Presentation 5 – Marina Morris

Low Level Chemical Toxicity Study of Autonomic Neural Balance

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

DAYTON DAILY NEWS FRIDAY, SEPTEMBER 24, 1999

HEALTH

VA center joins study on Gulf War afflictions

▶ Volunteers will be followed through various therapies.

By James Hannah

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 testing treatment program, 8A

NEWS

VA tests remedies for Gulf illness

Dayton, Cincinnati centers each have trial programs under way

By Kevin Lamb
Dayton Daily News

CINCINNATI — Gulf War veterans experiencing the joint pain, muscle aches, fatigue, concentration difficulties and rashes that have been termed Gulf War syndrome are invited to join the Cincinnati 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, therapeutic exercise, access to a support group and treatment for physical symptoms or underlying mental disorders such as depression or post-traumatic stress syndrome. For information, call Carolyn Homan toll-free at (888) 855-3321 or directly at (513) 861-3100, 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 268-6511, 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.

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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*

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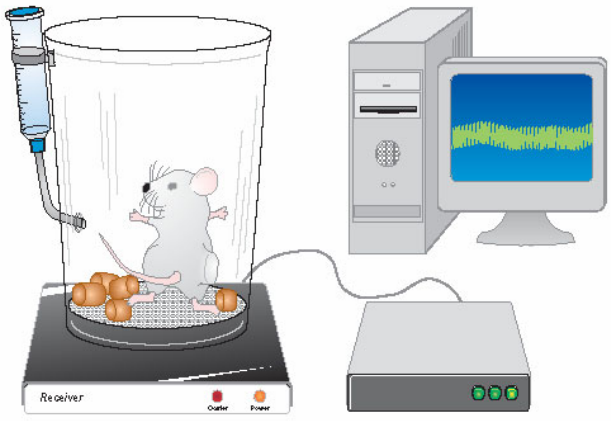
Studies of Autonomic Balance Integrative Cardiovascular Laboratory



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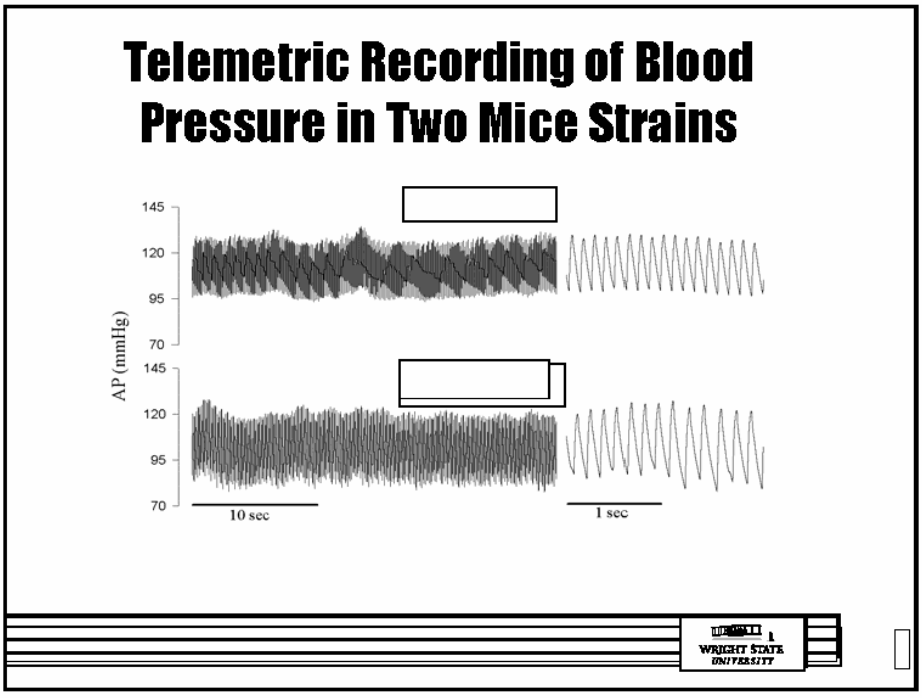
Telemetric Recording of Blood Pressure in Two Mice Strains
145
120
95
70
AP (mmHg)
145
120
95
70
10 sec
1 sec
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What is Spectral Analysis ?

- 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.

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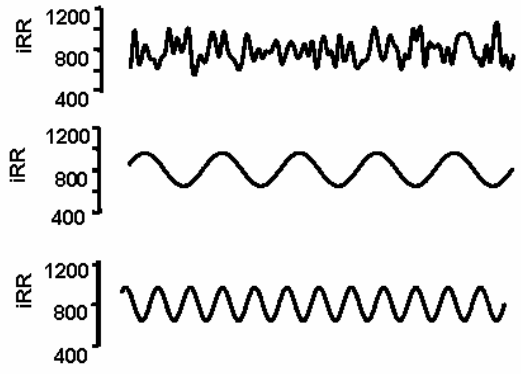
Signal Analysis



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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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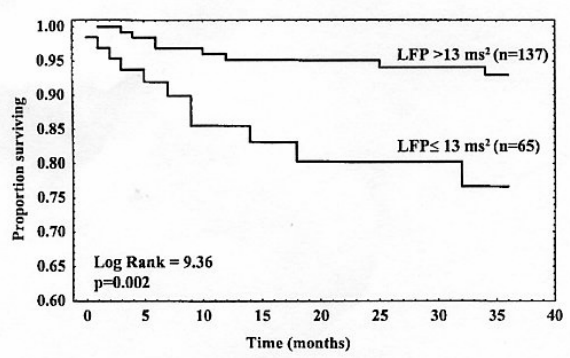
Reduced Heart Rate Variability Associated with Sudden Cardiac Death



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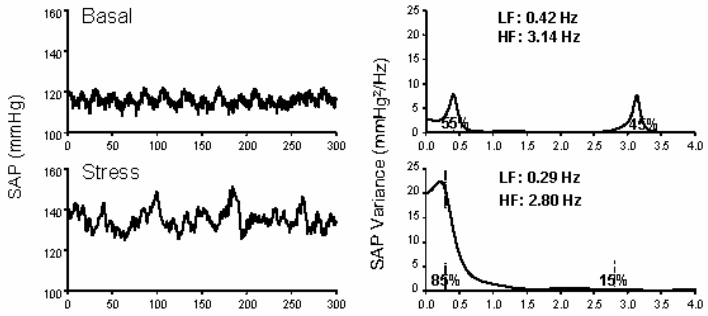
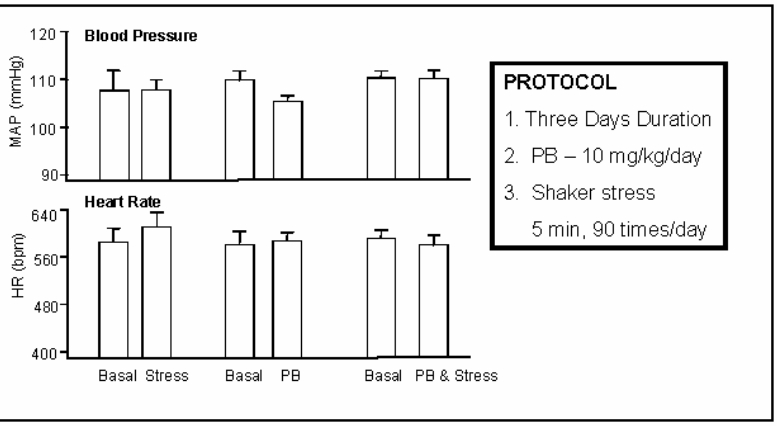
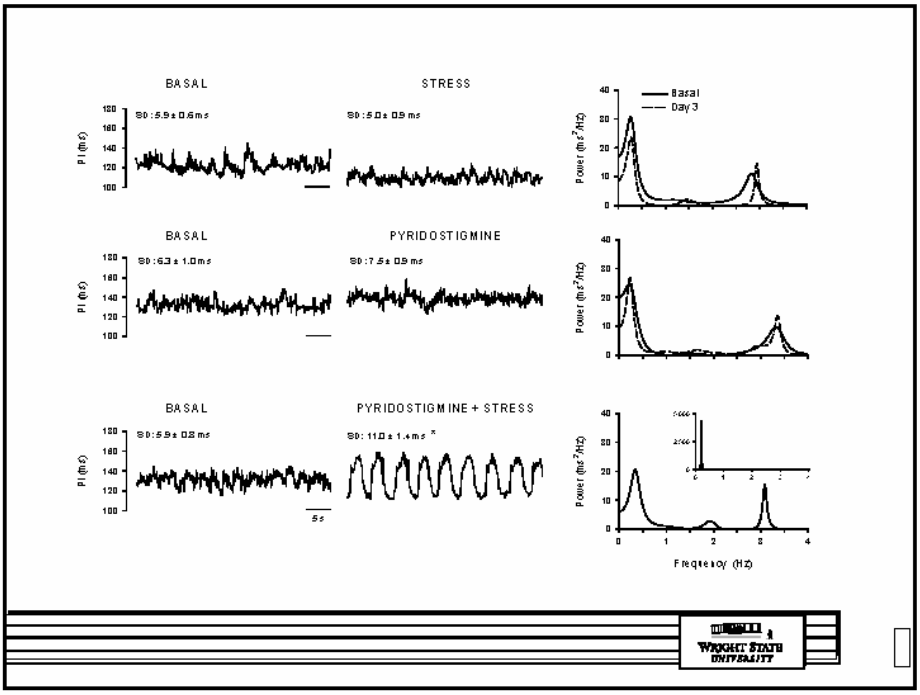
Stress and Autonomic Regulation



Blood Pressure and Heart Rate Effects of Chronic PB & Stress





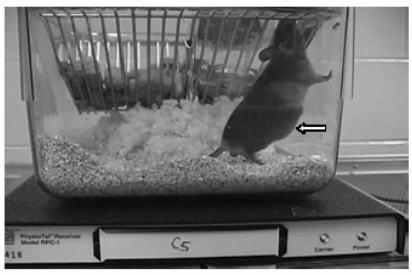
Use of AChE Inhibitors in the Clinic

- 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

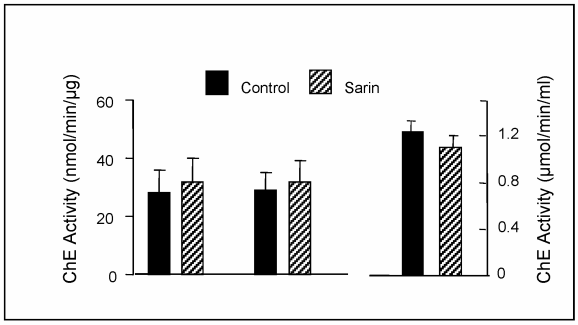
- Phase 2: Low Level Sarin Exposure
  - *Genomic and Proteomic Expression*
  - *Autonomic Neural Function*
  - *Neurobehavioral and Cholinergic Function*

Autonomic Cardiovascular Effects of Low Dose Sarin



- Radiotelemetry (5000Hz)
- Sarin sc (8 µg/kg)
- Spectral analysis - autoregressive method
- Blood and brain AChE

Low Dose Sarin
Brain and Blood Cholinesterase



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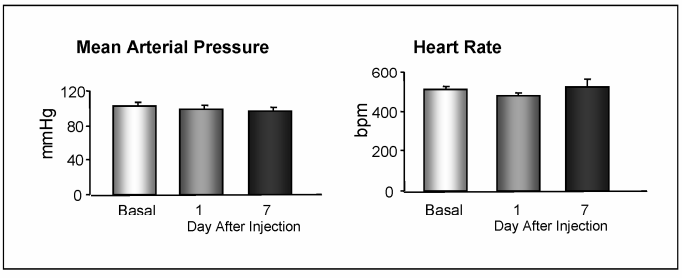
Low Dose Sarin
Blood Pressure and Heart Rate



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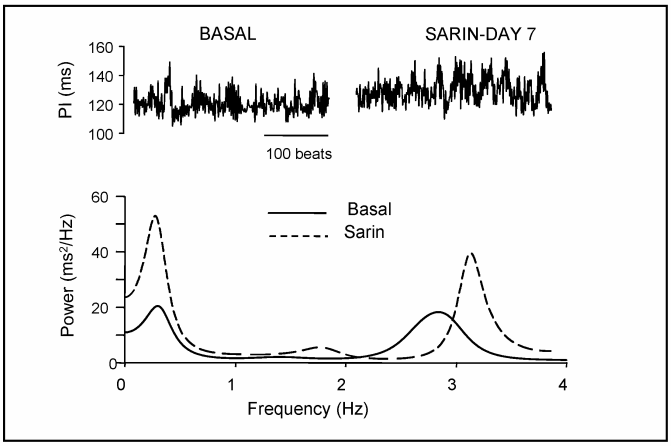
Low Dose Sarin: Acute Increase in Heart Rate Variance



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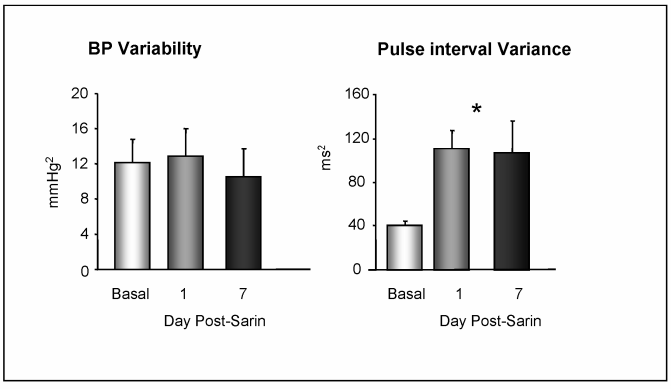
Acute Changes in Blood Pressure and Heart Rate Variance



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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.

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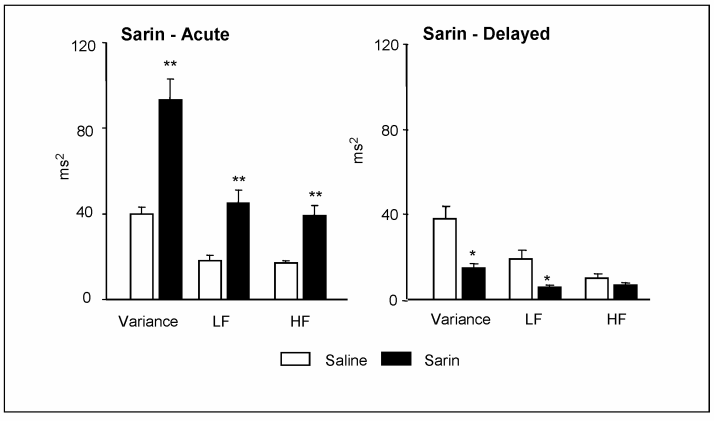
Delayed Effect of Sarin on PI Variance and Frequency Domains



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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

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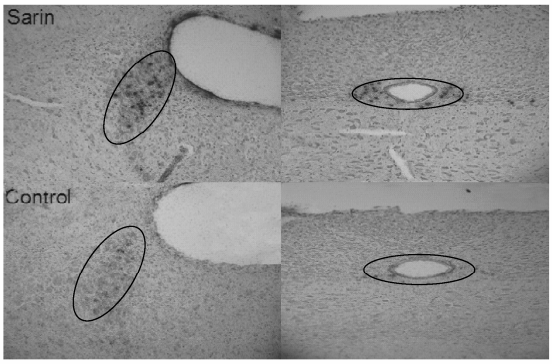
Effect of Low Dose Sarin on Brainstem Catecholamine Systems



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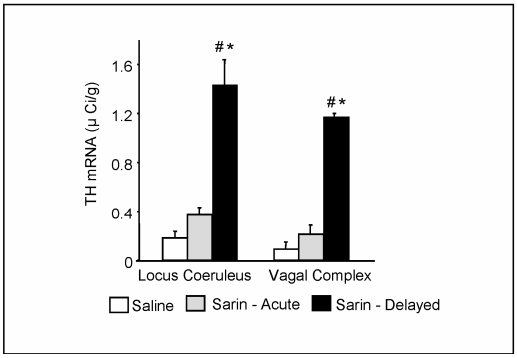
Low Dose Sarin Produces Delayed Changes in Brainstem Amine Function



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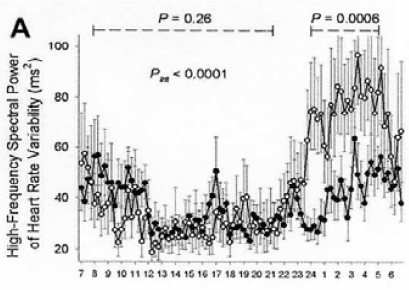
Blunted Circadian Variation in Autonomic Regulation of Sinus Node Function in Veterans with Gulf War Syndrome

Robert W. Haley, MD, Wanpen Vongpatanasin, MD, Gil I. 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



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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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