

ECBC

Cardiovascular Effects of Repeated Low-Level Exposure to Sarin Vapor

Paul Adam Dabisch, Ph.D.

NRC Postdoctoral Associate

US Army Edgewood Chemical Biological Center



Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 16 NOV 2004		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE Cardiovascular Effects of Repeated Low-Level Exposure to Sarin Vapor				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) US Army Edgewood Chemical Biological Center				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES See also ADM001849, 2004 Scientific Conference on Chemical and Biological Defense Research. Held in Hunt Valley, Maryland on 15-17 November 2004., The original document contains color images.					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 21	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			



ECBC

Purpose

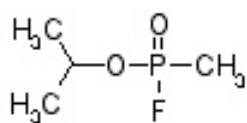
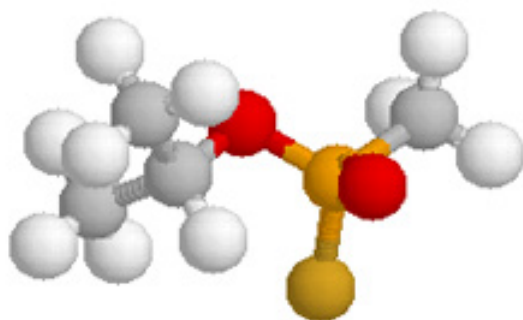
To determine the effect of multiple low-level exposures to sarin vapor on the heart. Endpoints investigated included:

- lead II electrocardiogram
- blood pressure
- heart rate and heart rate variability
- ultrasonographic monitoring of cardiac contractility and cardiac texture



ECBC

Background



Sarin (GB)

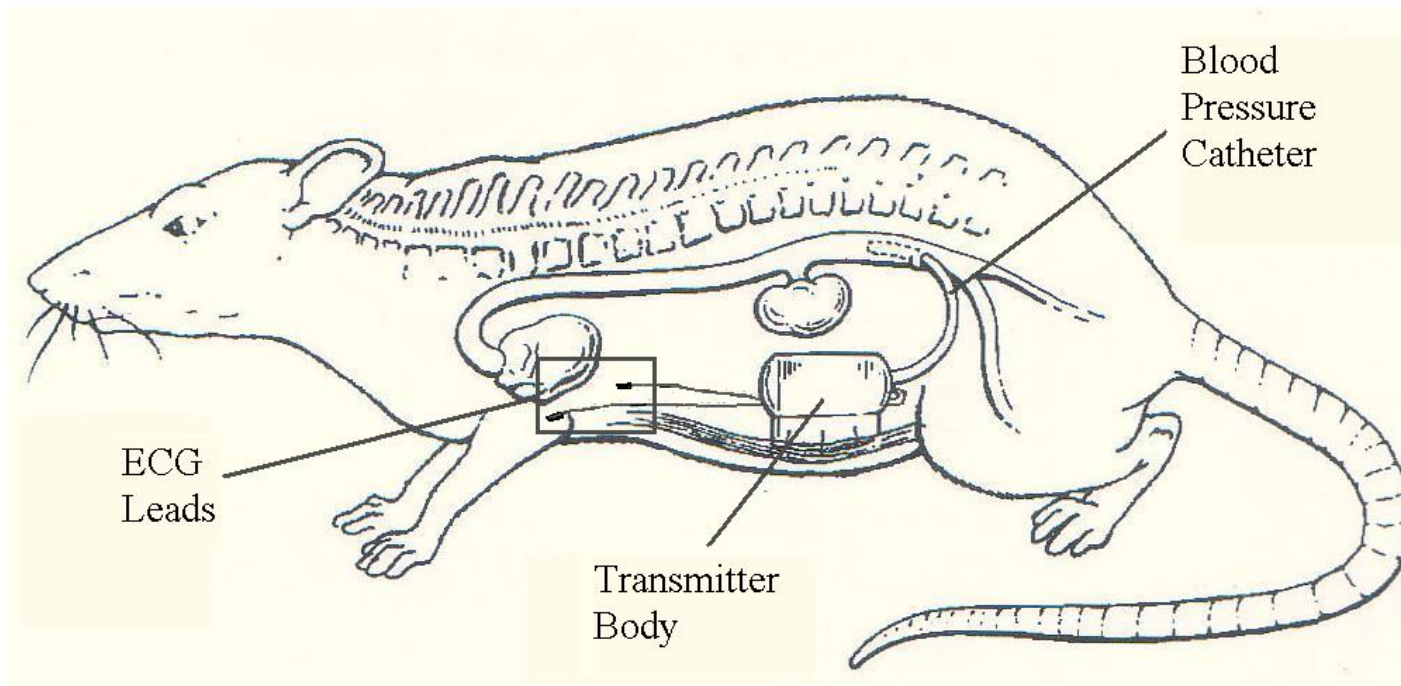
COURTESY NATIONAL LIBRARY OF MEDICINE

- Also known as German Nerve Agent B, or GB.
- Organophosphorus nerve agent
- More volatile than GA, GD, or VX → greater inhalation hazard



ECBC

Telemetric Implant



- Telemetric transmitters (Data Sciences, Inc.) were implanted into male Sprague-Dawley rats 8 days pre-exposure

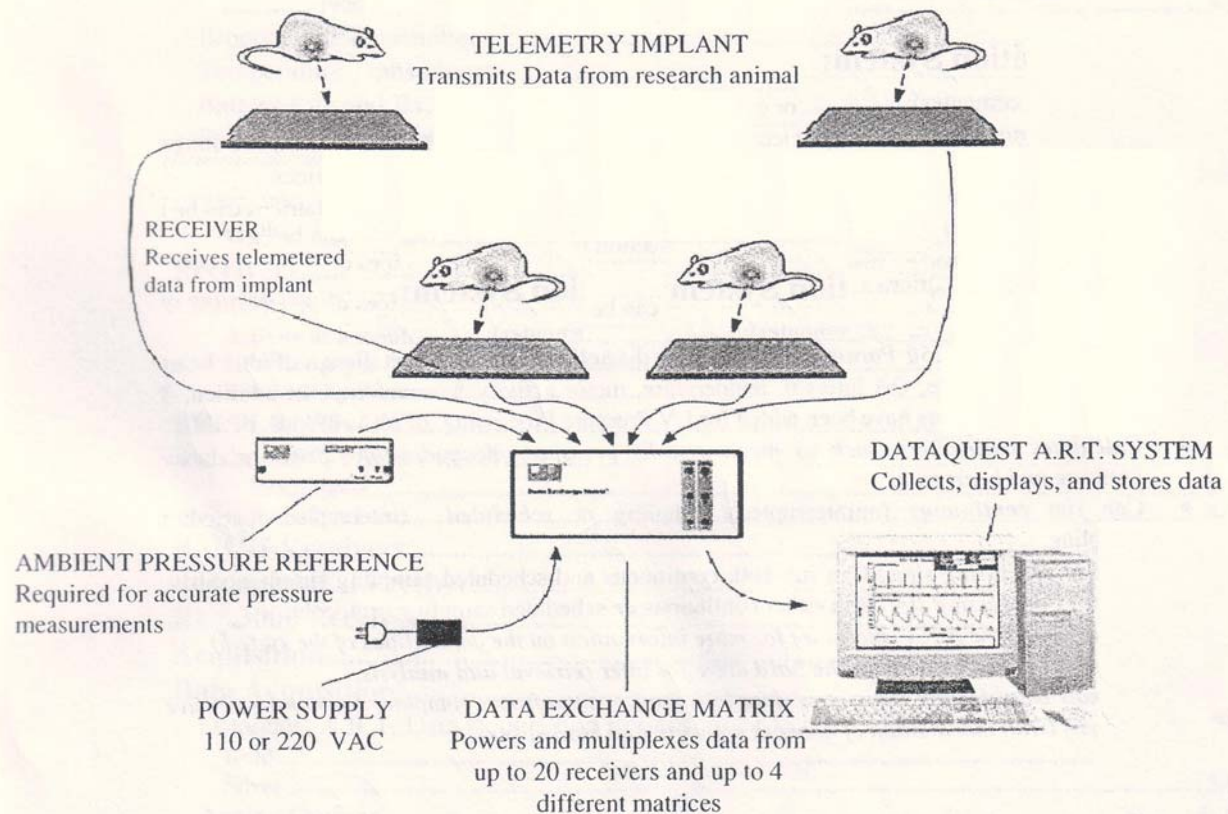


ECBC

Telemetric Monitoring System

Principles of Operation

Basic Components of Telemetry System

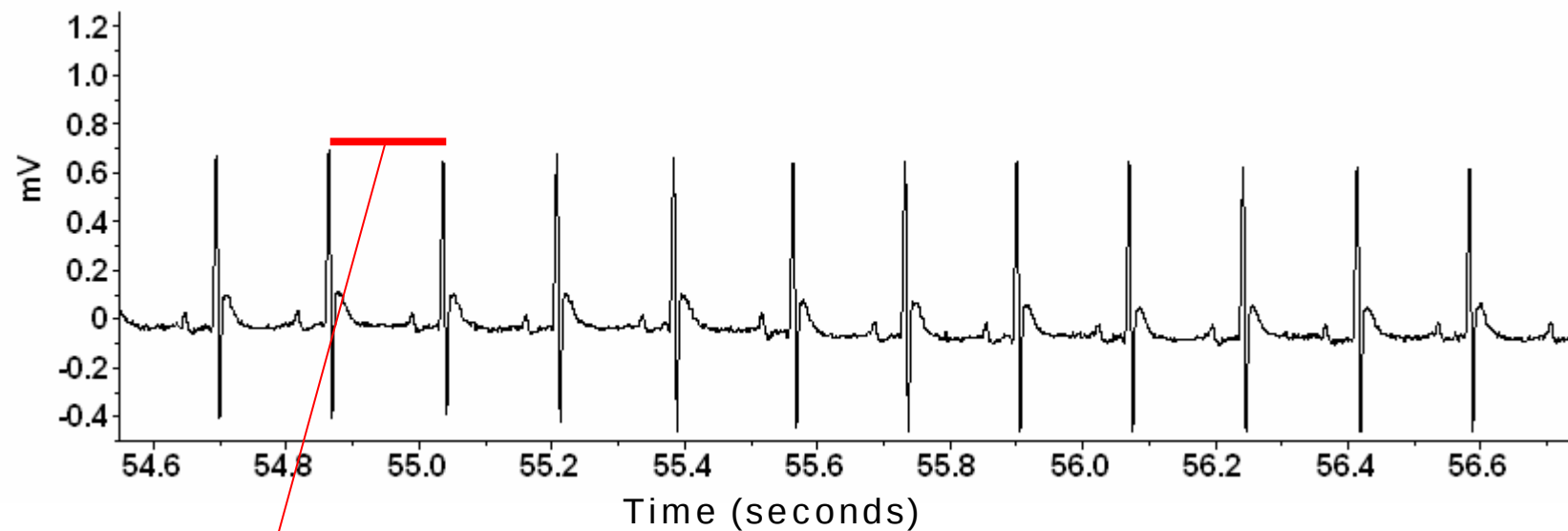




ECBC

Interbeat Intervals

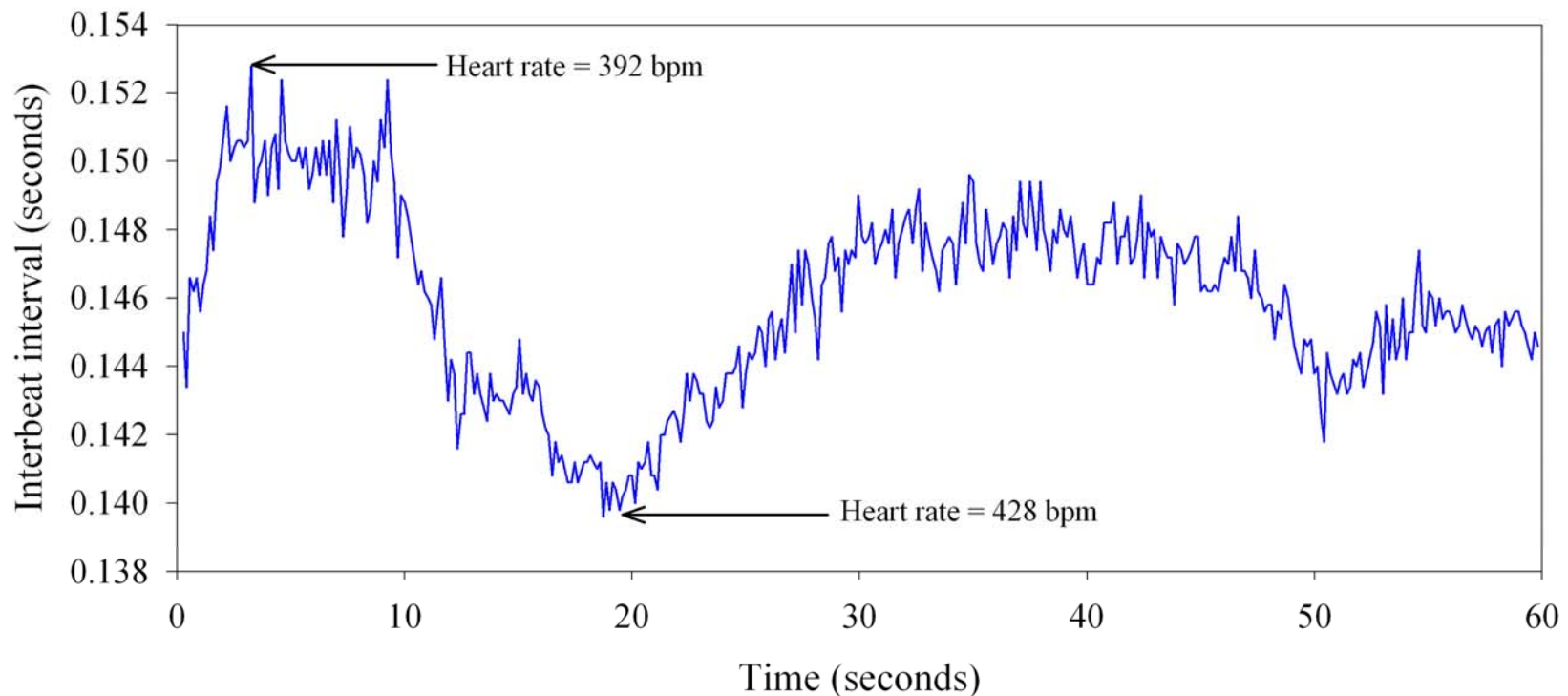
Lead II electrocardiogram — 5000 Hz sampling rate; 1250 Hz filter cutoff



Interbeat or R-R interval



Time Domain Analysis



- Instantaneous heart rate is not stable over time – this is often referred to as **heart rate variability (HRV)**
- This instability results from slight changes in the balance between the sympathetic and parasympathetic nervous systems.



ECDC

Experimental Design

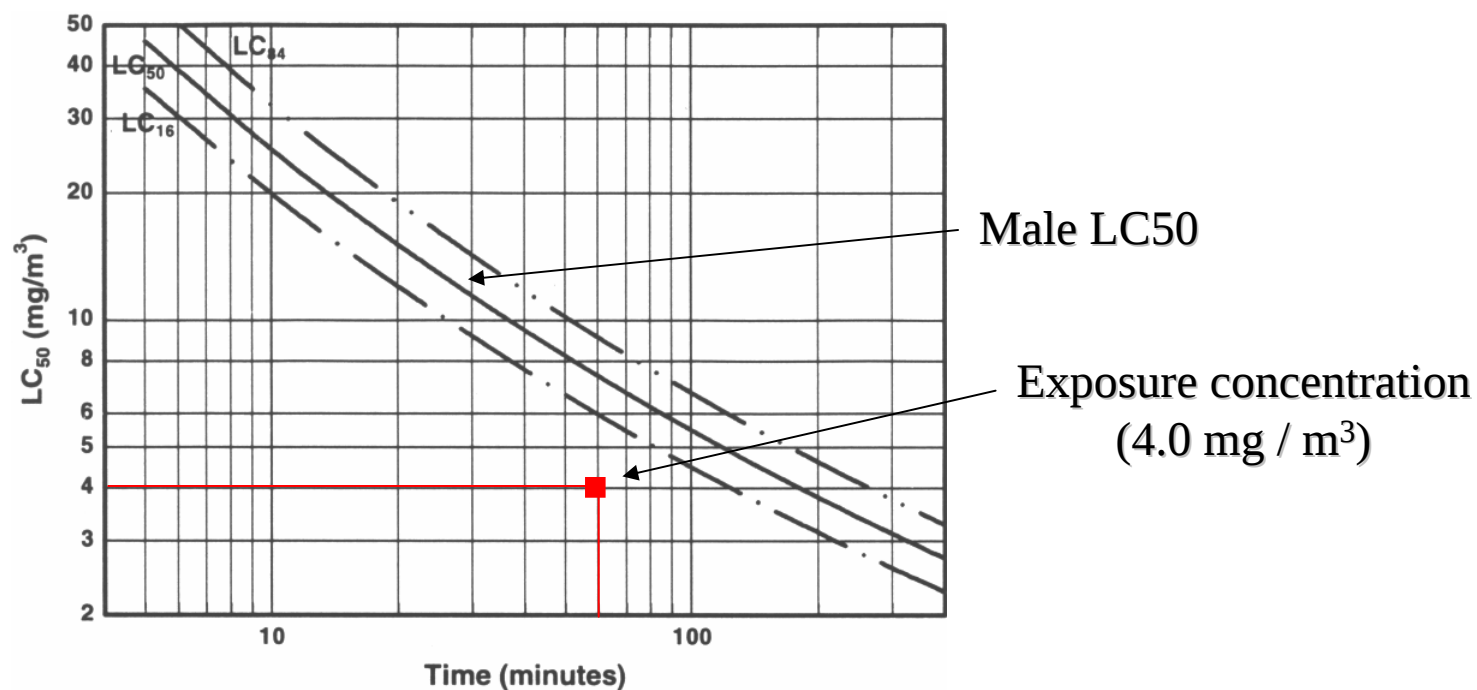
- Adult male Sprague-Dawley rats were exposed to GB vapor in a 750-L dynamic airflow chamber.
- GB vapor was generated using a spray atomization system.
- Chamber concentrations were determined using thermal desorption tubes (Tenax-TA) and GC-FID analysis.





Experimental Design

- Rats were exposed to GB vapor for 1 hour on each of 3 consecutive days. Exposures occurred 24 hours apart



- The concentration of GB vapor chosen was well above the EC₅₀ for miosis (0.030 mg/m³ for a 60 minute exposure), but below the LC₅₀ (7.7 mg/m³ for a 60 minute exposure). *Mioduszewski et al. 2001, 2002*

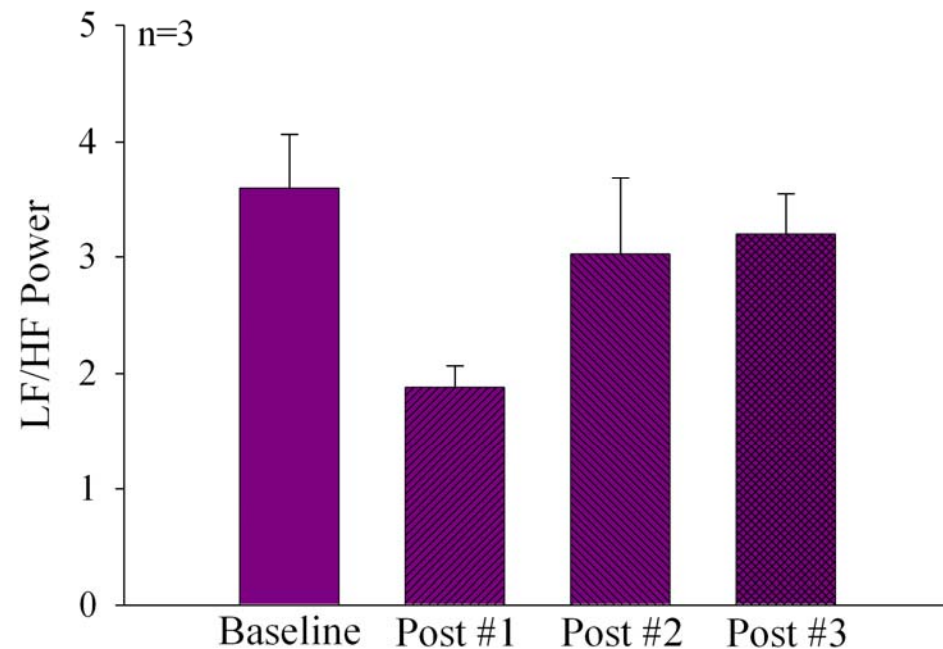


ECBC

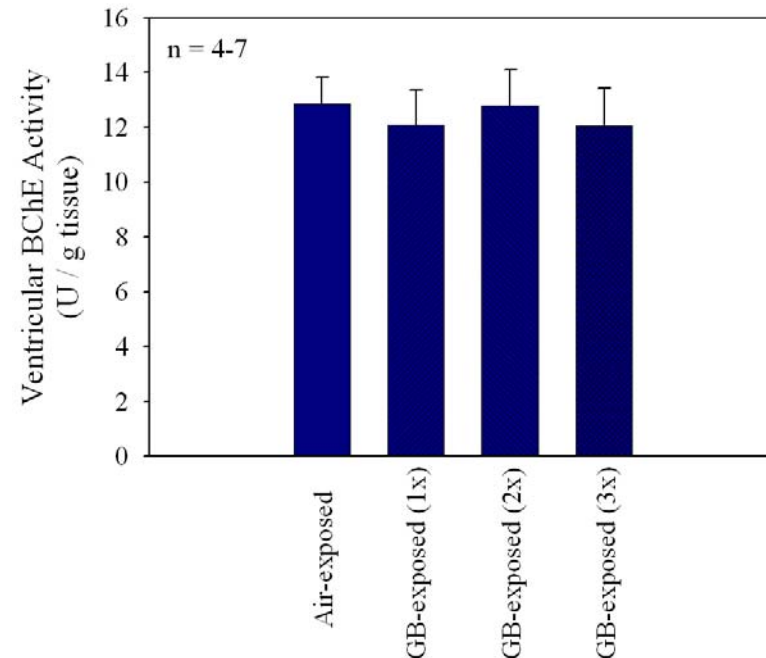
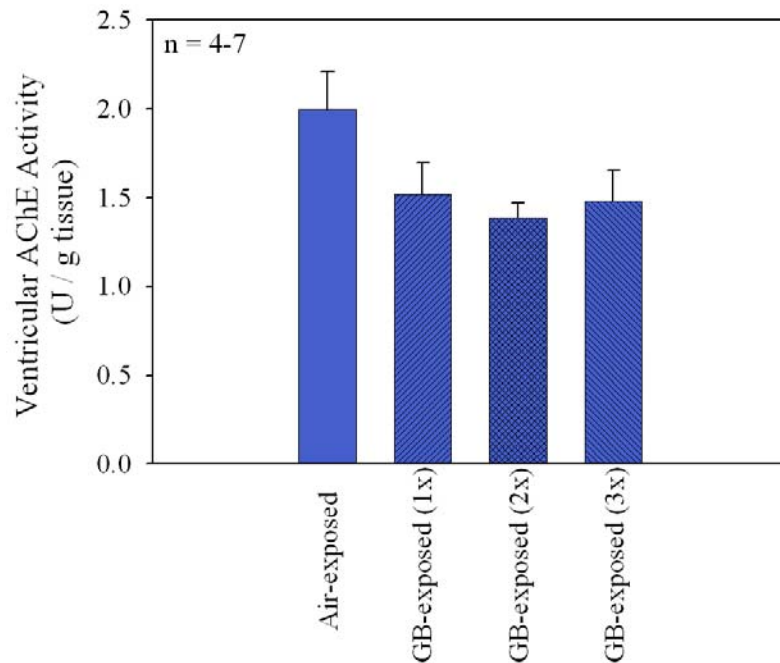
Effect of GB vapor on Autonomic Tone

- Parasympathetic activity was enhanced following exposure #1.
- This change was not seen following the 2nd and 3rd exposures, suggesting that tolerance had developed.

db7 Wavelet Transform



Ventricular Cholinesterase Activity

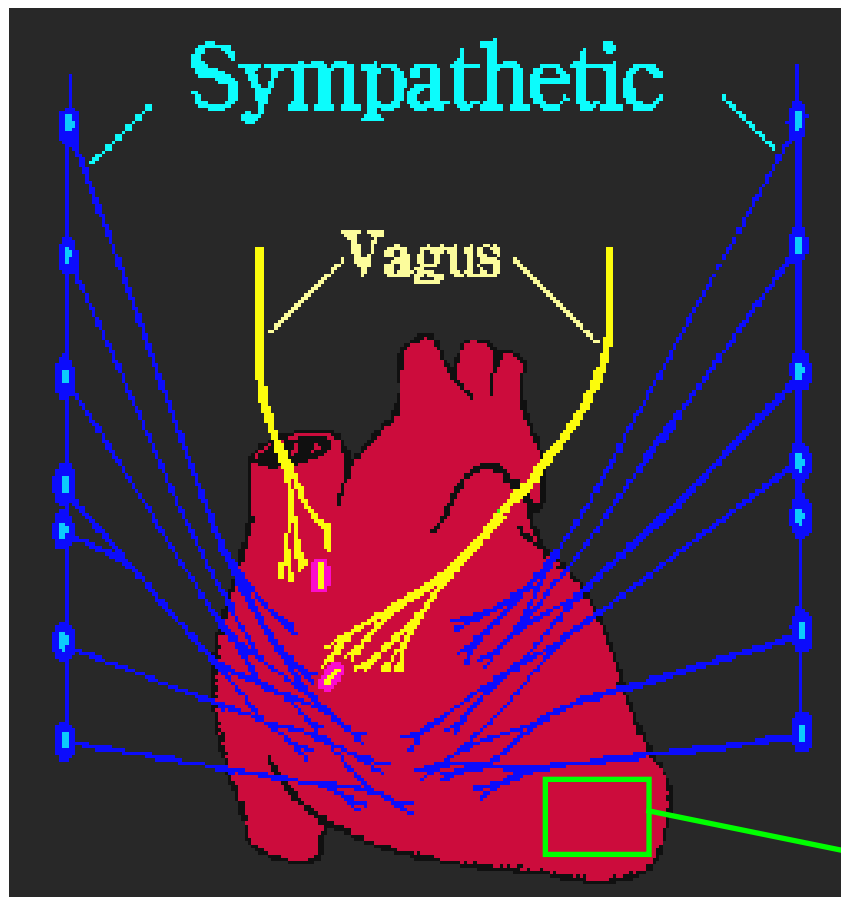


- AChE activity in the left ventricle decreased over the 3-exposure sequence
- BChE activity in the left ventricle was unaffected by exposure to GB



ECPC

Innervation of the Heart



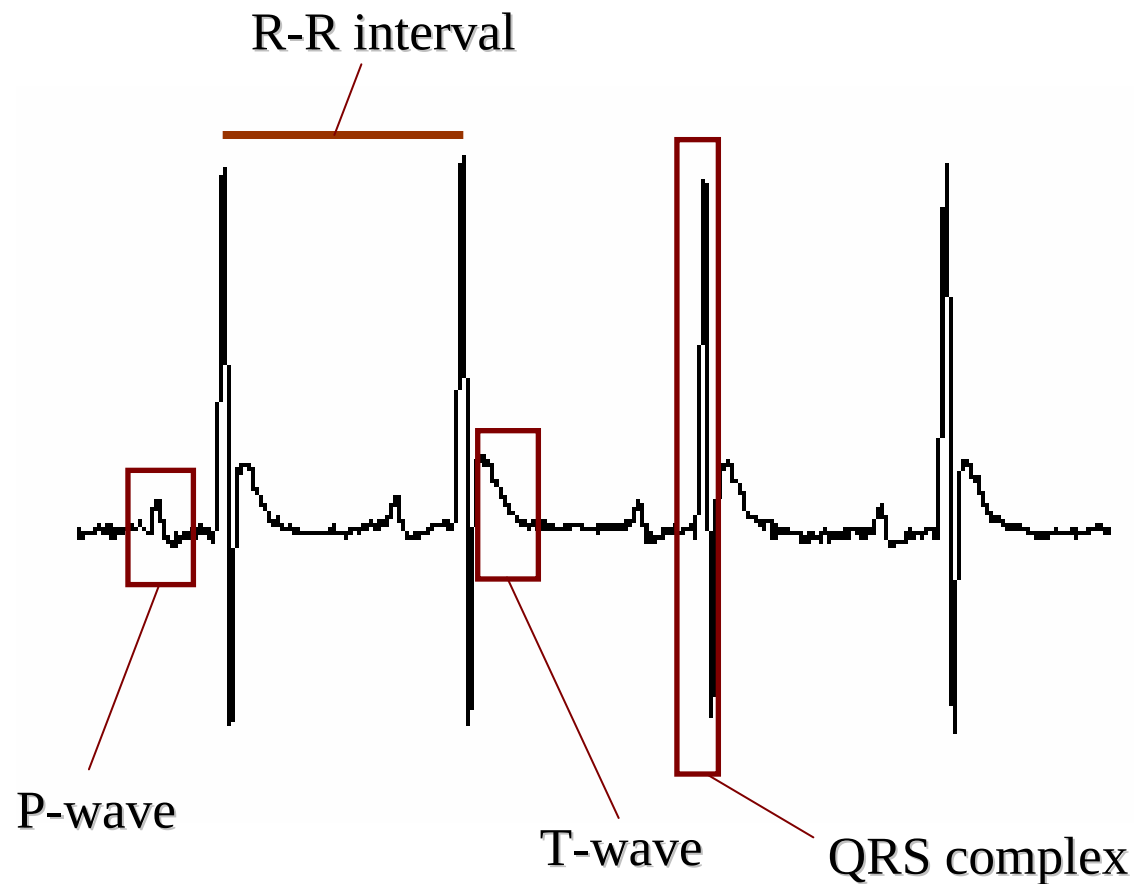
- Parasympathetic innervation is concentrated at the SA and AV nodes.

Region of ventricular tissue sample



ECBC

ECG Analysis



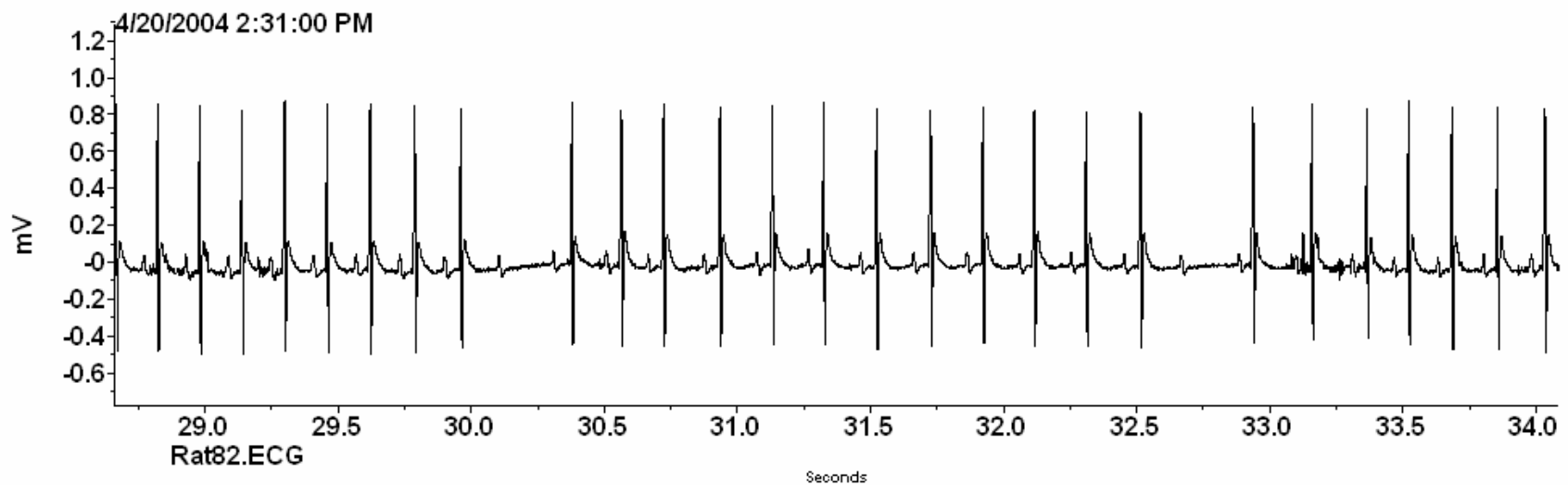
- R-R interval – time between successive ventricular beats
- QRS complex – ventricular contraction
- T-wave – ventricular repolarization
- QT segment – time from ventricular contraction to the end of ventricular repolarization
- PR segment – time for atrial depolarization to enter the ventricles via the AV node



ECBC

Arrhythmias

Transient Ventricular Asystole following GB exposure

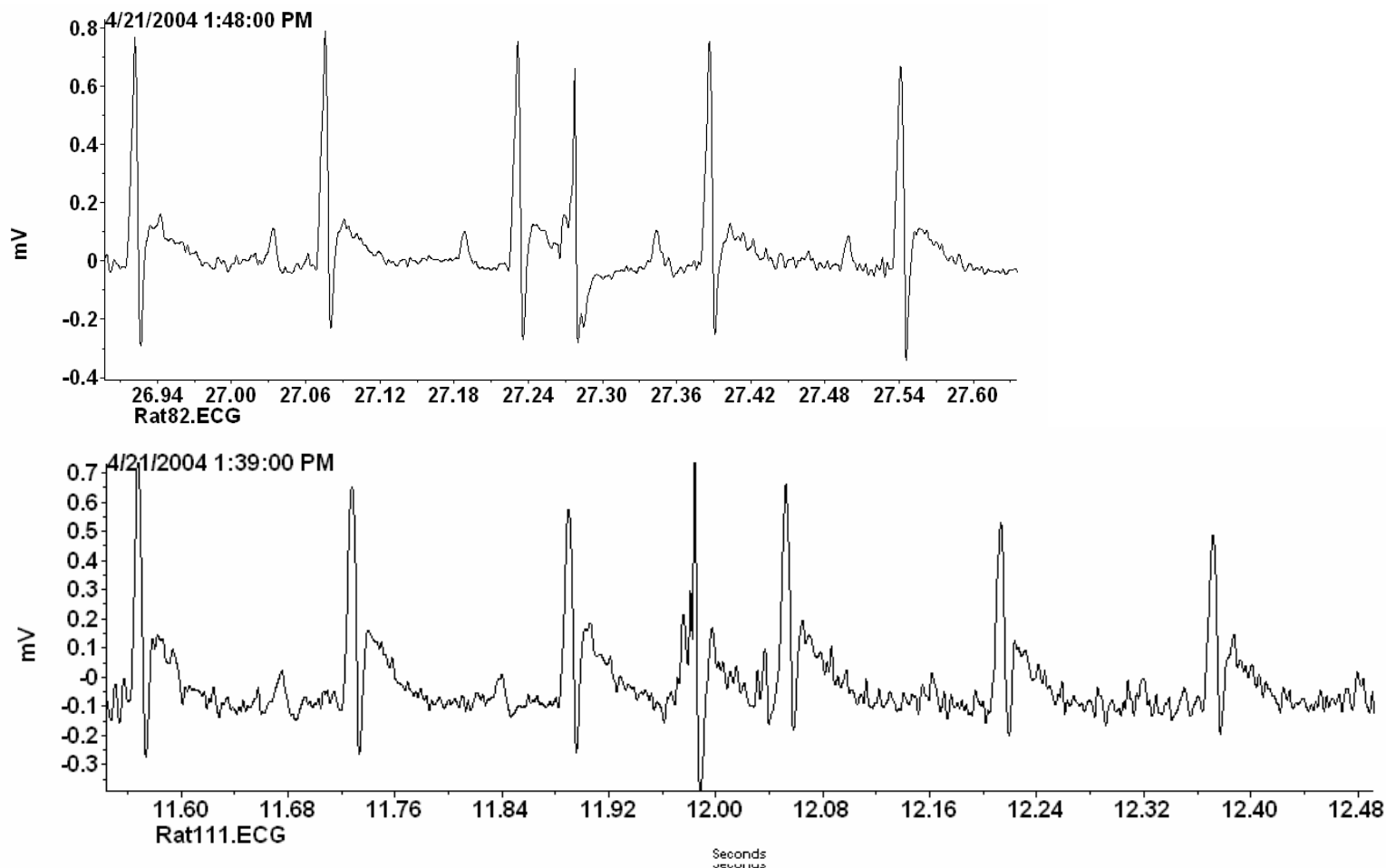




ECBC

Arrhythmias

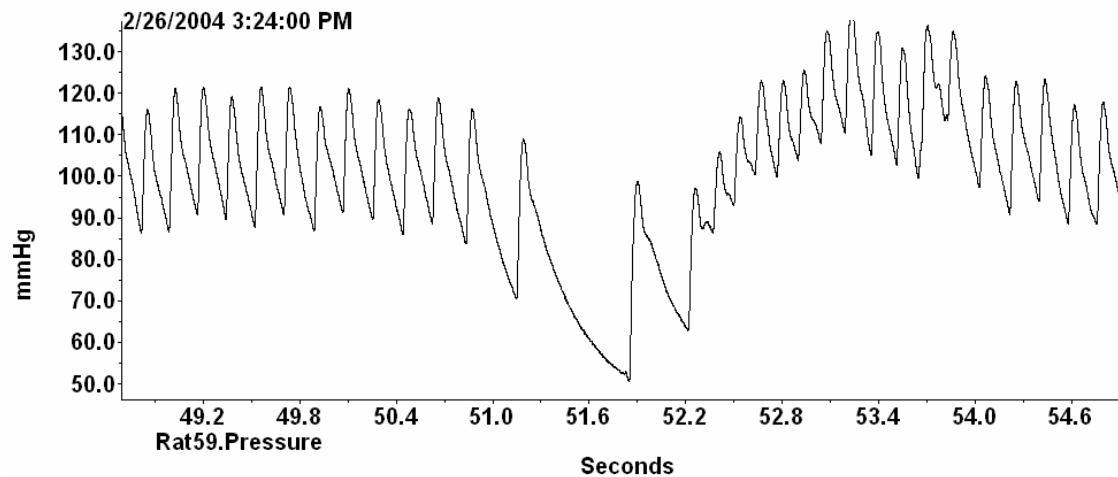
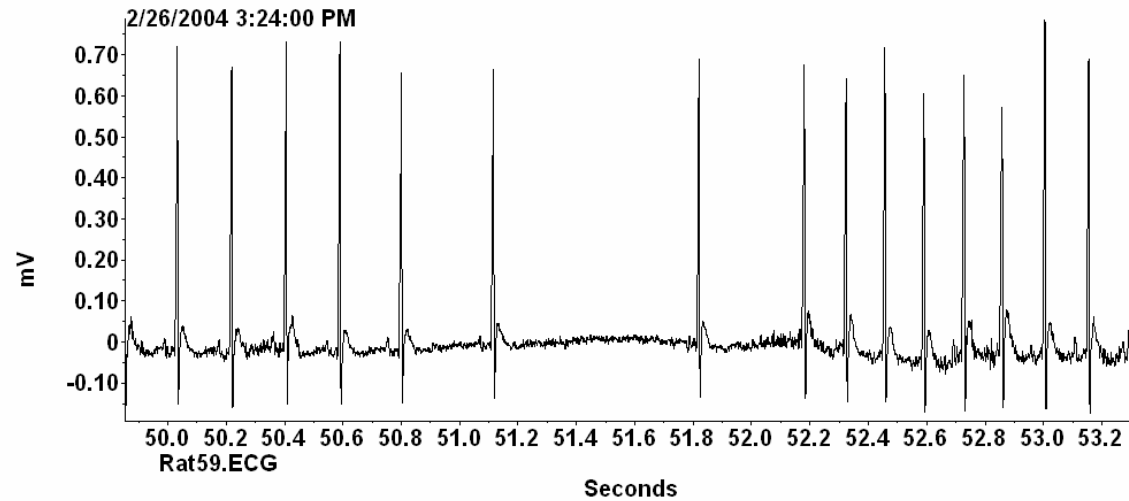
Pre-mature ventricular beats following GB exposure





ECBC

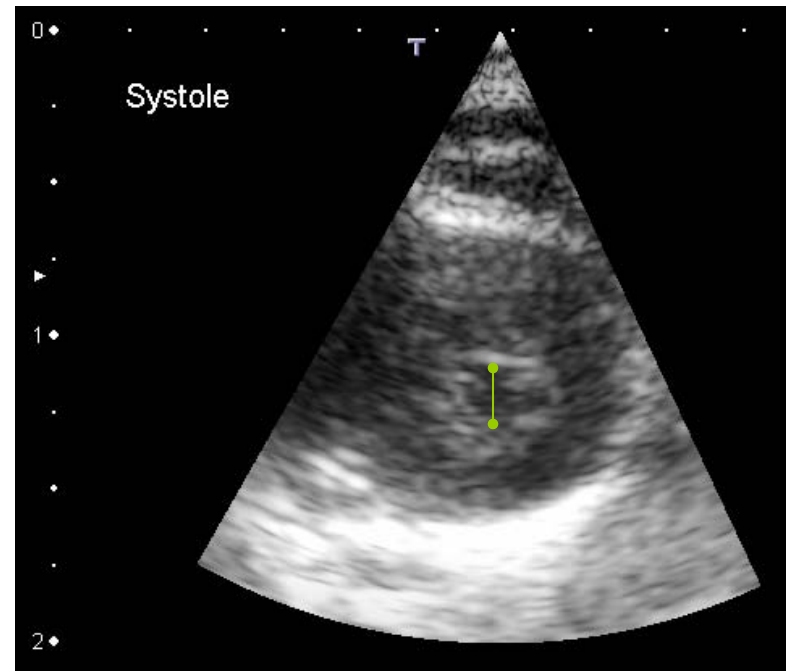
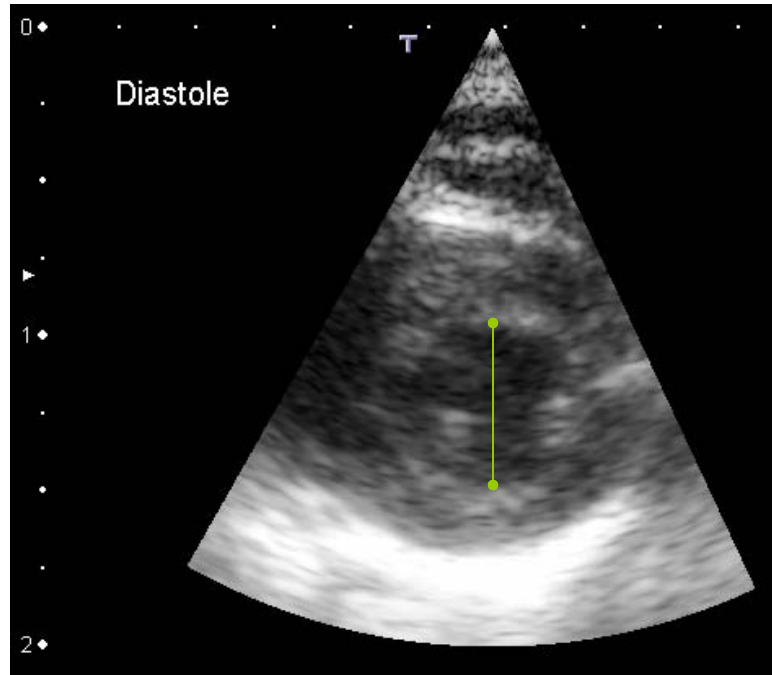
Arrhythmias





ECBC

Ventricular Ultrasound



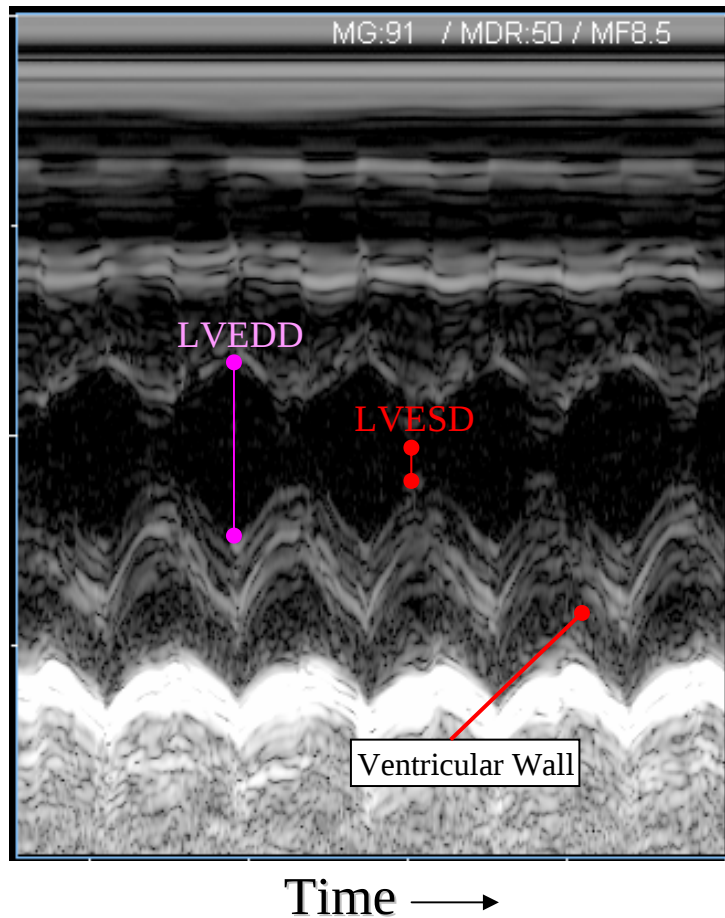
- Two-dimensional echo M-mode images were obtained (2cm depth, focus 0.75cm) from a left parasternal window.
- M-mode left ventricular measurements were made according to American Society of Echocardiography guidelines (Sahn et al. 1978).



ECBC

Fractional Shortening

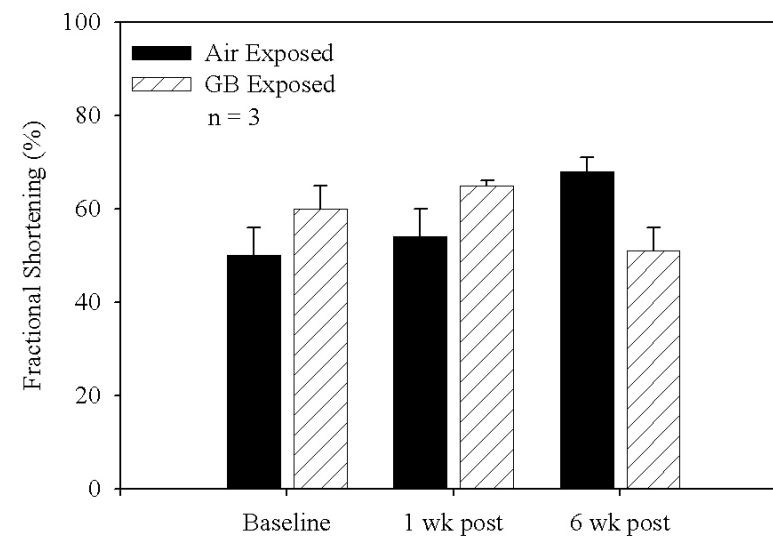
Left Ventricular Diameter



LVEDD = left ventricular end diastolic dimension

LVESD = left ventricular end systolic dimension

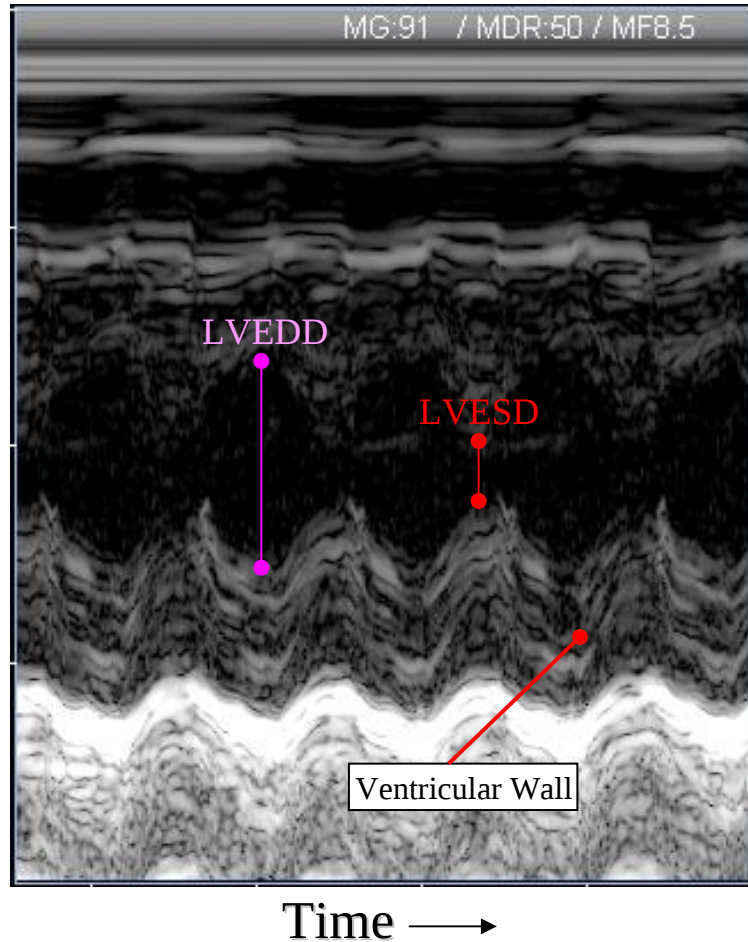
- A measure of left ventricular contractility
- Fractional shortening (%) = $\frac{(\text{end-diastolic dimension} - \text{end-systolic dimension})}{\text{end-diastolic dimension}} \times 100$





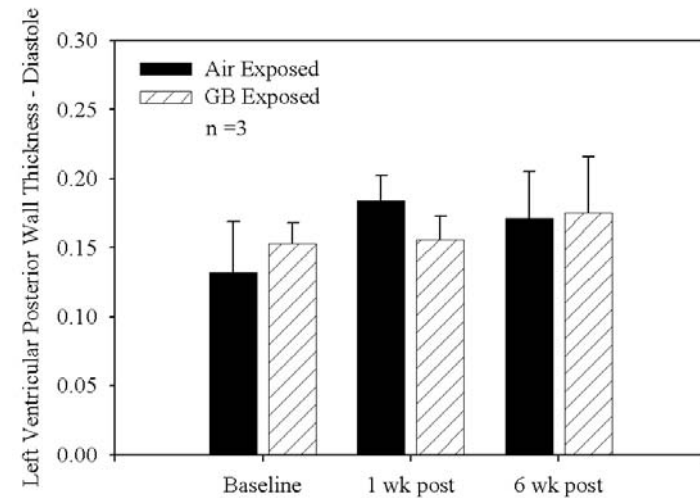
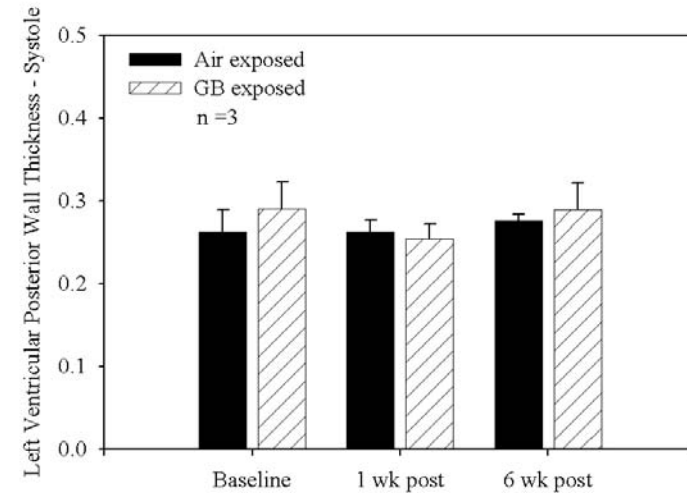
Ventricular Wall Thickness

Left Ventricular Diameter



LVEDD = left ventricular end diastolic dimension

LVESD = left ventricular end systolic dimension





ECBC

Summary

- Exposure to a non-lethal level of GB vapor produces changes in autonomic tone in the heart.
- Repeated exposure produces tolerance to this effect of GB vapor.
- Tolerance in the heart is not likely due to decreased inhibition of AChE, increased BChE activity.
- There is no chronic change in ventricular function, suggesting that GB-induced cardiac changes are transient.



ECBC

Acknowledgements



Stanley Hulet, Ph.D.
Edward M. Jakubowski, Ph.D.
David Burnett
William Muse
Jacqueline Scotto
Emily Davis
Bernard Benton
Jeffry S. Forster
Sharon Reutter, Ph.D.
Robert Mioduszewski, Ph.D.
Sandra Thomson, Ph.D.



George Wien
Michele Smith
Michele Vero
Leslie Hamilton
Darren Yaeger



S. Filip To, Ph.D.



Edmund K. Kerut, M.D.
Thomas Giles, M.D.



Dennis B. Miller
Jill R. Jarvis
Kathy Matson
Charles Crouse
Ronald Evans
Jeff McGuire
Timothy T. Belski
Julie Renner
Megan Harris