

Presentation 5 – Marina Morris

Low Level Chemical Toxicity Study of Autonomic Neural Balance

Mariana Morris, Ph.D.
Pharmacology &
Toxicology
Boonshoft School of
Medicine
Wright State University
Dayton, Ohio
mariana.morris@wright.edu



Research Advisory Committee on Gulf War Veterans' Illnesses August 14, 2006

DAYTON DAILY NEWS
FRIDAY,
SEPTEMBER 29, 1999

VA center joins study on Gulf War afflictions

Volunteers will be
relieved through various
therapies.

War veterans are seeking
relief from chronic health
problems that are linked
to the Persian Gulf. And the
VA is now offering a program
that may help them. The
study will last

Ailments may be linked to nerve gas antidote

250,000 U.S. troops
received the drug
during the Gulf War

RELATED STORY
Cincinnati VA Center leading
treatment program, BA

VA tests remedies for Gulf illness

Dayton, Cincinnati
centers each have trial
programs under way

By KEVIN LAMB
Dayton Daily News

CINCINNATI — Gulf War veter-
ans experiencing the joint pain,
muscle aches, fatigue, concentra-
tion difficulties and rashes that
have been termed Gulf War syn-
drome are invited to join the Cin-
cinnati VA Medical Center's

demonstration treatment program
for veterans with these symptoms.
Cincinnati is one of five U.S. sites
conducting the one-year treatment
trial, which will become a model for
further programs if it is effective.

The individualized treatment
includes physical therapy, thera-
peutic exercise, access to a support
group and treatment for physical
symptoms or underlying mental dis-
orders such as depression or post-
traumatic stress syndrome. For
information, call Carolyn Haman,
toll-free at (888) 855-3321 or directly
at (513) 861-9100, extension 4255.

The Cincinnati trial is different
from two other trials for Gulf War
syndrome for which the Dayton VA
Center is among 30 participating
centers.

One trial is to determine whether
exercise alone or in combination
with psychological cognitive
behavioral therapy can diminish
the severity of symptoms, and the
other will test whether an antibiotic
can effectively treat the symptoms.
Call 284-6011, Ext. 1212, for
information on the Dayton trials.



NORTH CAROLINA VETERAN Brian Martin suffers from ailments he
attributes to toxins to which he was exposed during the Persian Gulf War.
The ailments cannot be ruled out as a cause of
Gulf War syndrome.

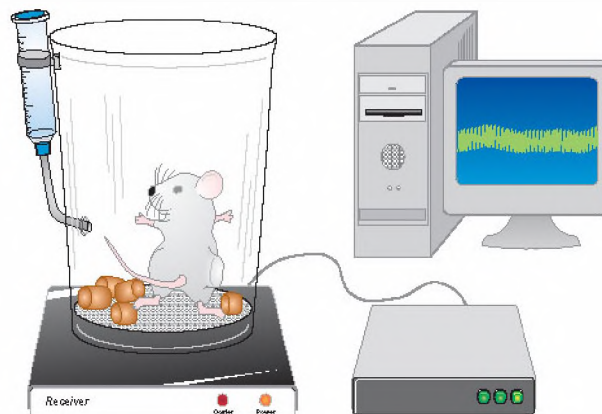
Beatrice Alexander Gohelski of
Rural Center, who headed the
testing, told as Pentagon says con-
ference she speculated that 70

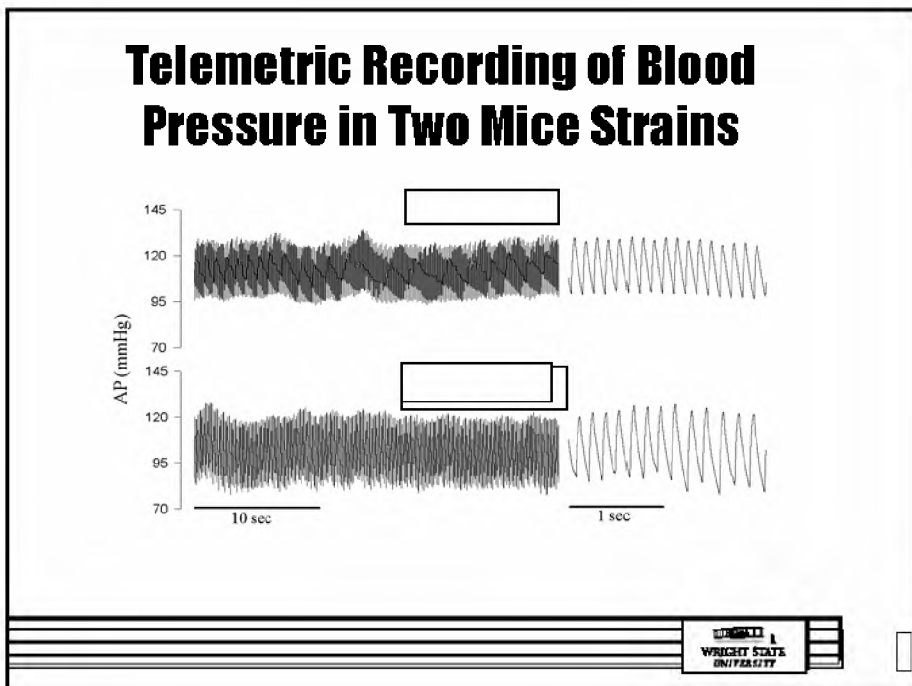


Experimental Goals

- ◆ Phase 1: Stress/Chemical Interactions
 - *How does stress alter the body's ability to resist chemical challenges?*
 - *Studies of pyridostigmine/stress interactions: focus on autonomic neural function*

Studies of Autonomic Balance Integrative Cardiovascular Laboratory

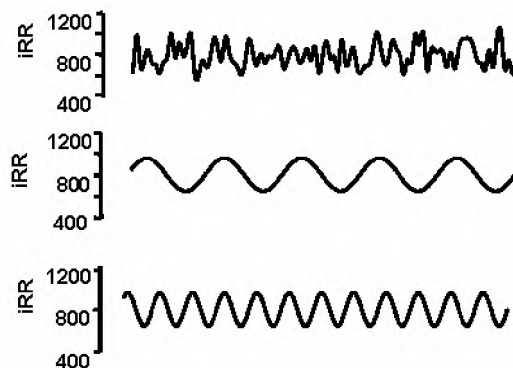




What is Spectral Analysis ?

- ◆ A statistical method for characterization of parameters of variability. Variation over time is considered variance. Power spectra of variability are composed of two oscillatory components; low frequency (LF: 0.1-1 Hz) and high frequency (HF: 1- 5.0 Hz).
- ◆ The components are associated with autonomic balance. For HR and BP variability, LF is related to sympathetic modulation, whereas, for PI variability the HF is related to vagal modulation of the sinus node.

Signal Analysis

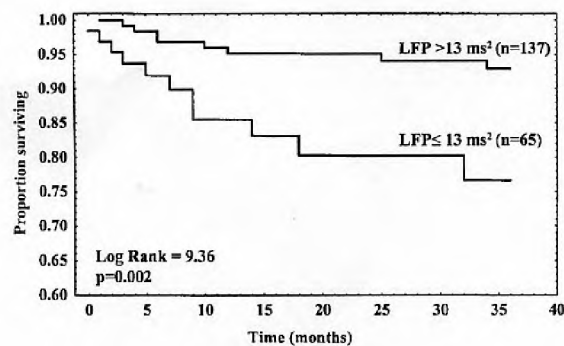


Clinical Relevance of Heart Rate Variability (HRV)

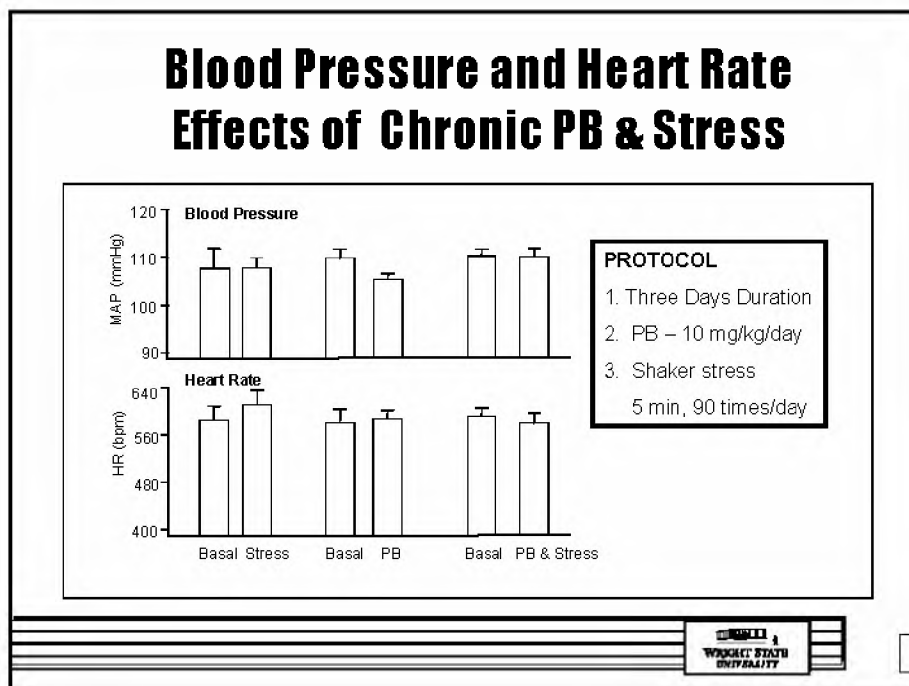
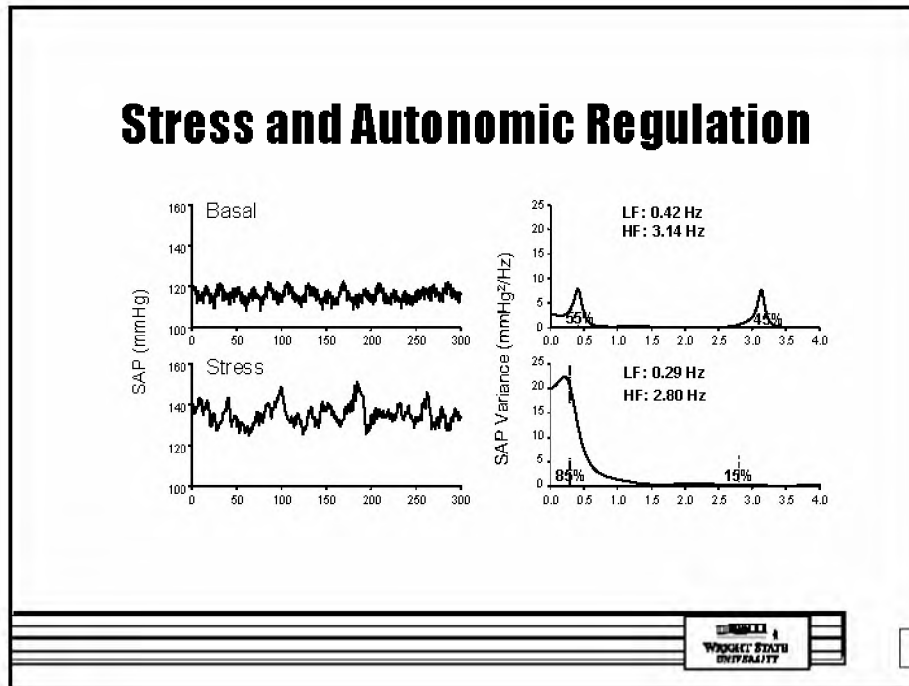
- ◆ HRV variability in chronic heart failure: Target for therapy? Sueta, 2003
- ◆ Decreased HRV variability is associated with increased mortality after acute myocardial infarction. Kleiger et al., 1987
- ◆ HRV strongly predicts cardiac death in heart failure patients. LaRovere et al., 2003

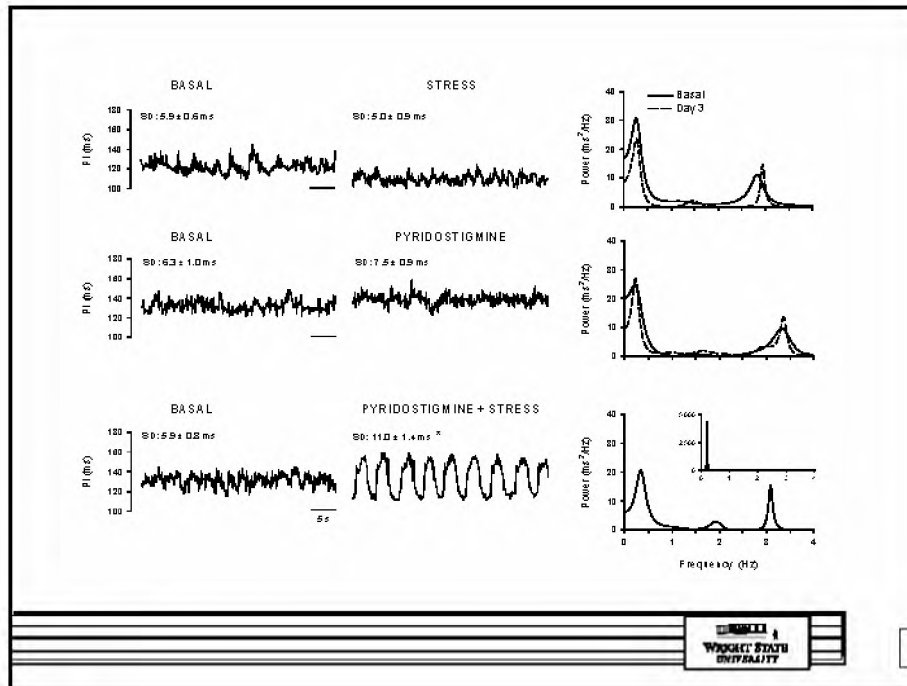
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Reduced Heart Rate Variability Associated with Sudden Cardiac Death



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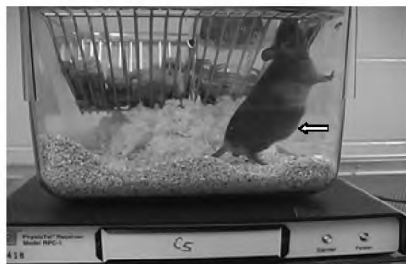
Use of AChE Inhibitors in the Clinic

- ◆ Cholinergic stimulation with pyridostigmine reduces ventricular arrhythmias and enhances heart rate variability in heart failure. Behling et al., 2003
- ◆ Cholinergic stimulation with pyridostigmine reduces the QTc interval in coronary artery disease. Castro et al., 2003

Experimental Goals

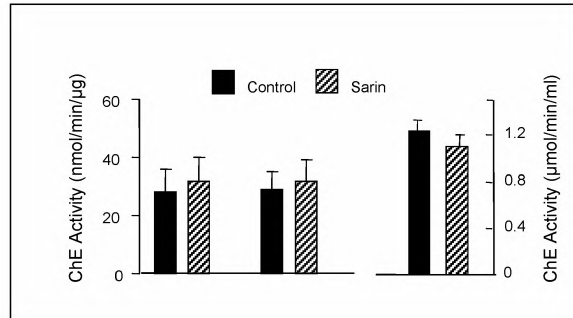
- ◆ Phase 2: Low Level Sarin Exposure
 - *Genomic and Proteomic Expression*
 - *Autonomic Neural Function*
 - *Neurobehavioral and Cholinergic Function*

Autonomic Cardiovascular Effects of Low Dose Sarin

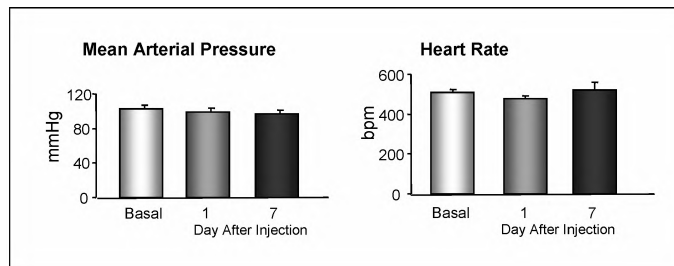


- ◆ Radiotelemetry (5000Hz)
- ◆ Sarin sc (8 $\mu\text{g}/\text{kg}$)
- ◆ Spectral analysis - autoregressive method
- ◆ Blood and brain AChE

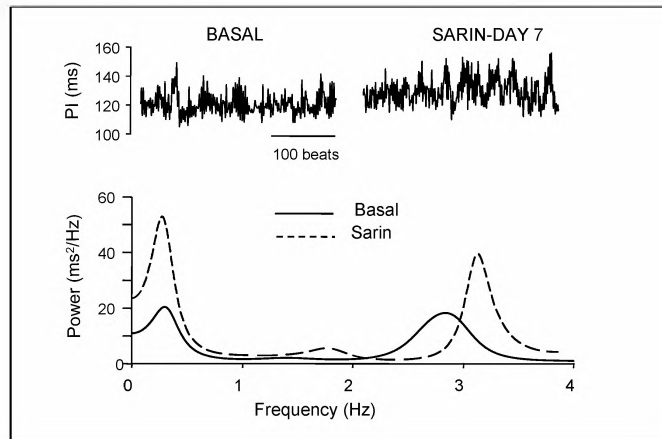
Low Dose Sarin Brain and Blood Cholinesterase



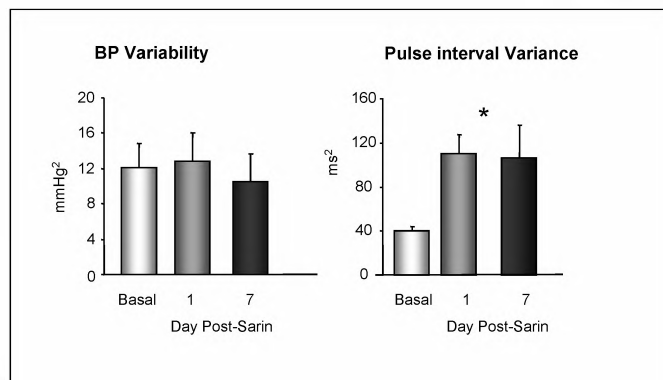
Low Dose Sarin Blood Pressure and Heart Rate



Low Dose Sarin: Acute Increase in Heart Rate Variance



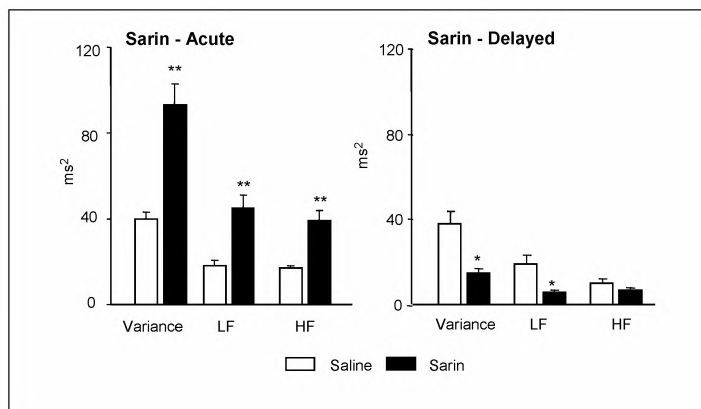
Acute Changes in Blood Pressure and Heart Rate Variance



Serendipity: The gift of finding valuable things not sought for

- ◆ Action: Your graduate student leaves the sarin treated mice in the animal facility for an extended vacation.
- ◆ Outcome: Cardiovascular monitoring shows that sarin produced delayed changes in heart rate variance, associated with cardiac dysfunction.

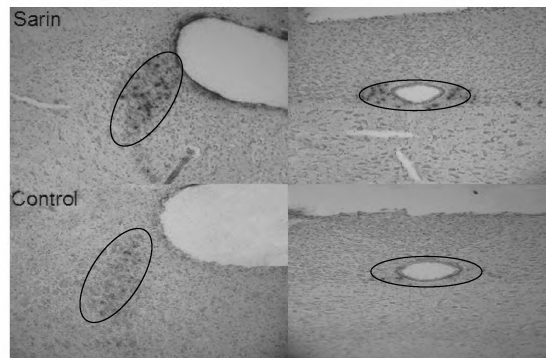
Delayed Effect of Sarin on PI Variance and Frequency Domains



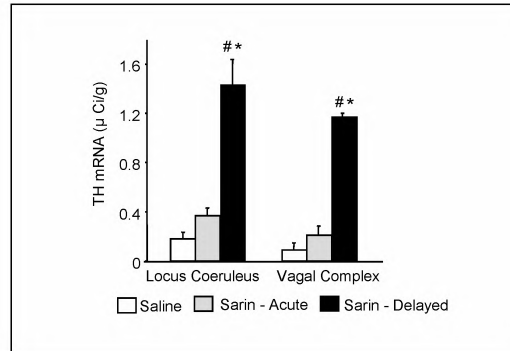
Sarin on Blood Pressure Variance

Treatment	Variance (mmHg ²)	Low Freq (mmHg ²)	High Freq (mmHg ²)
Saline	13 ± 2	9 ± 2	3 ± 0.3
Sarin Acute	13 ± 3	9 ± 3	3 ± 1
Sarin Delayed	14 ± 2	10 ± 3	3 ± 1

Effect of Low Dose Sarin on Brainstem Catecholamine Systems

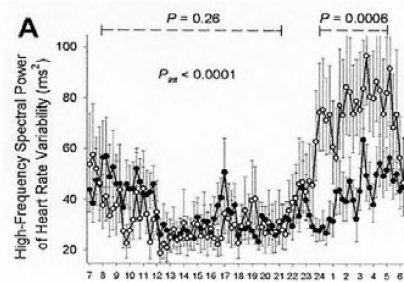


Low Dose Sarin Produces Delayed Changes in Brainstem Amine Function



Blunted Circadian Variation in Autonomic Regulation of Sinus Node Function in Veterans with Gulf War Syndrome

Robert W. Haley, MD, Wanpen Vongpatanasin, MD, Gil L. Wolfe, MD, Wilson W. Bryan, MD, Roseanne Armitage, PhD, Robert F. Hoffmann, PhD, Frederick Petty, PhD, MD, Timothy S. Callahan, PhD, Elizabeth Charuvastra, RN, William E. Shell, MD, W. Wesley Marshall, MD, Ronald G. Victor, MD



**Sarin Produces Delayed Cardiac
and Central Autonomic Changes**

Mariana Morris, Mary P. Key, Vera Farah

Experimental Neurology, Sept-2006

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Conclusions

Sarin has effects on the brain and cardiovascular system at doses that cause no detectable clinical symptoms. These studies document the possible public health problems associated with low dose, non-symptomatic exposure to sarin .

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