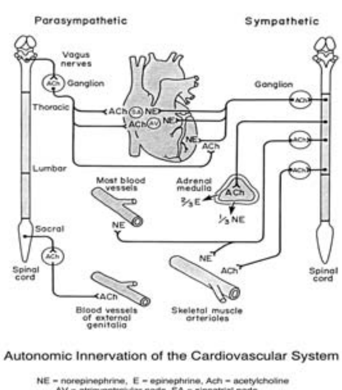
Cardiac Autonomic Remodeling and Susceptibility to Sudden Cardiac Death: Effect of Endurance Exercise Training

George E. Billman, Ph.D., F.A.H.A.
Department of Physiology and Cell Biology,
The Ohio State University, Columbus, OH

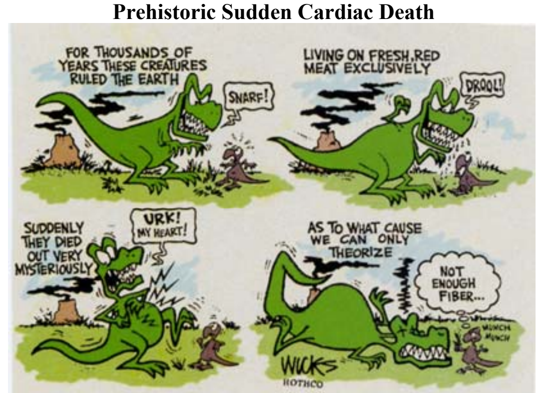
Review of the Autonomic Nervous System

Three Divisions:

- **Parasympathetic Nervous System**
- **Sympathetic Nervous System**
- **Enteric Nervous System**

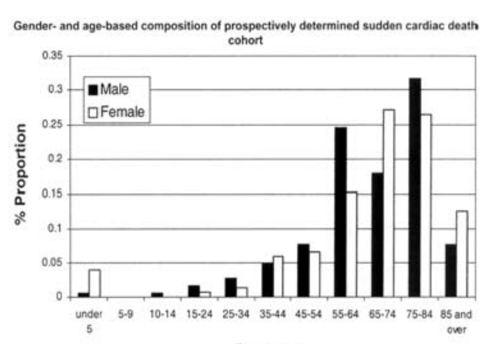


Prehistoric Sudden Cardiac Death



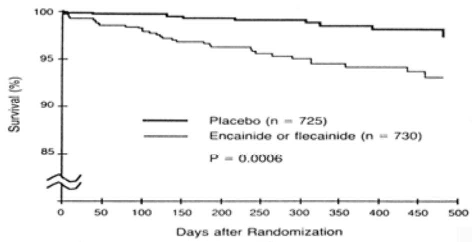
Sudden Death Background Information

- **Sudden death is the leading cause of death in industrial countries. In the United States 300,000 to 500,000 die suddenly each year. (Zheng et al., *Circulation* 104: 2158-2163, 2001; Abildstrom et al., *Cardiac Electrophysiol Rev.* 3: 177-179, 1999)**
- **Holter analysis reveals that ventricular tachyarrhythmias account for 75-93% of the deaths. (Hinkle & Thaler *Circulation* 65: 457-464, 1982, Bayes et al., *Am Heart J.* 117: 151-159, 1989)**
- **Only minority of these patients had a known history of heart disease yet up to 90% were shown to have coronary artery disease post mortum**
- **"Only about 1% of the victims of cardiac arrest are resuscitated and survive to leave the hospital." (Bigger, *Cardiac Electrophysiol Rev.* 1/2: 198-204, 1997)**



(Chugh et al., *Prog Cardiovasc Dis* 51: 213-228, 2008)

Results of the CAST Study



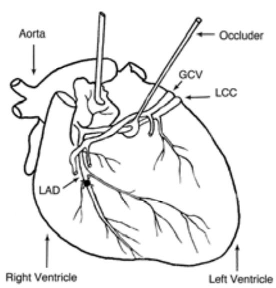
Survival among 1455 patients randomly assigned to receive encainide or flecainide or matching placebo.

Cause of Death was arrhythmia or cardiac arrest.
(*N Engl J Med* 321: 406-412, 1989)

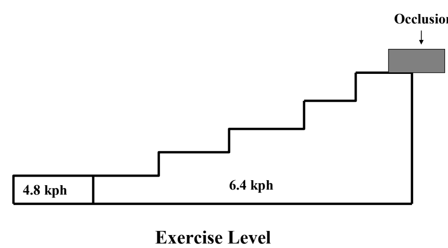
Feline Model of Sudden Death

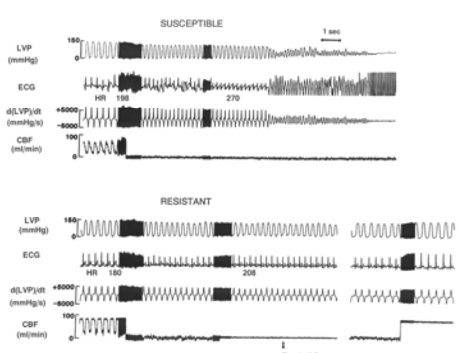
"Curiosity."

Cardiac Instrumentation



Exercise Plus Ischemia test





Myocardial Infarction
(n = 895, 241 died within 72 hr)

Exercise + Ischemia Test
(n = 654, occluder failure n = 49)

Susceptible
(had VF, n = 365, 60.2%)

Defib*
(n = 310)

No Defib
(n = 55, 15.1 %)

Resistant
(no VF, n = 240)

***Only 5.2% (16 of 310) did not have VF on a 2nd test**

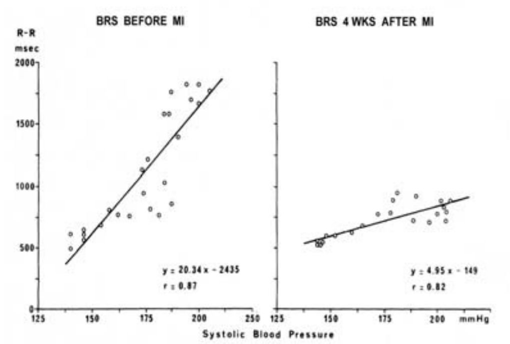
Alterations in Cardiac Autonomic Regulation

- •Cardiac Parasympathetic Remodeling
  - •Baroreceptor Reflex Sensitivity
  - •Heart Rate Variability
- •Cardiac Sympathetic Remodeling
  - •β-adrenergic Receptor Balance

Cardiac Parasympathetic Remodeling

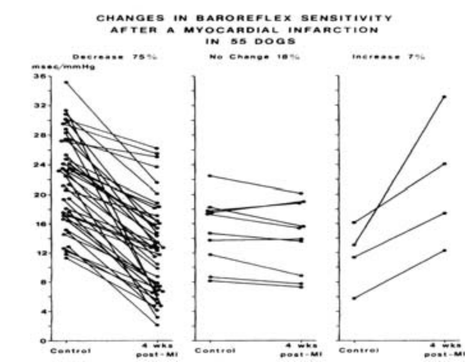
Baroreceptor Reflex Sensitivity

BRS Before and After Myocardial Infarction



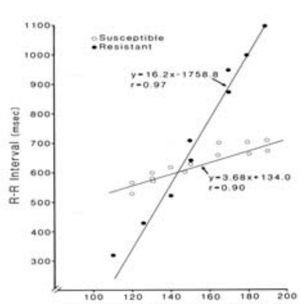
(Schwartz et al. *Circulation* 78:969-979,1988)

BRS Before and After Myocardial Infarction



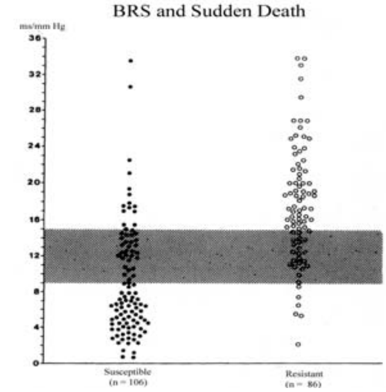
(Schwartz et al. *Circulation* 78:969-979, 1988)

Baroreceptor Reflex Sensitivity



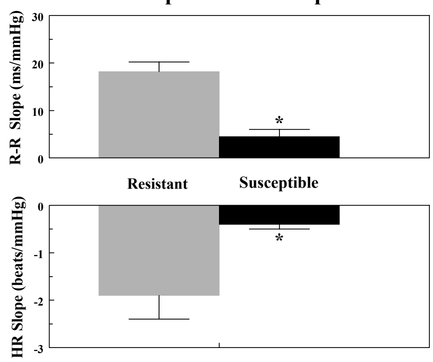
(Billman et al., *Circulation* 66: 874-880, 1982)

BRS and Sudden Death



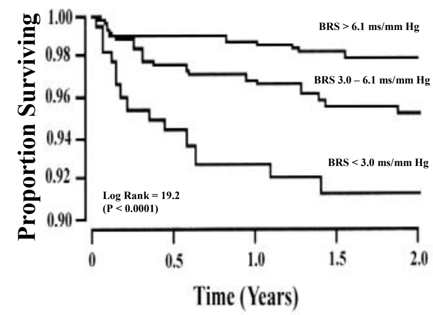
(Schwartz et al. *Circulation* 78:969-979, 1988)

Baroreceptor Reflex Response



(Billman *Pharmacol & Therap* 111:808-835, 2006)

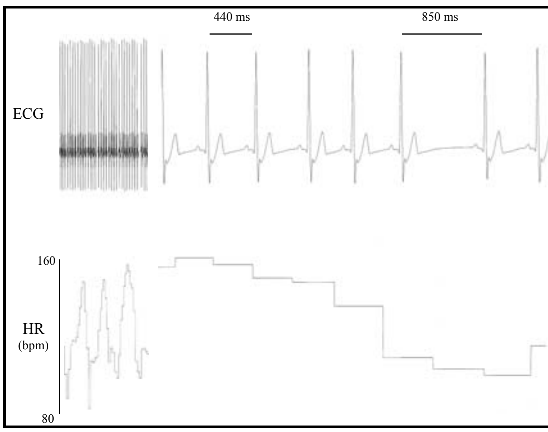
BRS and Cardiac Mortality after Myocardial Infarction



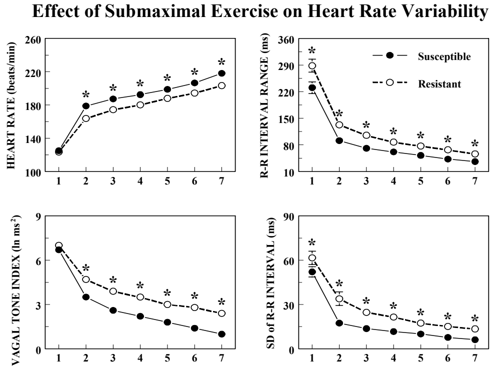
(La Rovere et al., *Lancet* 351: 478-484, 1998)

Cardiac Parasympathetic Remodeling

Heart Rate Variability (HRV)

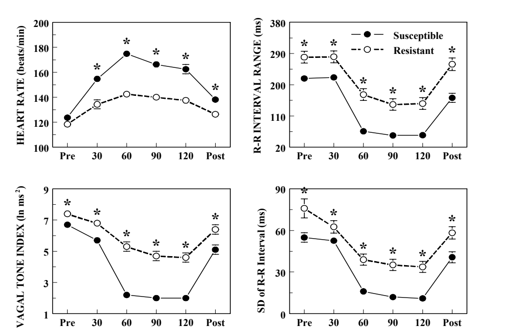


Effect of Submaximal Exercise on Heart Rate Variability



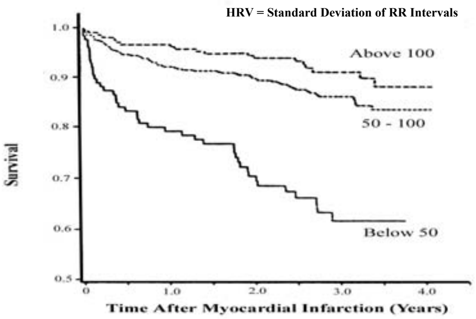
(Billman *Pharmacol & Therap* 111:808-835, 2006)

Effect of Coronary Artery Occlusion on Heart Rate Variability



(Billman *Pharmacol & Therap* 111:808-835, 2006)

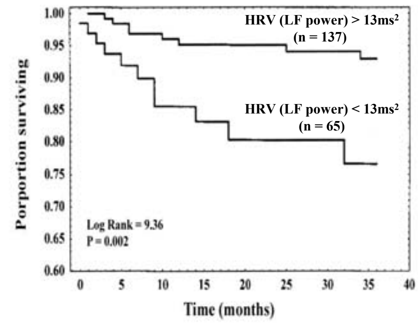
HRV and Survival Post-MI



(Kleiger et al., *Am J Cardiol* 59: 256-262, 1987)

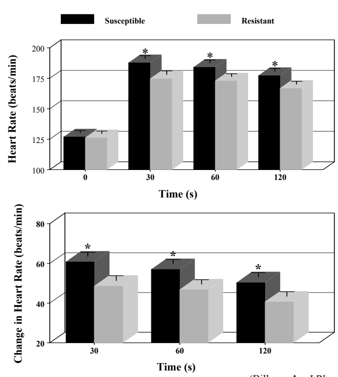
HRV and Sudden Cardiac Death

Congestive Heart Failure Patients



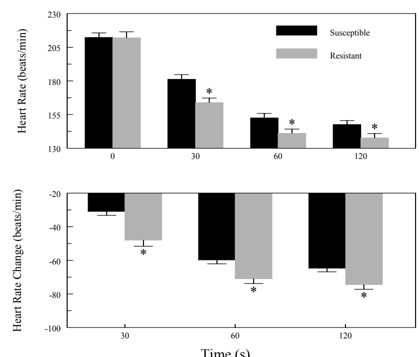
(La Rovere et al., *Circulation* 107: 565-570, 2003)

Heart Rate Response to the Onset of Exercise



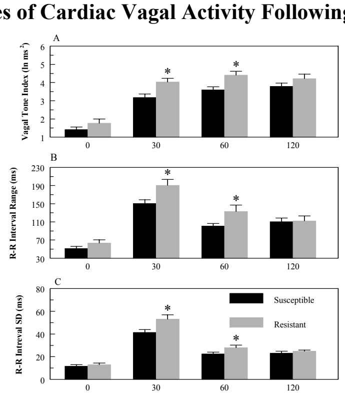
(Billman *Am J Physiol* 291:H429-H435, 2006)

Heart Rate Recovery Following Exercise



(Smith et al., *Am J Physiol* 288:H1763-H1769, 2005)

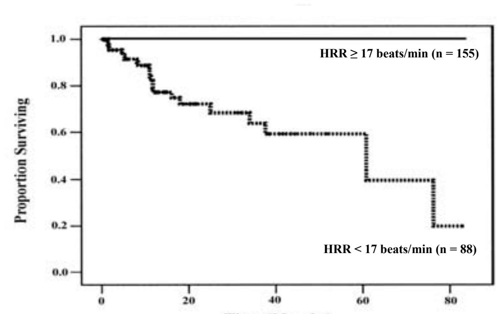
Indices of Cardiac Vagal Activity Following Exercise



(Smith et al., *Am J Physiol* 288:H1763-H1769, 2005)

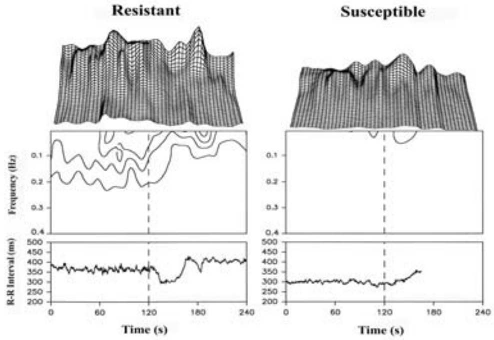
Heart Rate Recovery (HRR) and Sudden Cardiac Death

Heart Failure Patients



Guazzi et al., *Int J Cardiol* In press, 2009)

Wavelet Analysis

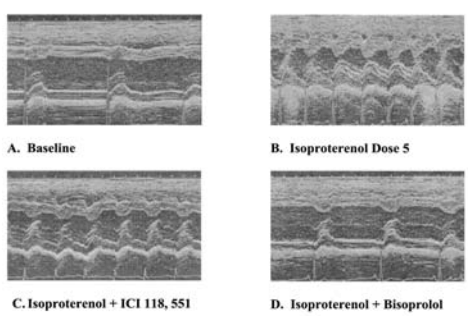


(Billman *Pharmacol & Therap* 111:808-835, 2006)

Cardiac Sympathetic Remodeling

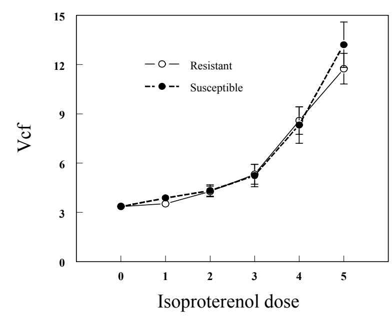
β-adrenergic receptor Balance

Susceptible Animal Echocardiogram



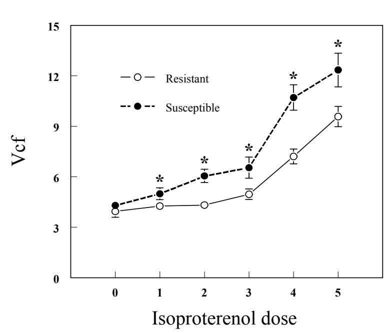
(Houle et al., *J Appl Physiol* 91: 1627-1637, 2001)

Pre-Infarct Isoproterenol Response



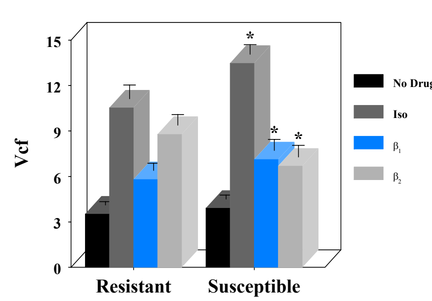
(Houle et al., *J Appl Physiol* 91: 1627-1637, 2001)

Post-Infarct Isoproterenol Response



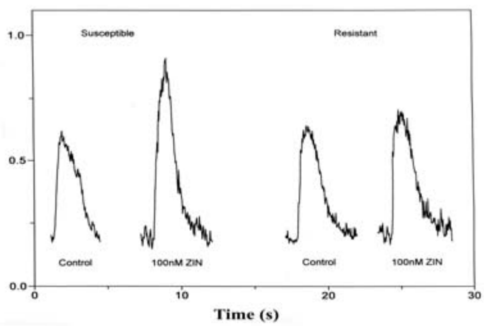
(Houle et al., *J Appl Physiol* 91: 1627-1637, 2001)

Beta-adrenergic Receptor Effects on Cardiac Contractility



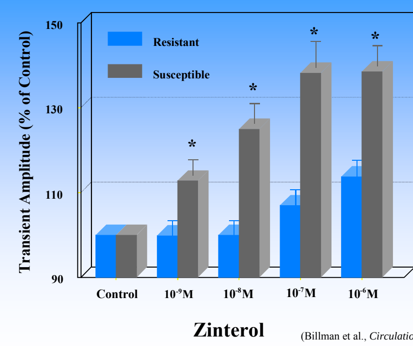
(Houle et al., *J Appl Physiol* 91: 1627-1637, 2001)

Cardiomyocyte Calcium Transient



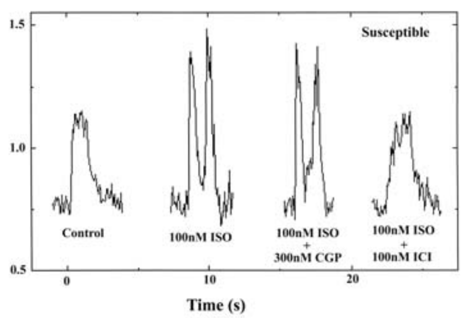
(Billman et al., *Circulation* 96:1914-1922, 1997)

Effect of Zinterol on Myocyte Calcium Transient Amplitude



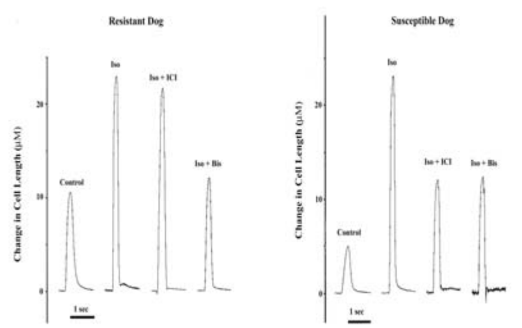
(Billman et al., *Circulation* 96:1914-1922, 1997)

Calcium Aftertransients in a Single Cell



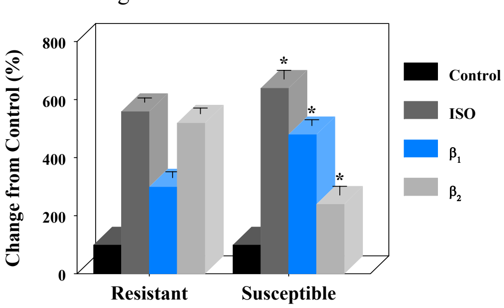
(Billman et al., *Circulation* 96:1914-1922, 1997)

Beta-adrenergic Receptor Effects on Single Cell Length



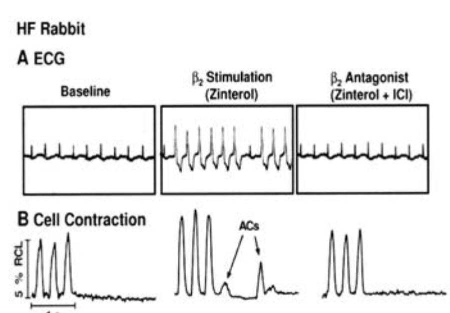
(Houle et al., *J Appl Physiol* 91: 1627-1637, 2001)

Single Cell dL/dt Maximum



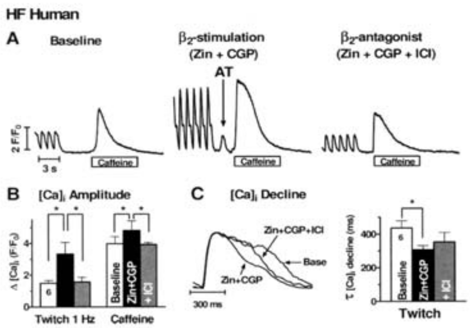
(Houle et al., *J Appl Physiol* 91: 1627-1637, 2001)

β_2-adrenoceptor-induced Arrhythmias



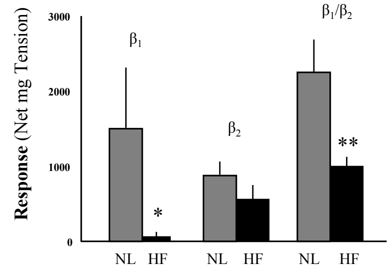
(DeSantiago et al., *Circ Res* 102: 1389-1397, 2008)

Heart Failure Enhanced β_2-adrenoceptor Response



(DeSantiago et al., *Circ Res* 102: 1389-1397, 2008)

Maximum Tension (Human Right Ventricular Trabeculae)



NL = normal, n = 7; HF = heart failure, n = 9)

(Bristow et al., *Circ Res* 59: 297-309, 1986)

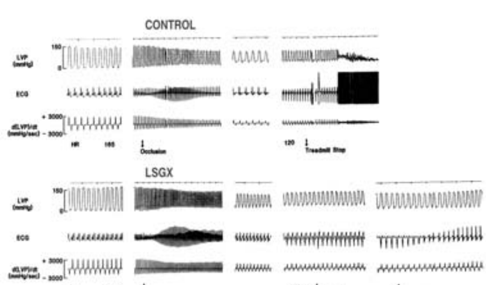
Conclusions

Cardiac Autonomic Remodeling

- **Both myocardial infarction and heart failure provoke reductions in indices (BRS and HRV) of cardiac vagal regulation.**
- **Both myocardial infarction and heart failure also alter cardiac β-adrenergic balance that leads to an enhanced β_2-adrenergic receptor sensitivity**
- **Cardiac autonomic remodeling (decreased cardiac vagal and enhanced sympathetic activity) results in an increased risk for sudden cardiac death (VF)**

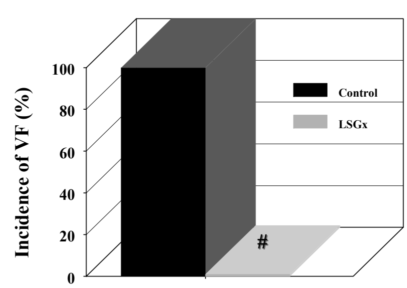
Effect of Autonomic Interventions on Susceptibility to Ventricular Fibrillation

Effect of Left Stellectomy on Susceptibility to VF



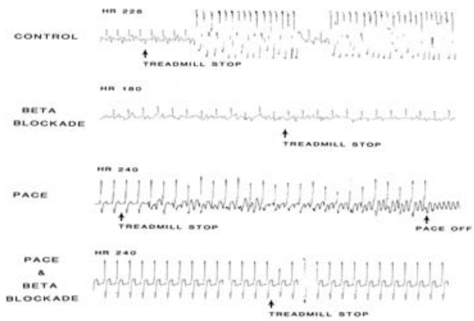
(Billman *Pharmacol & Therap* 111:808-835, 2006)

Effect of Left Stellectomy on Susceptibility to VF

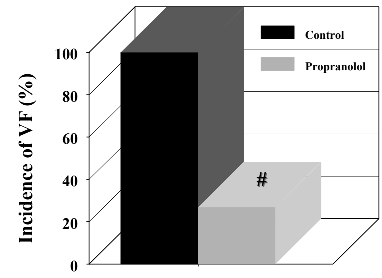


(VF prevented in 11 of 11 dogs, 100%)

Effect of Beta-adrenergic Receptor Blockade

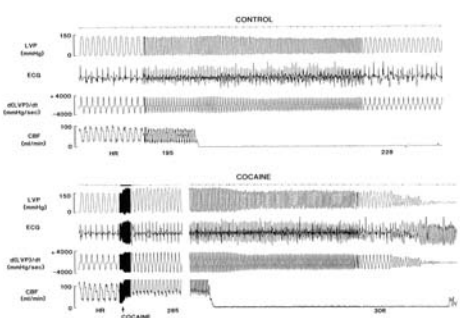


Effect of a Non-selective Beta-adrenergic Receptor Antagonist on Susceptibility to VF



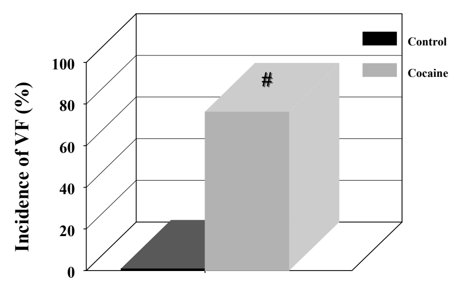
(VF prevented in 24 of 38 dogs, 63%)

Effect of Cocaine on Susceptibility to VF



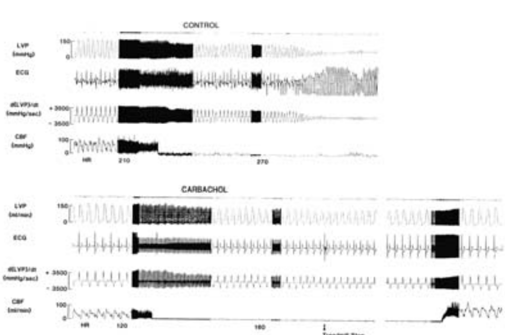
(Billman & Hoskins *FASEB J* 2:2990-2995, 1989)

Effect of Cocaine on Susceptibility to VF



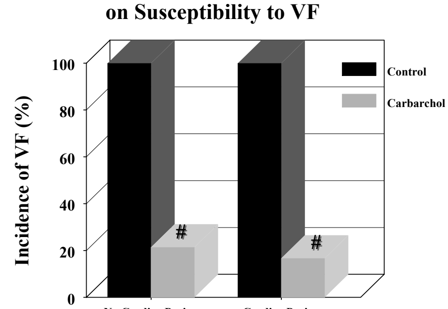
(VF induced in 42 of 55 dogs, 76%)

Effect of a Cholinergic Agonist on Susceptibility to VF



(Billman *FASEB J* 4:1668-1673, 1990)

Effect of a Muscarenic Receptor Agonist on Susceptibility to VF



(VF prevented in 11 of 14 dogs, 79%) (VF prevented in 5 of 6 dogs, 83%)

(Billman *FASEB J* 4:1668-1673, 1990)

Conclusion

Interventions that either enhance cardiac vagal regulation or reduce cardiac sympathetic activity can protect against ventricular fibrillation

Interventions to "Reverse" Cardiac Autonomic Remodeling

- **Endurance Exercise Training**

Myocardial Infarction
(n = 60, 14 died within 72 hr)

Exercise + Ischemia Test
(n = 46, occluder failure n = 7)

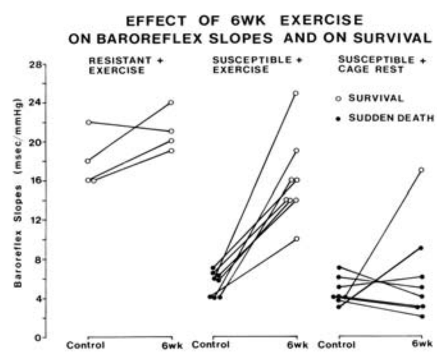
Susceptible
(had VF, n = 26, unable to defib n = 3)

- **Ex Training** (n = 9)
- **Sedentary** (n = 14*)

Resistant
(no VF, n = 13)

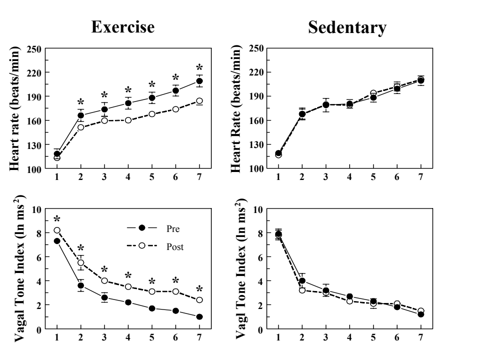
- **Ex Training** (n = 8)
- **Sedentary** (n = 5)

* 4 animals died, unable to re-test 3 dogs due to occluder failure



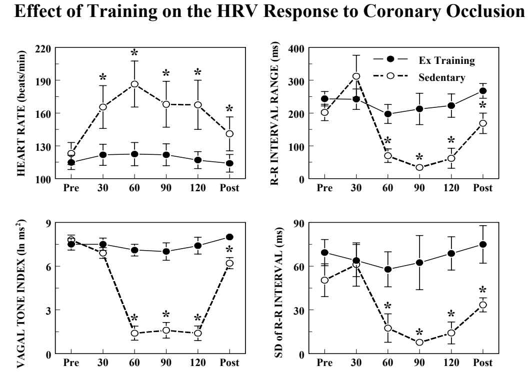
(Billman et al., *Circulation* 69: 1182-1189, 1984)

Effect of Training on the HRV Response to Exercise



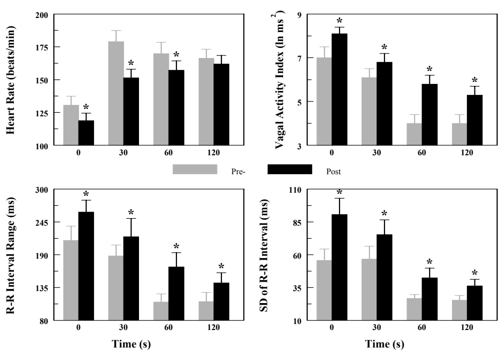
(Billman et al., *Am J Physiol* 290: H2590-H2599, 2006)

Effect of Training on the HRV Response to Coronary Occlusion



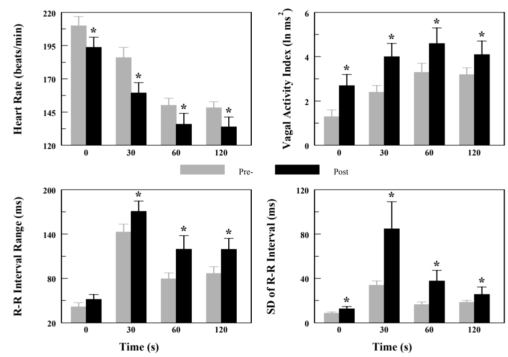
(Billman & Kukielka *J Appl Physiol* 100: 896-906, 2006)

Effect of Training on the HRV Response to Exercise Onset



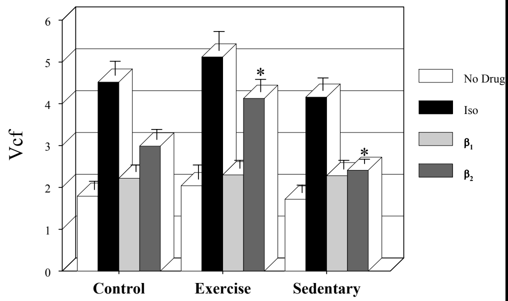
(Billman & Kukielka *J Appl Physiol* 102: 231-240, 2007)

Effect of Training HR Recovery After Exercise



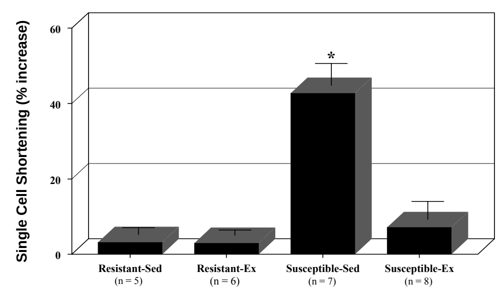
(Billman & Kukielka *J Appl Physiol* 102: 231-240, 2007)

Effect of Beta-adrenoceptor Antagonists on the Maximum Isoproterenol Induced Contractile Response



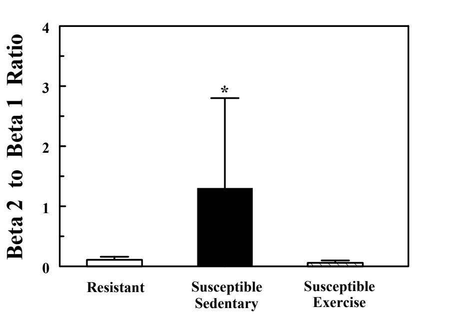
(Billman et al., *Am J Physiol* 290: H2590-H2599, 2006)

Effect of Training on Single Cell Shortening Response to Beta$_2$-adrenoceptor Stimulation



(Billman et al., *Am J Physiol* 290: H2590-H2599, 2006)

Ratio of Beta$_2$- to Beta$_1$- Adrenoceptor mRNA Levels



(Holycross et al. *Am J Physiol* 293: H2702-H2709, 2007)

Conclusion

Endurance exercise training (10-wk treadmill running) produced large increases in cardiac vagal tone and may also have reduced β_2-adrenergic receptor sensitivity in animals susceptible to VF

The Effect of Regular Exercise on Sudden Cardiac Death

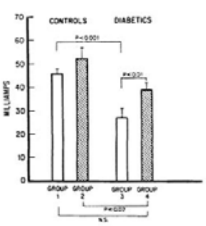
- **Animal Studies**

Exercise Training and Ventricular Arrhythmias: Animal Studies

Study	**Model**	**Results**
Noakes et al. *Circ* 67: 24-30, 1983	Rat - isolated heart, ischemia	↑ VF threshold
Bakth et al. *J Clin Invest* 77: 382-395, 1986	Dog - diabetic and normal, without and without epinephrine	↑ VF threshold
Posel et al. *Circ* 80:138-145, 1989	Rat - isolated heart post MI, ischemia	↑ VF threshold
Arad et al. *Cardiosci* 1:295-299, 1990	Rat- isolated heart (swim training)	No Δ VF threshold
Belichard et al. *Bas Res Cardiol* 87:344-355, 1989	Rat – ischemia (swim training)	↓ arrhythmias
Hamra & McNeil *Med Sci Sports Exerc* 27:993-1002, 1995	Dog- purkinje fibers Ischemia or catechomalines	↓ arrhythmias -ischemia ↑ arrhythmias - catecholamines
Collins et al., *Am J Physiol* 288: H532-H540, 2005	Rat- hypertensive, ischemia	↑ time to arrhythmias
Lujan et al. *Am J Physiol* 291: H2933-H2941, 2006	Rat- bred for high aerobic capacity, ischemia	↓ arrhythmias

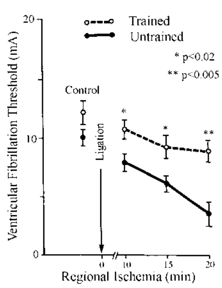
Effect of Exercise Training on Ventricular Fibrillation Threshold

Dog

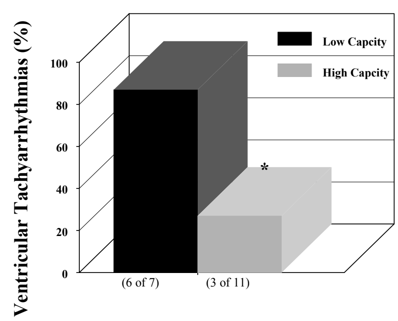


(Bakth et al., *J Clin Invest* 77: 382-389, 1986)

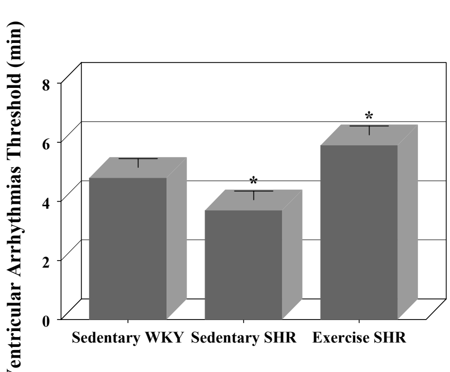
Rat



(Noakes et al., *Circulation* 67: 24-30, 1983)

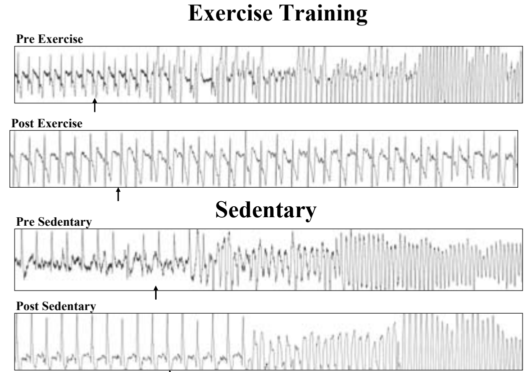


(Lujan et al., *Am J Physiol* 291: H2933-2941, 2006)



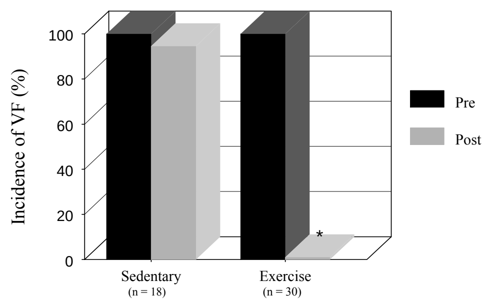
(Collins et al, *Am J Physiol* 288: H532-H540, 2005)

Exercise Training



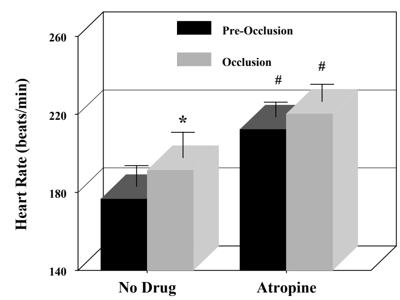
(Billman et al. *Am J Physiol* 290: H2590-H2599, 2006)

Effect of Training on the Susceptibility to Ventricular Fibrillation



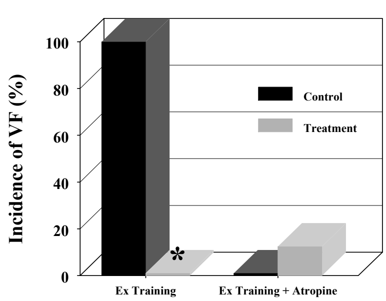
(Billman et al., *Circulation* 69: 1182-1189, 1984; Hull et al., *Circulation* 89: 548-552, 1994; Billman & Kukielka, *J Appl Physiol* 100: 896-906, 2006)

Heart Rate Response to the Exercise + Ischemia Test Atropine Effects - Susceptible



(Billman & Kukielka *J Appl Physiol* 100: 896-906, 2006)

Effect of Atropine on Susceptibility to Ventricular Fibrillation



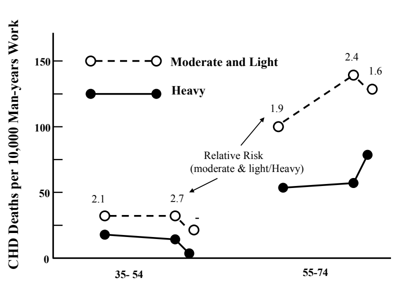
(VF induced in 1 of 8 dogs, 12%)

(Billman & Kukielka *J Appl Physiol* 100: 896-906, 2006)

The Effect of Regular Exercise on Sudden Cardiac Death

•Human Studies

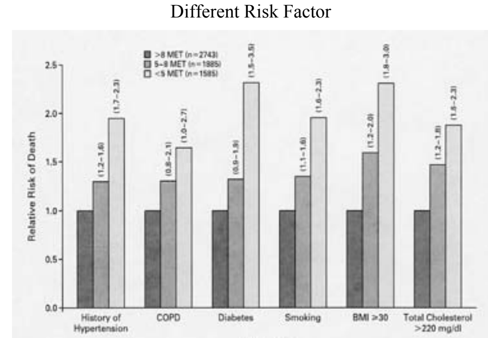
Work Activity and Coronary Heart Mortality



Meta-analysis (32 studies) found that the risk of death from coronary artery disease was significantly lower in individuals with active compared to sedentary occupations.

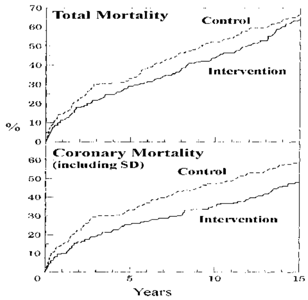
(Berlin & Colditz *Am J Epidemiol* 132: 612, 628, 1990)

Effect of Exercise Capacity on Mortality Risk for Different Risk Factor



(Myers et al. *N Engl J Med* 346: 793-801, 2002)

Exercise Training and Mortality Post-Myocardial Infarction

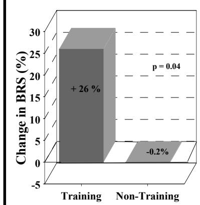


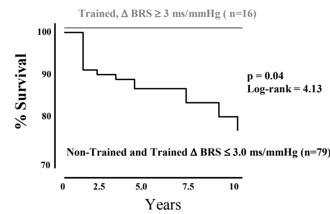
(Hamalainen et al., *Eur Heart J* 16: 1839-1884, 1995)

Meta-analysis (22 studies) found that exercise produced a 20% reduction in overall Mortality. This reduction was due to a reduced cardiovascular mortality, fatal reinfarction, and sudden death during at least the first 3 years following infarction.

(O'Connor et al., *Circulation* 80: 234-244, 1989)

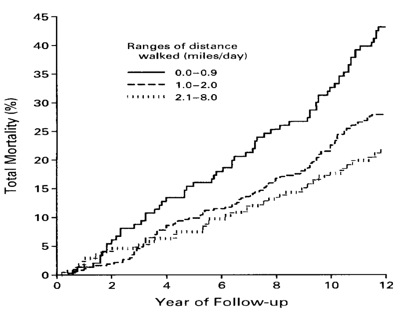
Effect of Exercise Training on Baroreceptor Reflex Sensitivity and Cardiac Mortality





(LaRovere et al. *Circulation* 106: 945-949, 2002)

Effect of Low Intensity Exercise (Walking) on Mortality: Honolulu Heart Program



(Hakim et al., *N Engl J Med* 338: 94-99, 1998)

Risk for Sudden Death During Exercise: Effect of Regular Physical Activity

- **Two different districts in Berlin (population = 219,251)**
- **18 month, 77 confirmed deaths due to VF**
- **activity level determined**

Activity Level	VF deaths/10^5 person years	Relative Risk for VF (during exercise)
1 (sedentary)	4.69	398.5
2	4.25	150
3	2.63	-
4 (highest)	0.92	4.0

"The protective effect of regular physical activity for scd by far exceeds the risk increase of the actual strenuous situation."

(Bartels et al., *Med Klin* 92: 319-325, 1997)

Risk for Sudden Death During Exercise: Effect of Regular Physical Activity (Harvard Physician Study)

Frequency of Habitual Vigorous Exercise	Sudden Deaths Total (n=122)	Sudden Deaths Related to Vigorous Exercise (n = 23)	Relative Risk (95% CI)
<1 time/wk	32	3	74.1 (22.0 – 249)
1 – 4 times/wk	67	13	18.9 (10.2 – 35.1)
≥ 5 times/wk	23	7	10.9 (4.5 – 26.2)

- **The relative risk for sudden death increased during or following vigorous exertion**
- **"However, the absolute risk for sudden death during any particular episode of vigorous exertion was extremely low (1 sudden death per 1.51 million episodes)."**
- **Habitual exercise significantly decreased even this small risk for sudden death**.

(Albert et al., *N Engl J Med* 343: 21355-1361, 2000)

Summary

- Individuals that are physically active have a lower risk for adverse cardiac events including sudden cardiac death.
- Although the absolute risk for sudden death increases during rigorous exertion the risk was extremely low, as low as 1 sudden death per 1.51 million exercise episodes. Even this low probability for sudden death during exercise was reduced in individuals with a history of regular physical activity compared with more sedentary patients.
- Endurance exercise training improved cardiac balance (increased cardiac vagal and reduced sympathetic activity) in both man and animals and prevented ventricular fibrillation in animals susceptible to malignant arrhythmias.

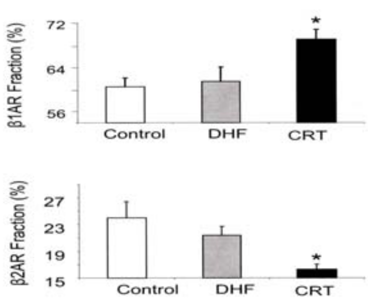
CONCLUSION

These data suggest that endurance exercise training can improve cardiac autonomic balance (increase cardiac vagal and decrease sympathetic activity) increasing cardiac electrical stability and could thereby, reduce the risk for lethal cardiac arrhythmias.

Interventions to "Reverse" Cardiac Autonomic Remodeling

- **Cardiac Resynchronization Therapy**

Effect of Cardiac Resynchronization Therapy on β-adrenoceptor Expression



(Chakir et al., *Circulation* 119: 1231-1240, 2009)

Summary

- **Both myocardial infarction and heart failure induce remodeling of cardiac autonomic regulation, decreasing cardiac vagal and enhancing β_2-adrenergic balance**
- **Alterations in cardiac autonomic balance increase the risk for sudden cardiac death due to ventricular fibrillation**
- **Both exercise training and CRT can reverse these abnormalities in cardiac autonomic balance**

Conclusion

Thus, by restoring a more normal cardiac autonomic balance (i.e., "reverse" remodeling) exercise training or CRT could increase the cardiac electrical stability and thereby, reduce the risk for lethal cardiac arrhythmias.

Some Unanswered Questions

1. **How are changes in atrial pacemaker activity (BRS & HRV) related to the changes ventricular electrical properties that trigger lethal arrhythmias?**
2. **What are the mechanisms responsible for altered cardiac autonomic regulation following myocardial infarction or heart failure? Afferent, efferent, central processing, or end organ changes?**
3. **What are the mechanisms responsible for the change in cardiac autonomic regulation induced by exercise training?**
4. **What are the cellular/molecular mechanisms that link changes cardiac autonomic regulation to an increased risk for sudden cardiac death and how are they altered by exercise training?**