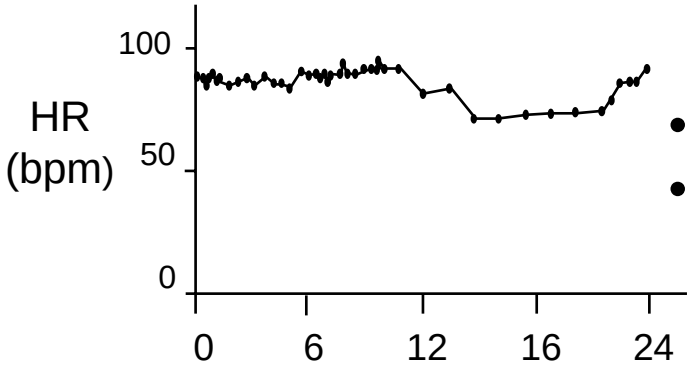


Loss of vagal input to the SA node





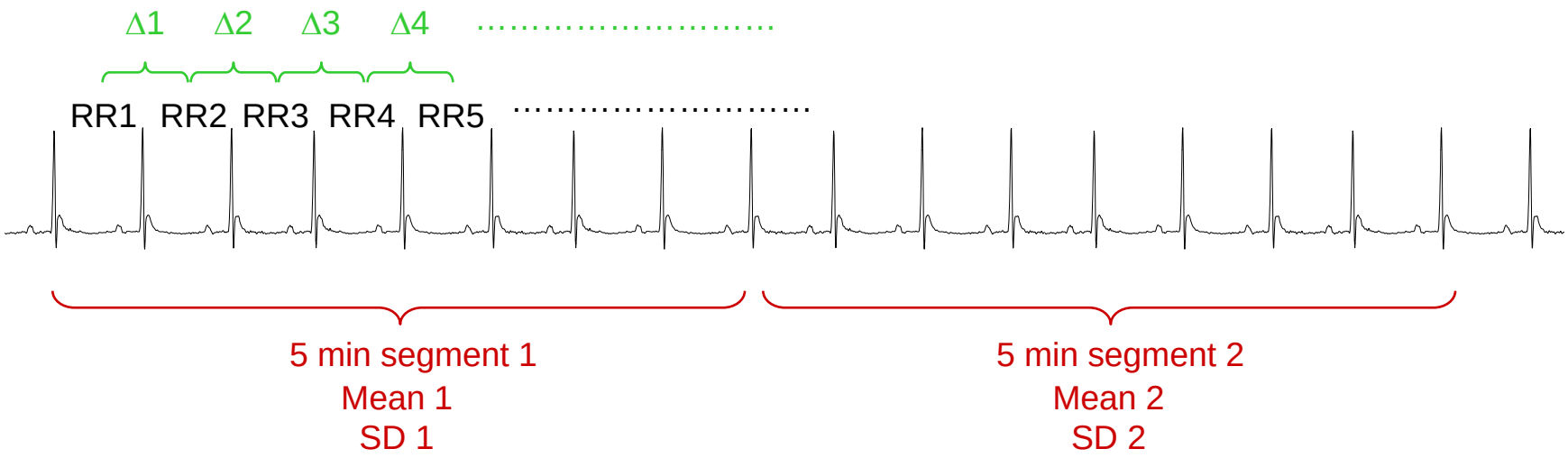
Normal HRV



↓HRV

- **vagal impairment**
- **normal sympathetic**

How do we quantitate HRV in the time domain?



SDNN: Standard deviation (SD) of all normal-to-normal RR intervals (NN)
CV%: $100 \times SDNN/Rr_{mean}$

rMSSD: SD of differences between adjacent normal RR intervals

SDANN: SD of averages of normal RR intervals in all 5 min segments
MSD: Mean of SD of normal RR intervals in all 5min segments
SDSD: SD of SD of normal RR intervals in all 5min segments

Day-night difference:

In the frequency domain?