# 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?

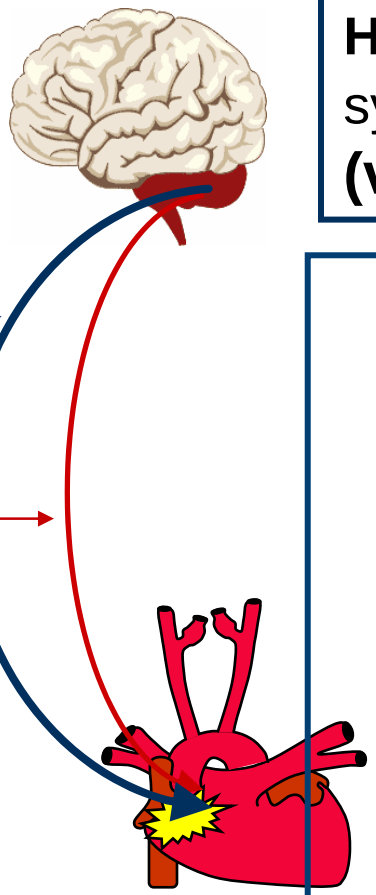
***Proposed mechanisms for arrhythmias, sudden cardiac death, stroke, and heart failure***

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



***Parasympathetic innervation "cardio-inhibitory"***

***Sympathetic innervation "cardio-excitatory"***

**Intrinsic HR** set by SA node pacemaker cells

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

Brainstem "vagal" neurons:

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

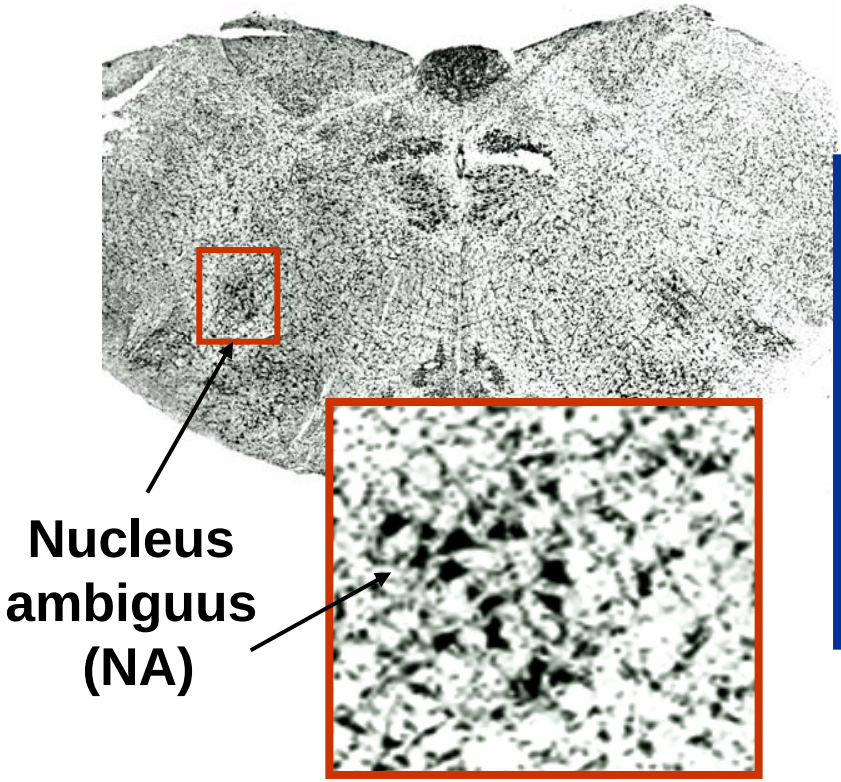
⇩

- 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

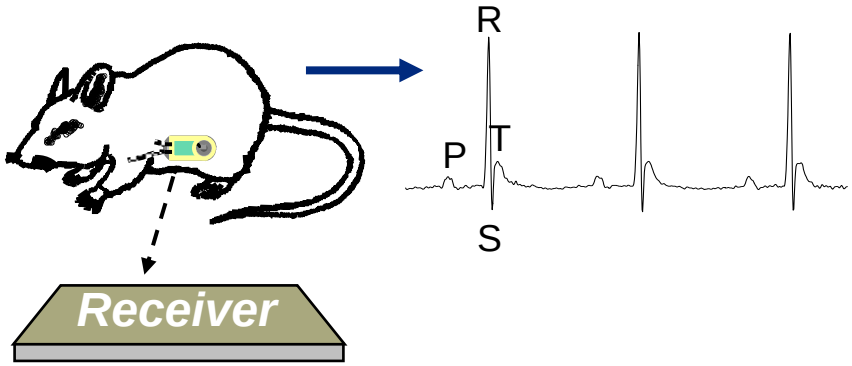
*Exposure Protocol*
*Surrogate for CAPS*

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/$m^3$

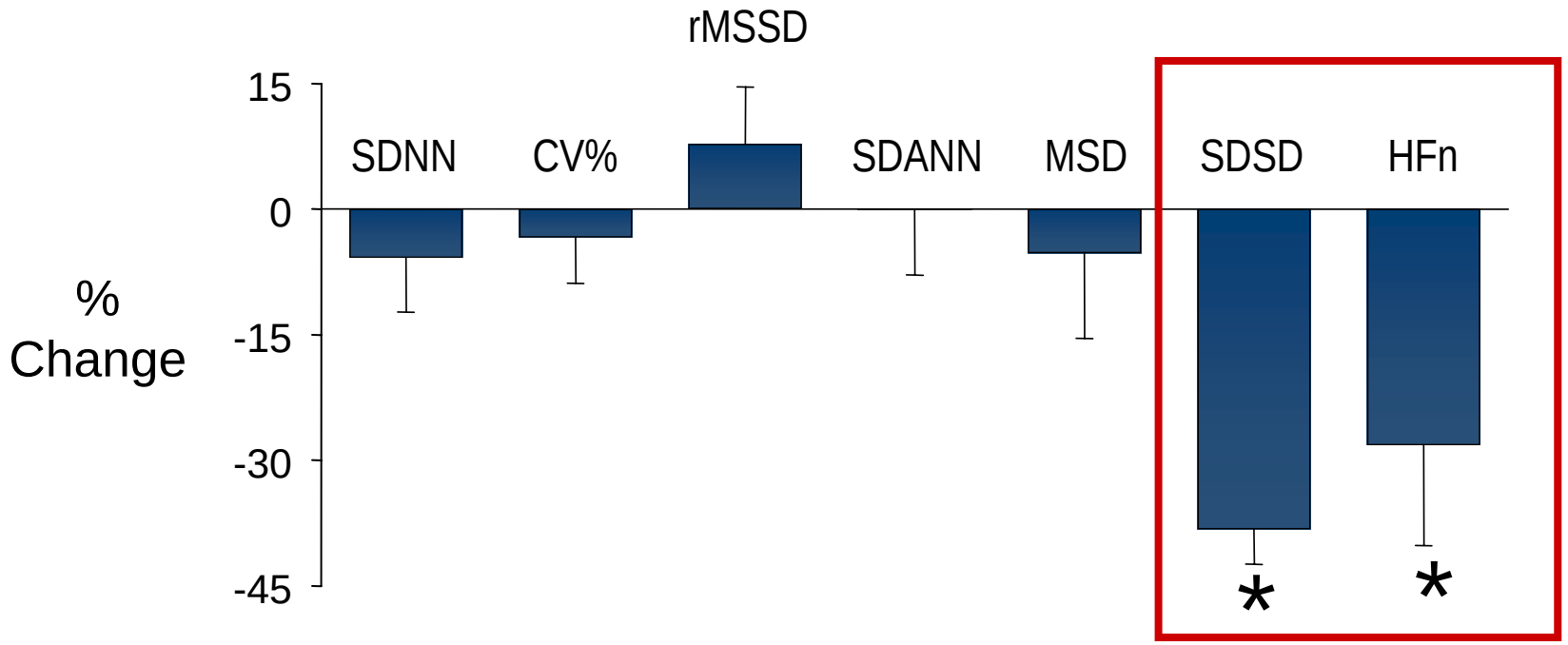
*Telemetry*




Analyze HRV in time and frequency domains:

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

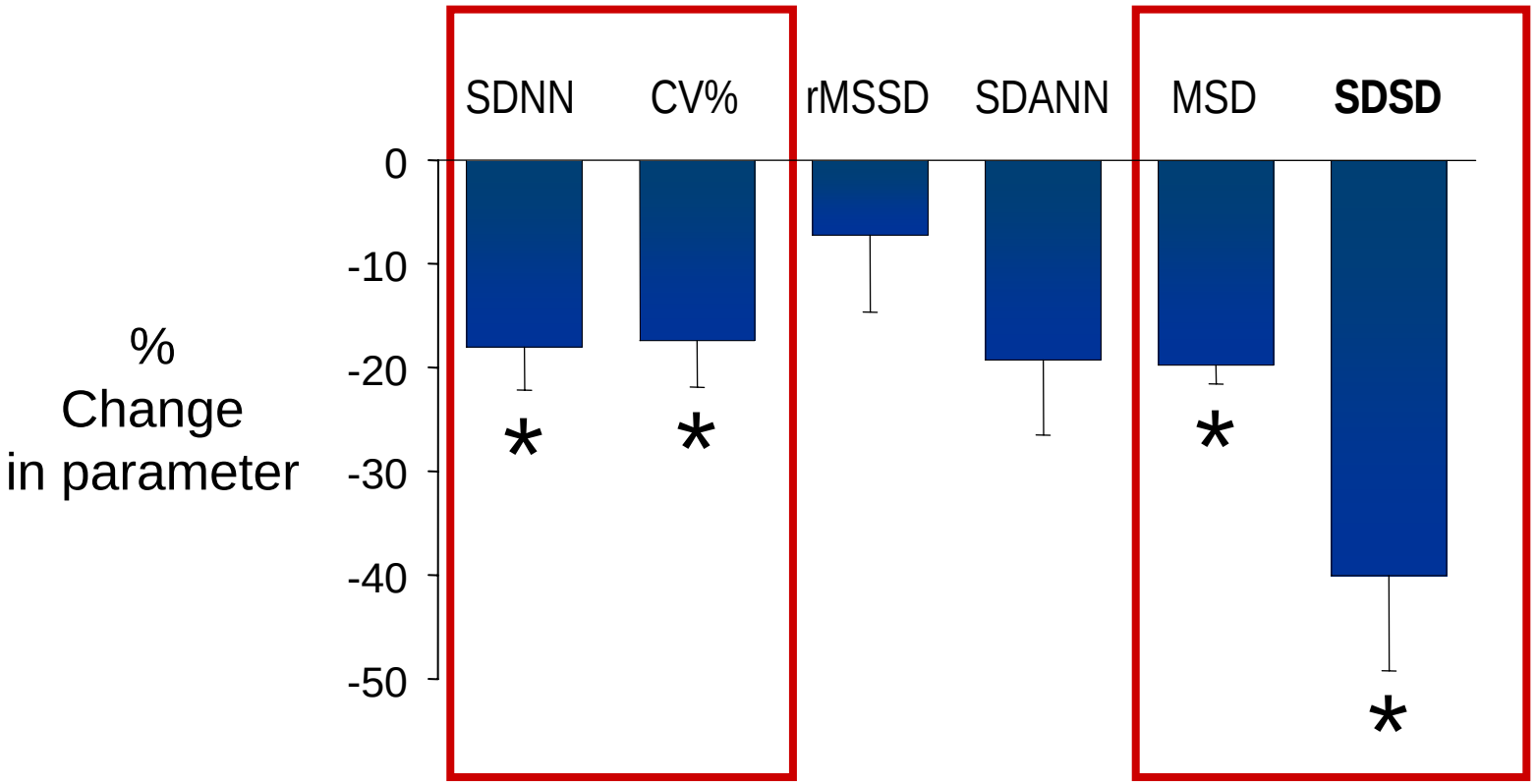
# Preliminary Results: Sidestream smoke decreased 24 hr HRV




**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



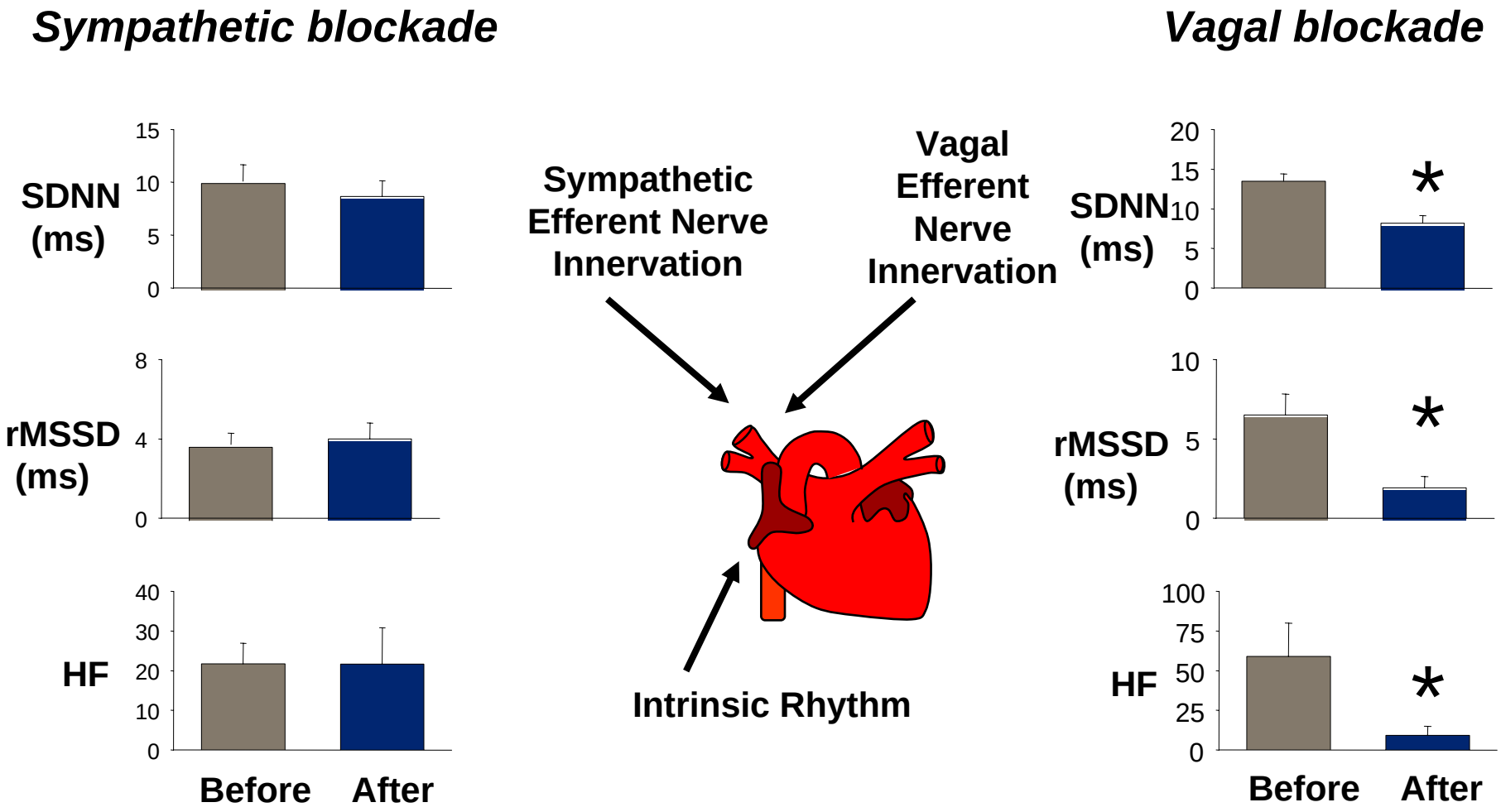
# What did we learn from our preliminary studies?

- 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



# Second Hypothesis

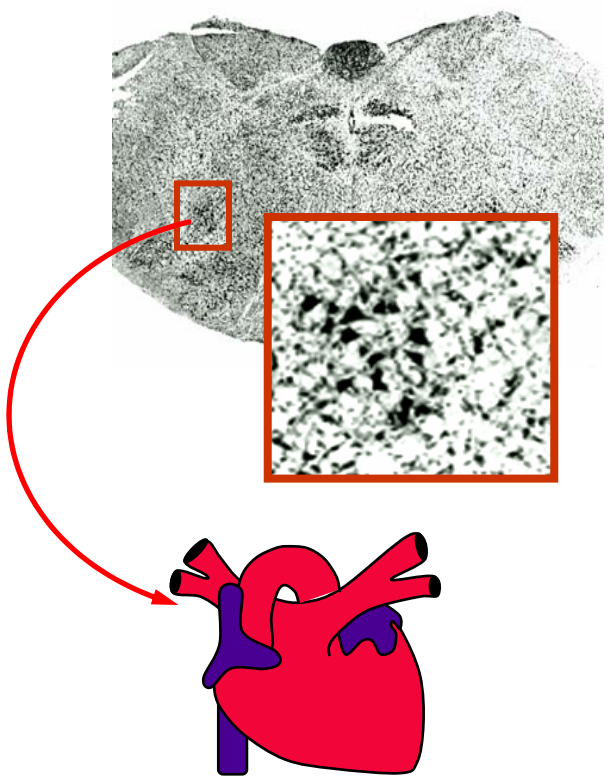
1. Short-term exposure to ambient air pollutants reduces HRV.

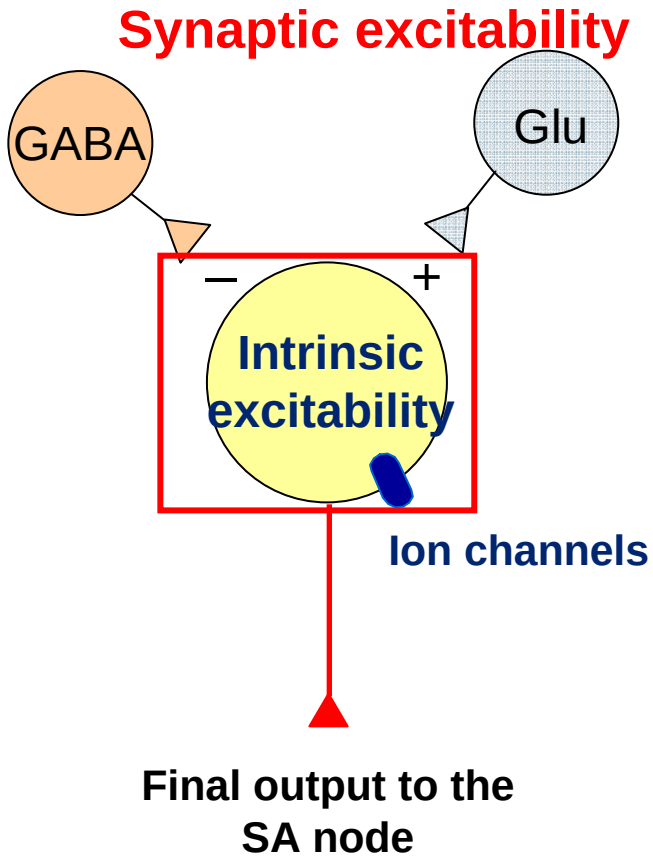
2. One underlying mechanism is *neuroplasticity* in brainstem neurons (nucleus ambiguus, NA) that regulate HRV.

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.

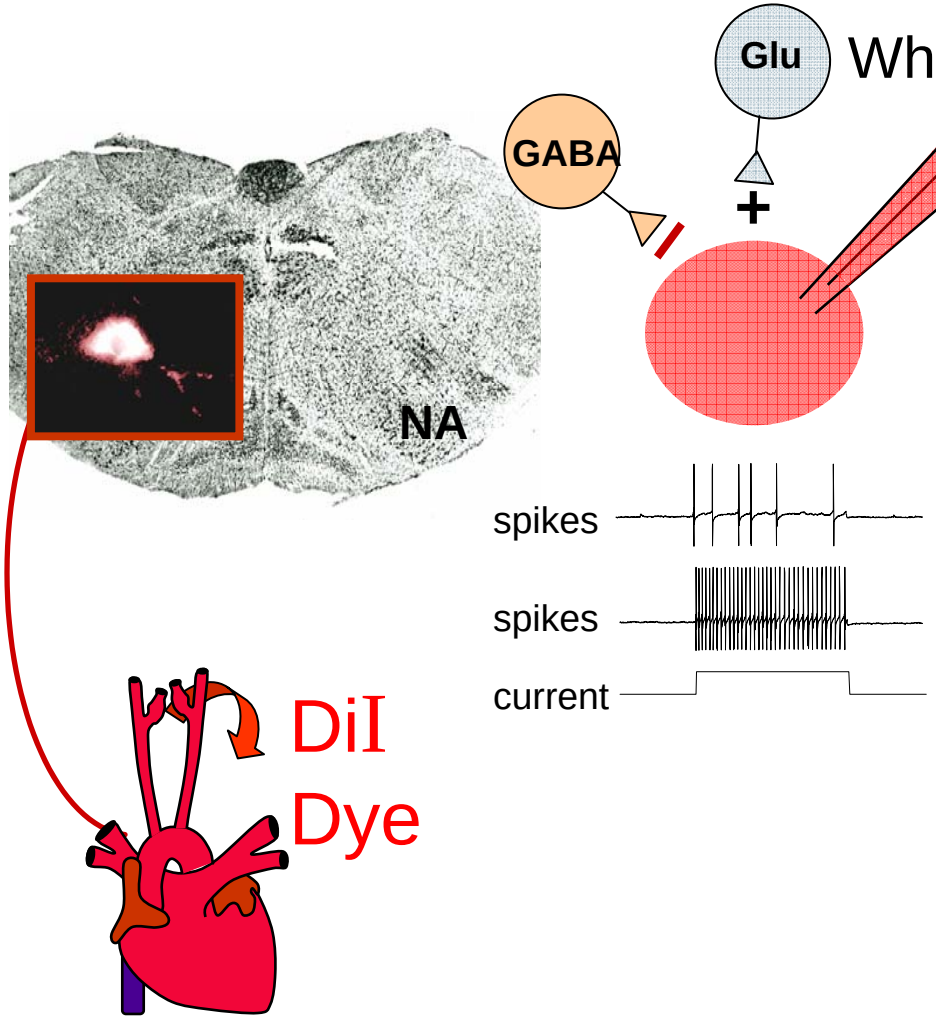
# What do we know about NA cardiac vagal neurons ?






*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

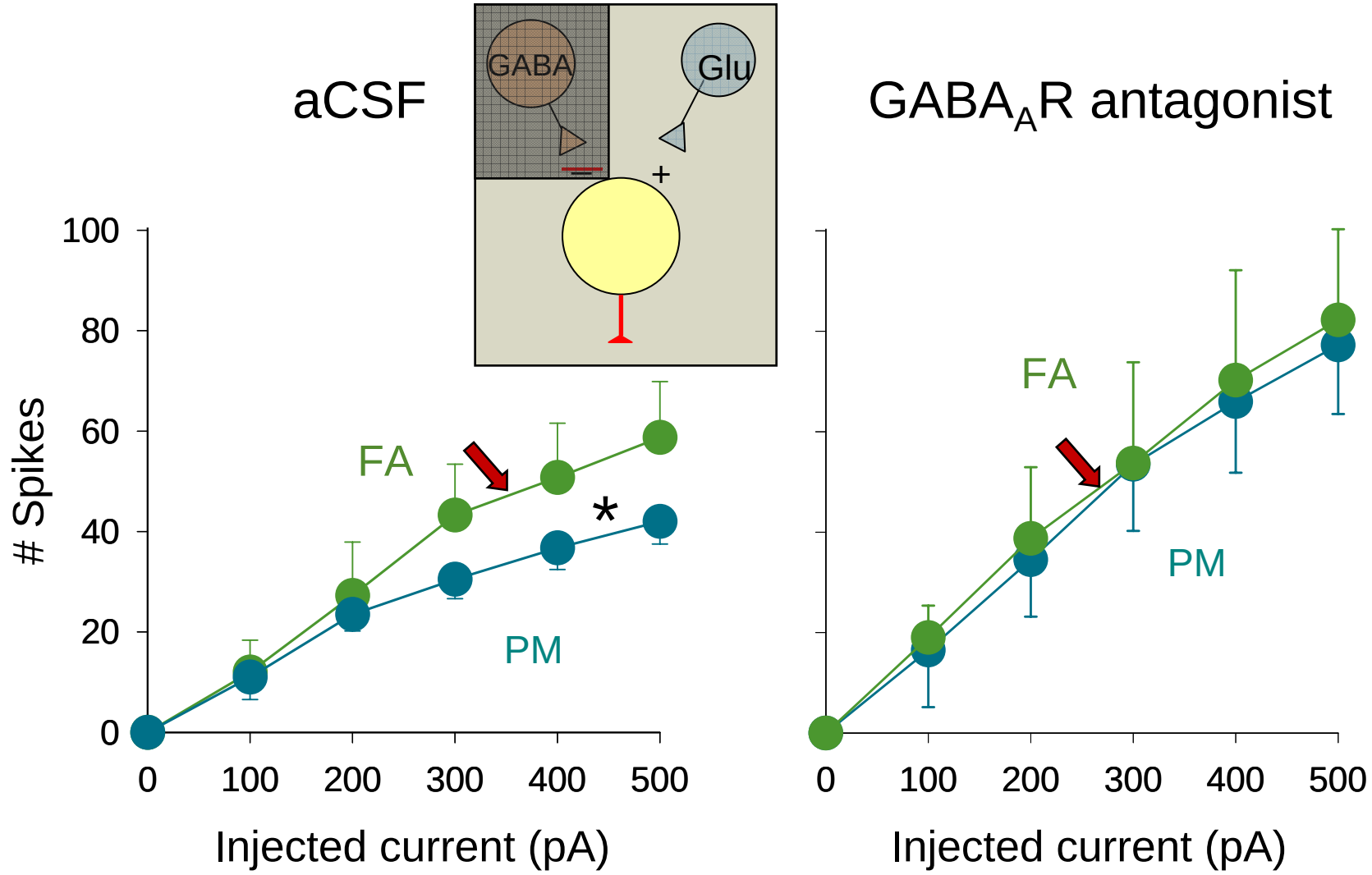
Measure intrinsic properties

- 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

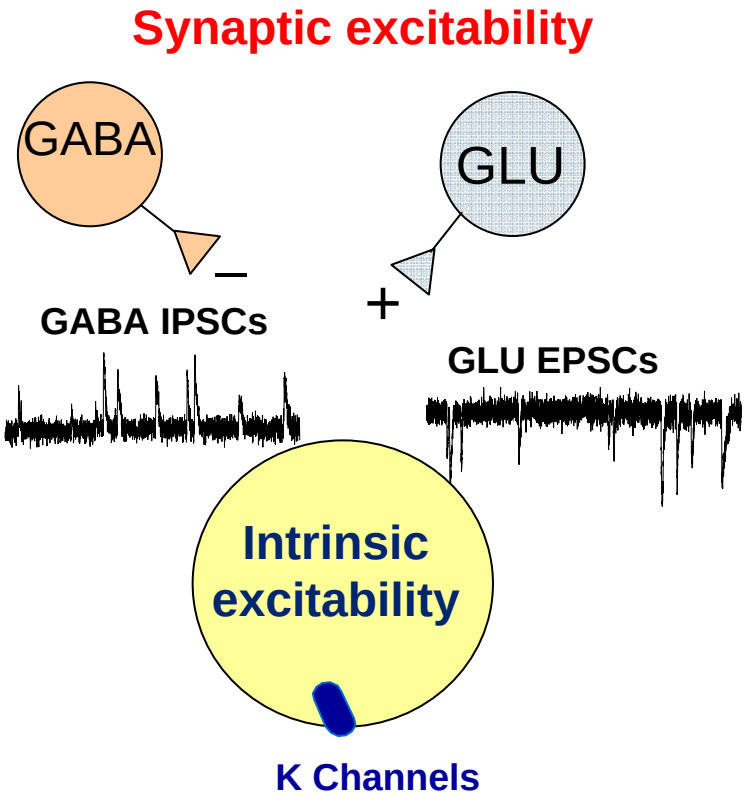
24 hour HRV

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*

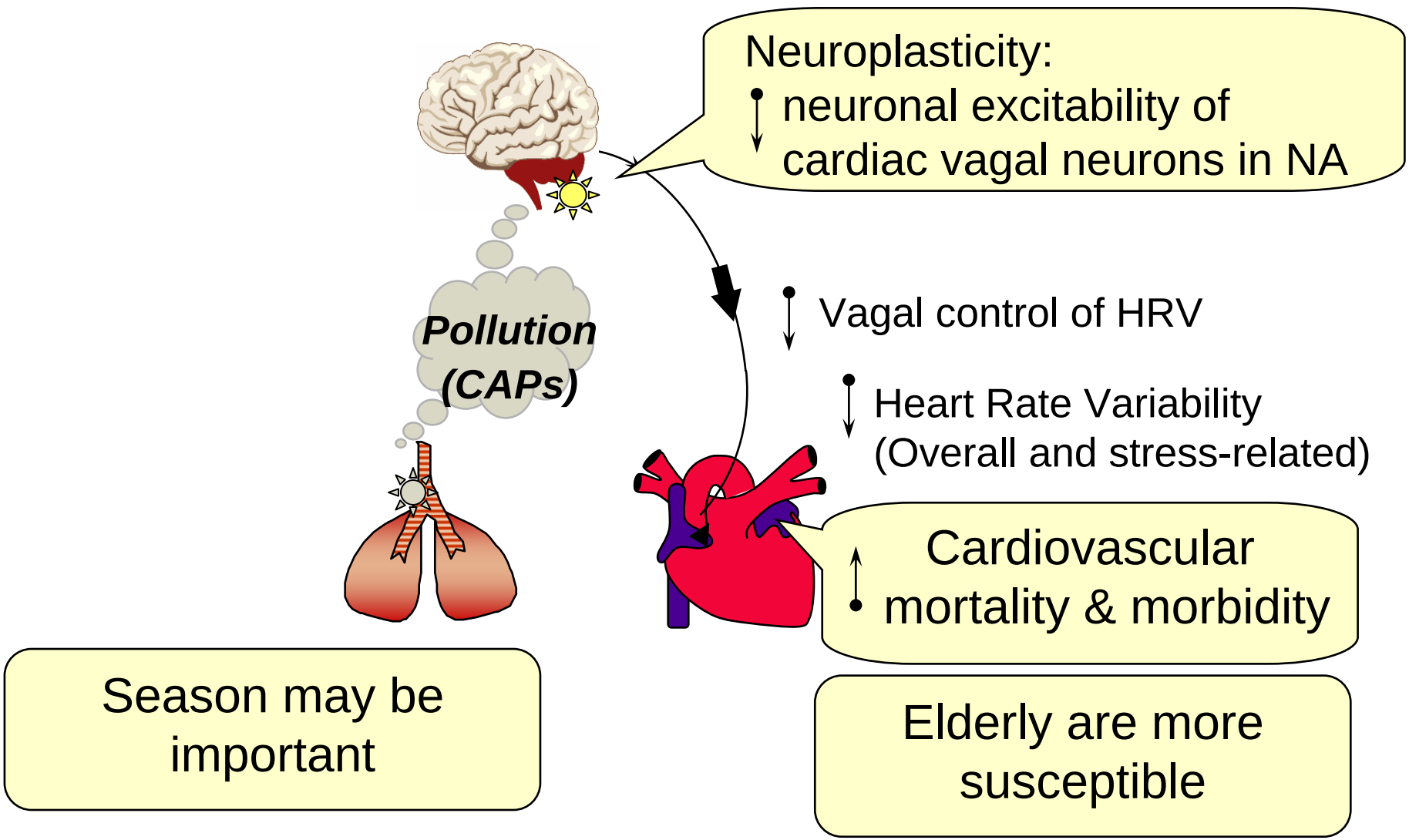
*Are there specific changes in K channel function:*
(conductances and kinetics)

*Decreased synaptic excitability*:

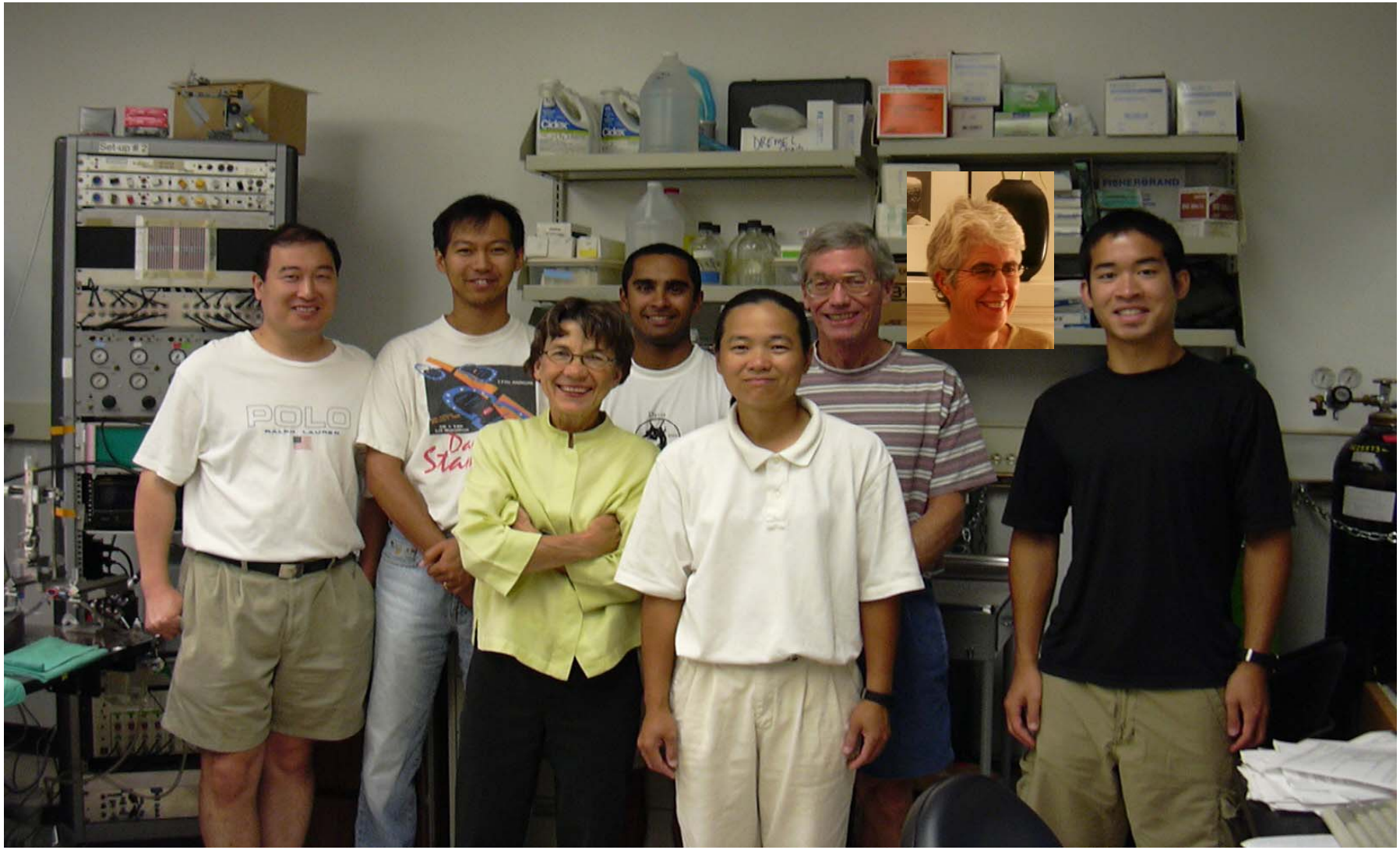
*upregulated* inhibitory GABA mechanisms (GABA IPSCs)

*downregulated* excitatory glutamatergic (GLU) mechanisms (GLU EPSCs)

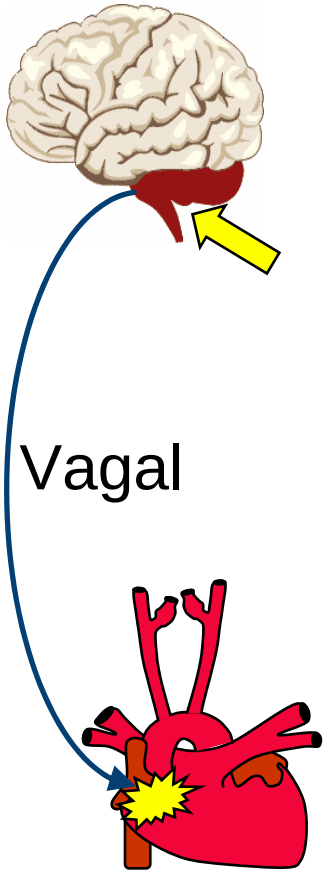
# What gaps do we hope to fill?

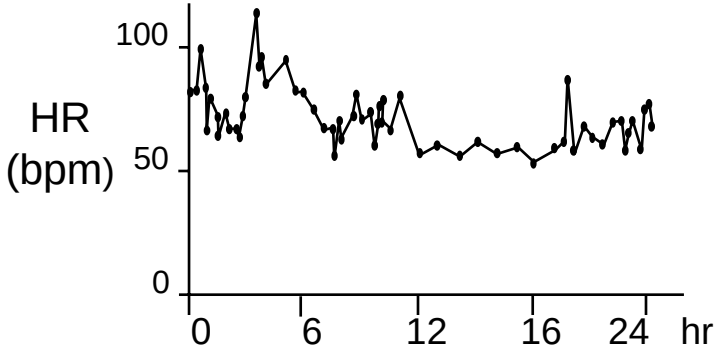


# The people who made this possible…

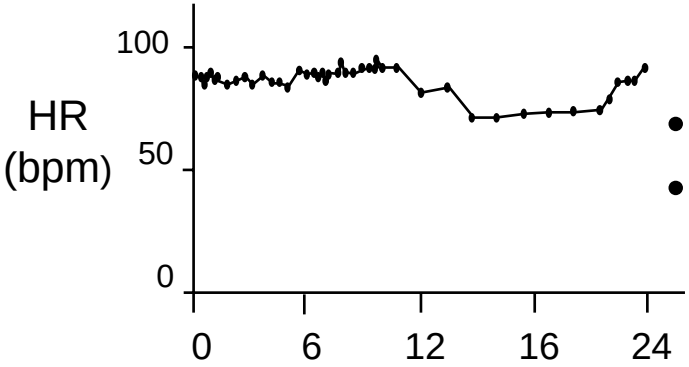


# Loss of vagal input to the SA node



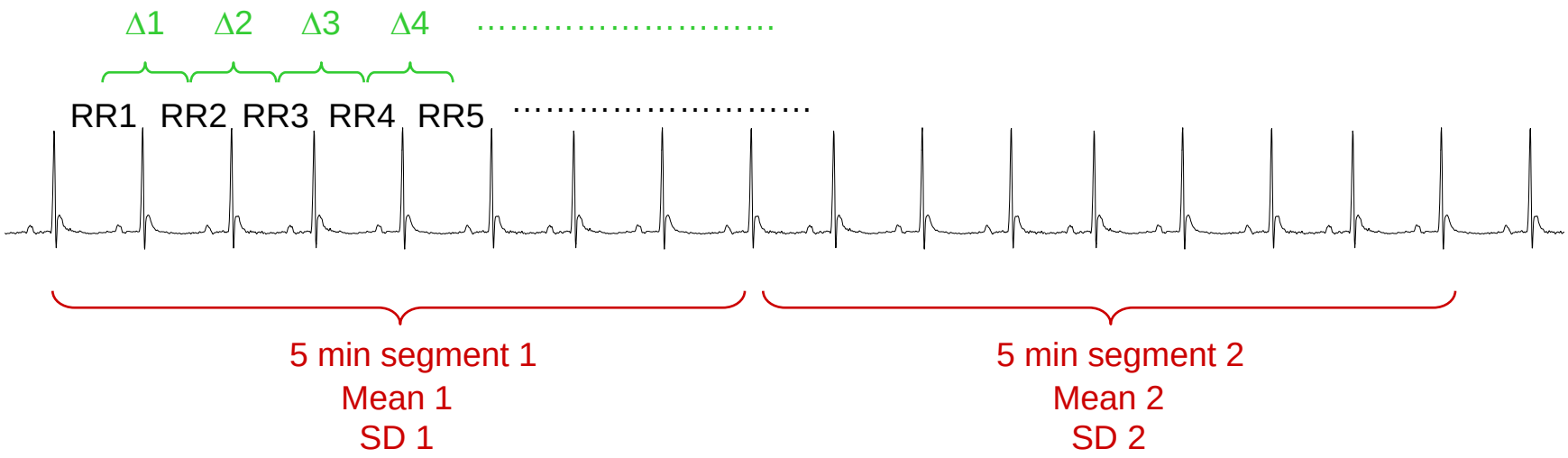

**Normal HRV**




**↓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?