

# Baroreflex Activation Therapy for the Treatment of Heart Failure

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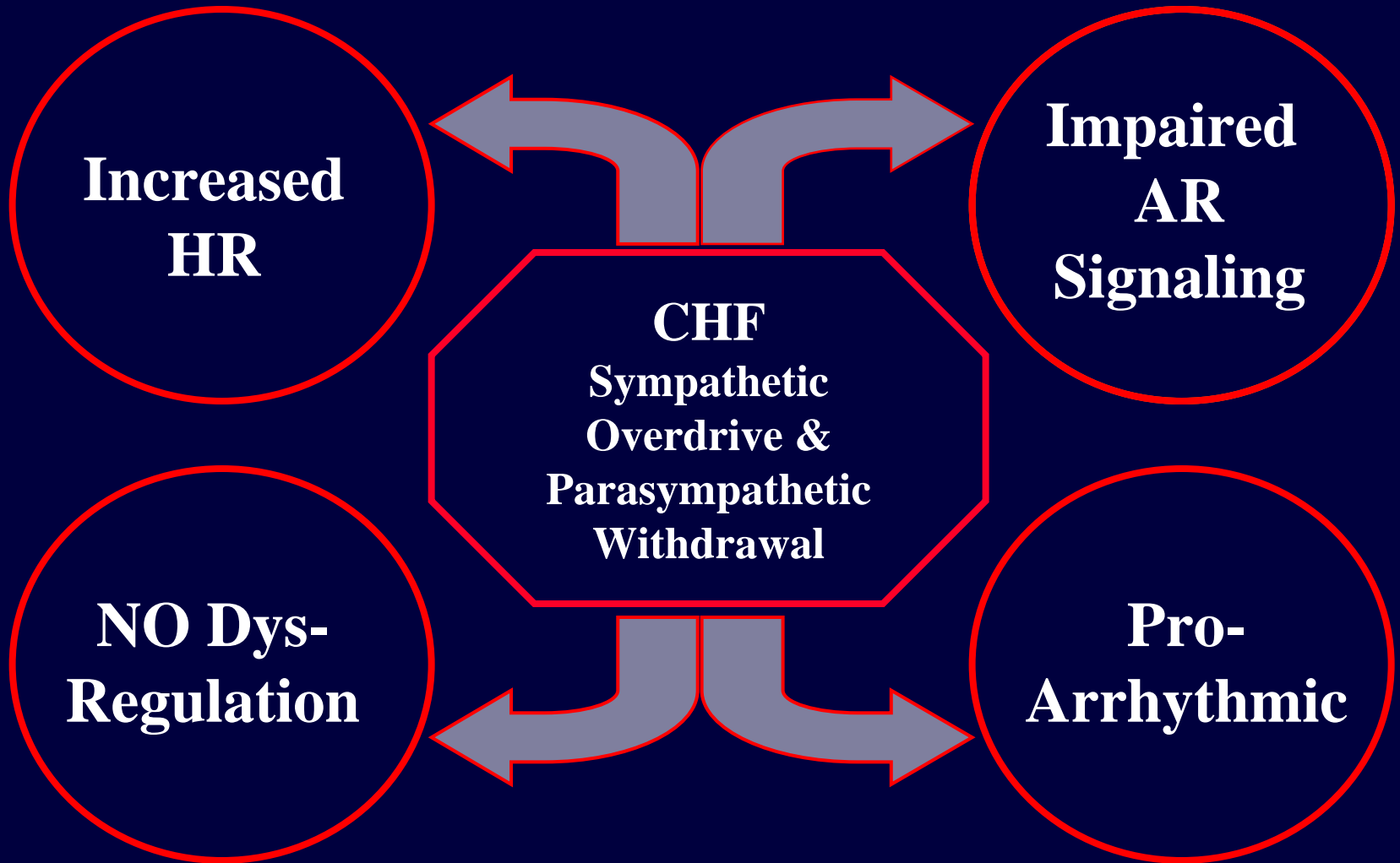
*Professor of Medicine*

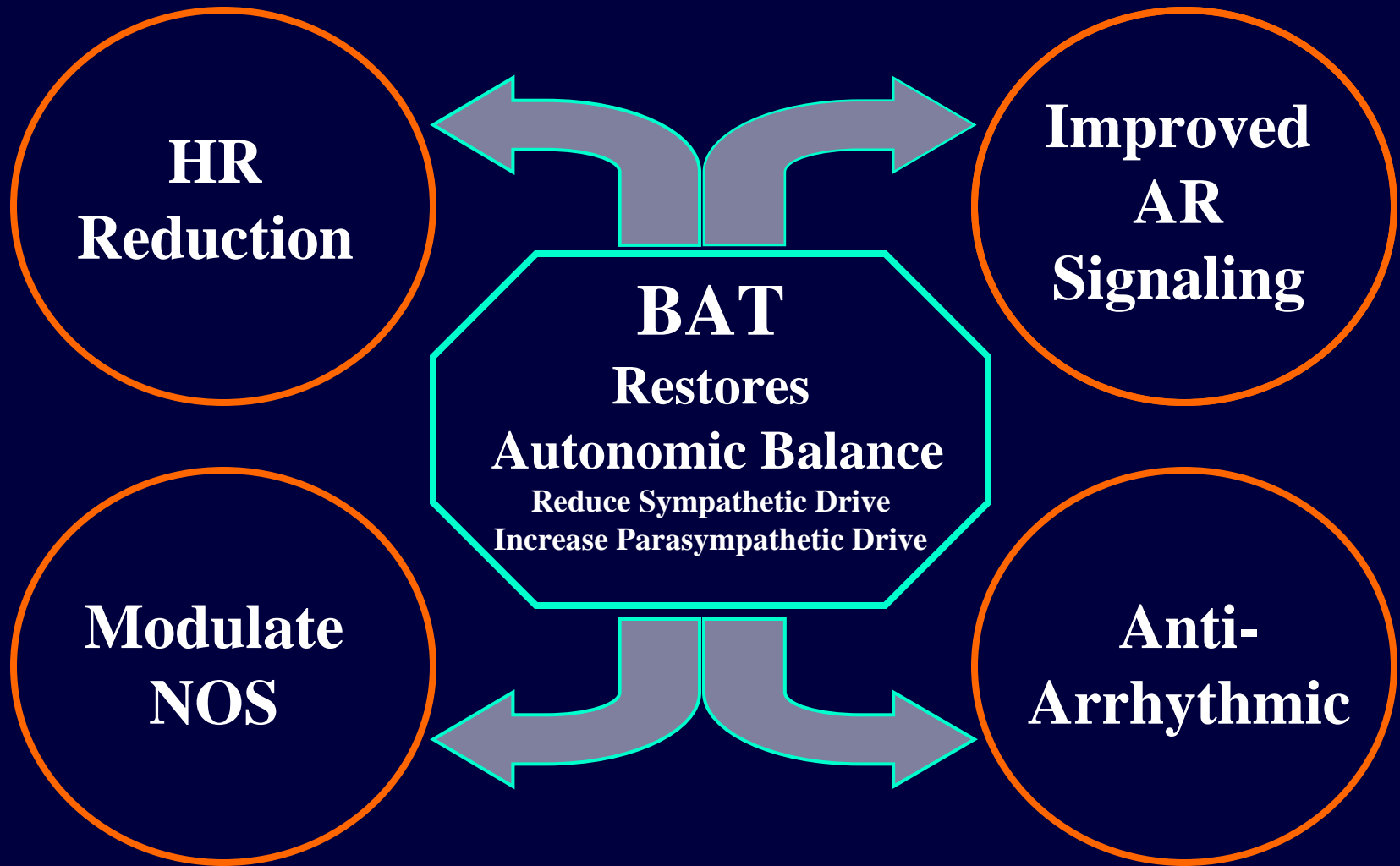
*Wayne State University &*

*Director of Cardiovascular Research*

*Henry Ford Health System*







# BAT in Dogs With Chronic Heart Failure

## Objective

- Assessment of efficacy of chronic BAT in dogs with heart failure using the *Rheos System* (CVRx, Inc.)

## Methods

- Heart failure produced by multiple intracoronary microembolizations
- The study includes 14 dogs: active group (n=8), sham-operated control group (n=6)
- 3 months follow up period

# Electrical Baroreflex Stimulation in Dogs with Coronary Microembolization-Induced Heart Failure

1. Bilateral Baroreflex Stimulation

2. Stimulation Protocol:

Frequency = 50-100 Hz

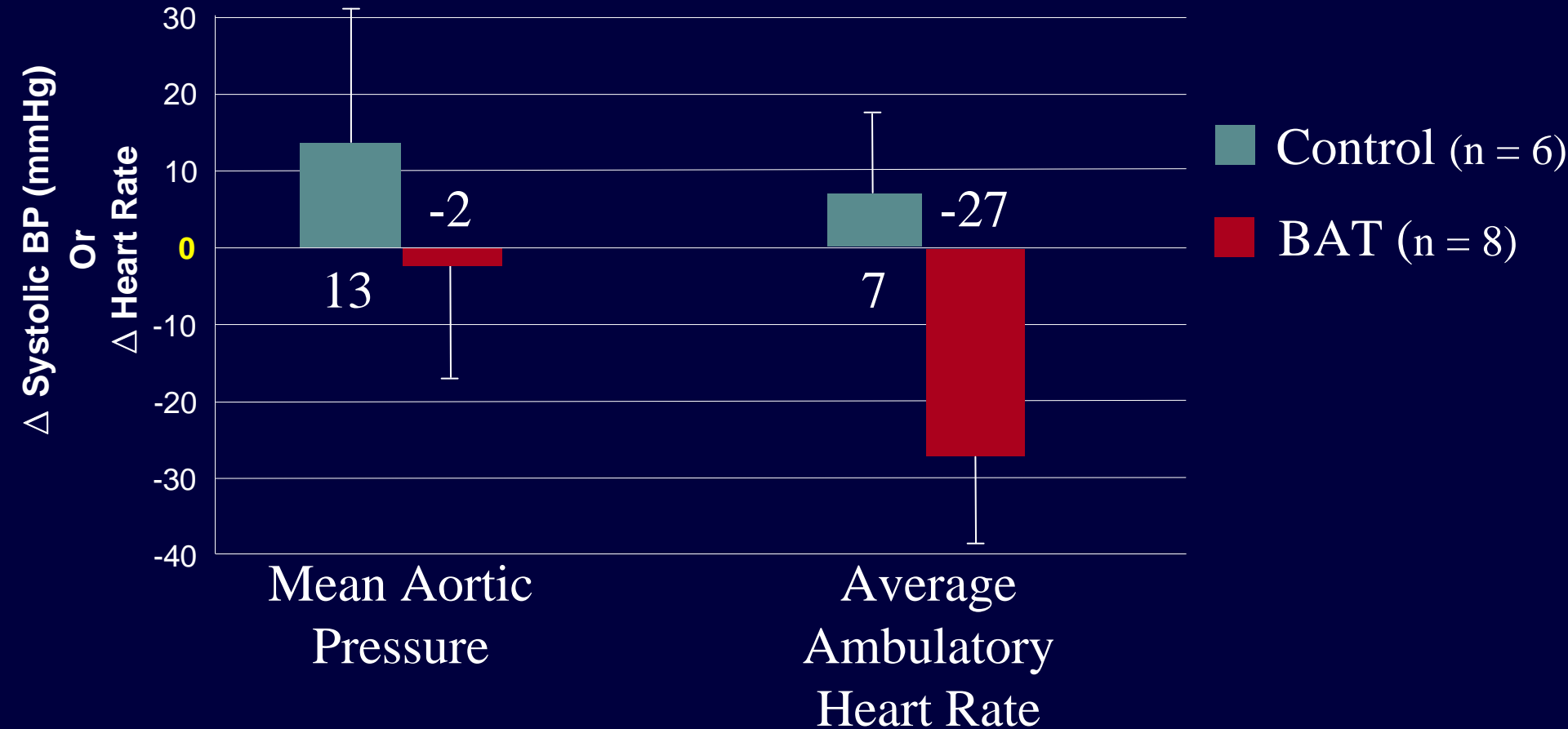
Pulse wave = 0.5 – 1.0 msec

Duty cycle 9 min ON 1 min OFF

*Sabbah et al, Circulation Heart Failure, 2011*



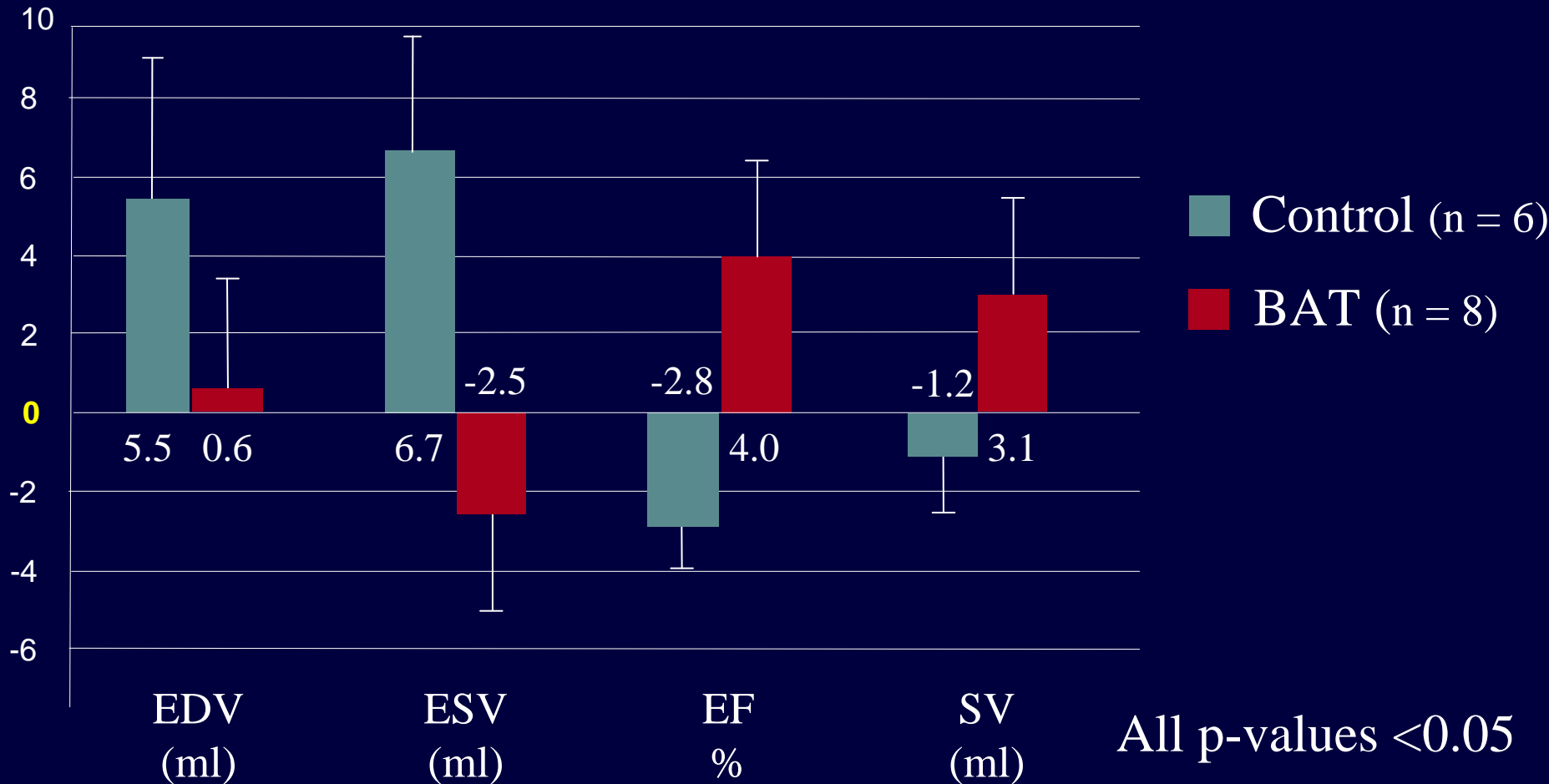
# △ Mean Aortic BP and Avg. Ambulatory HR



*Sabbah et al, Circulation Heart Failure, 2011*



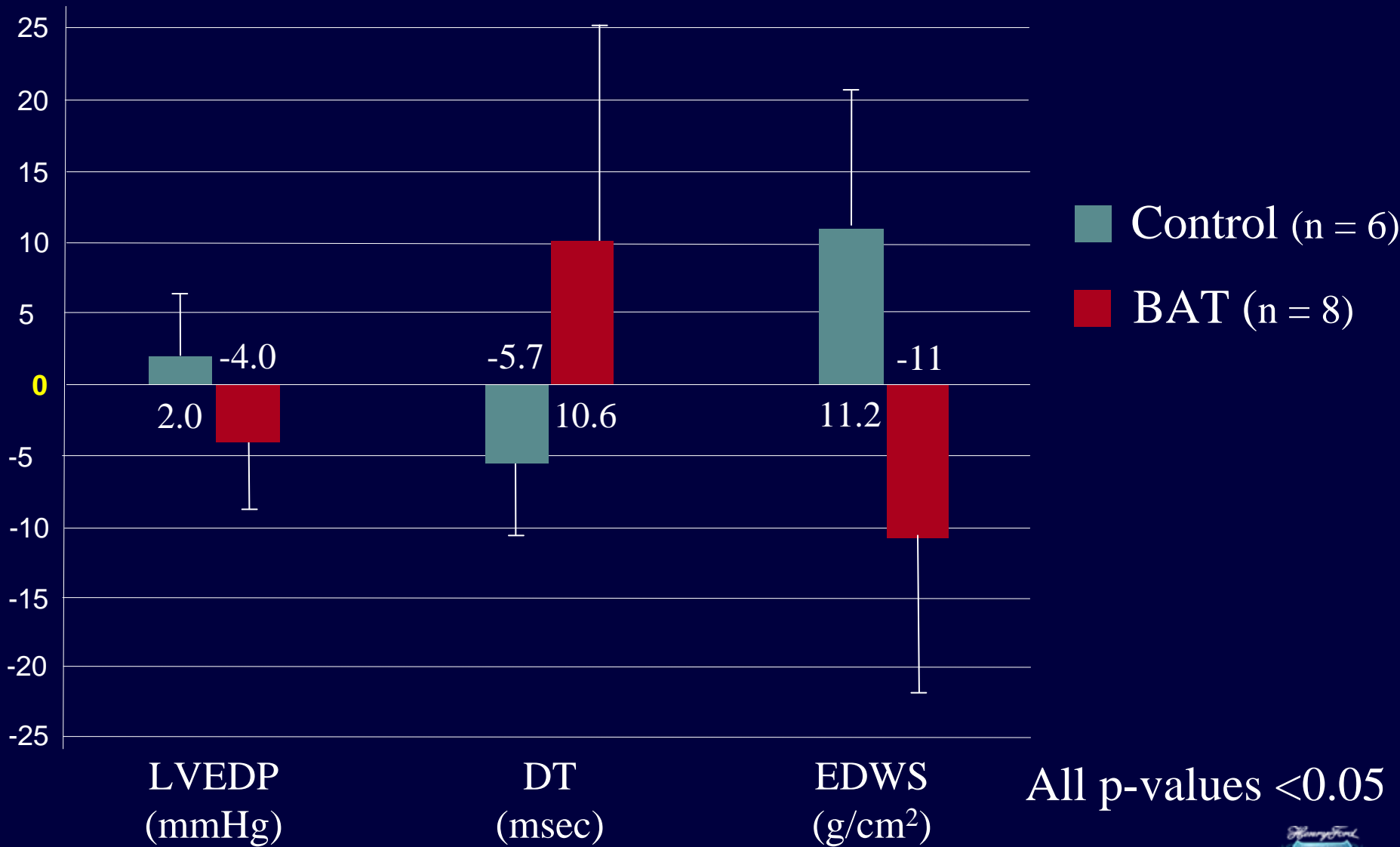
# △ LV Systolic Indexes Treatment Effect



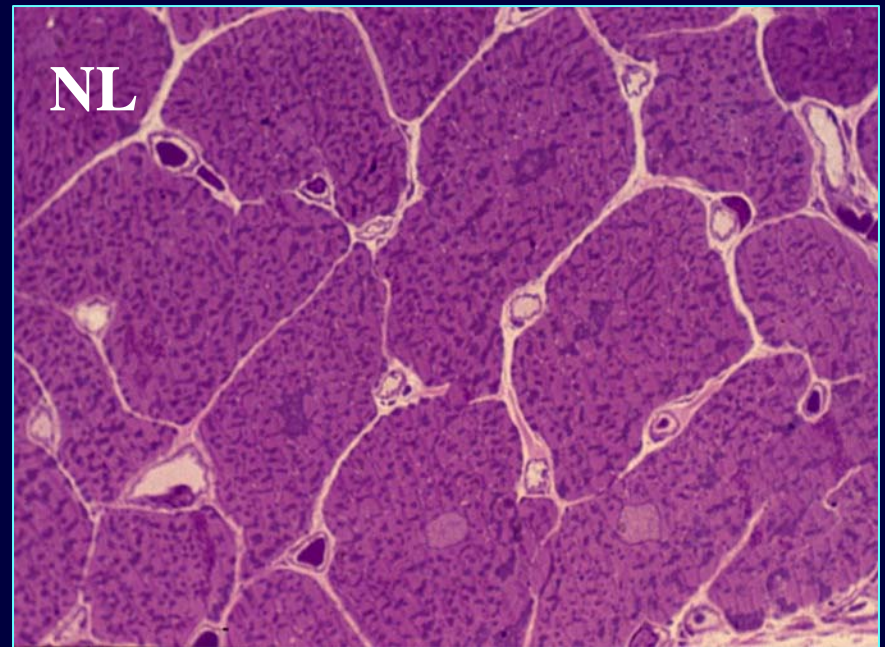
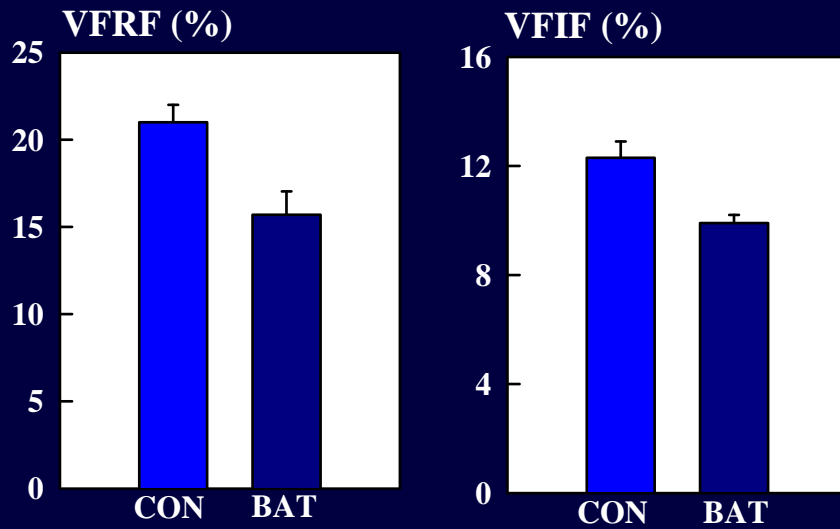
*Sabbah et al, Circulation Heart Failure, 2011*



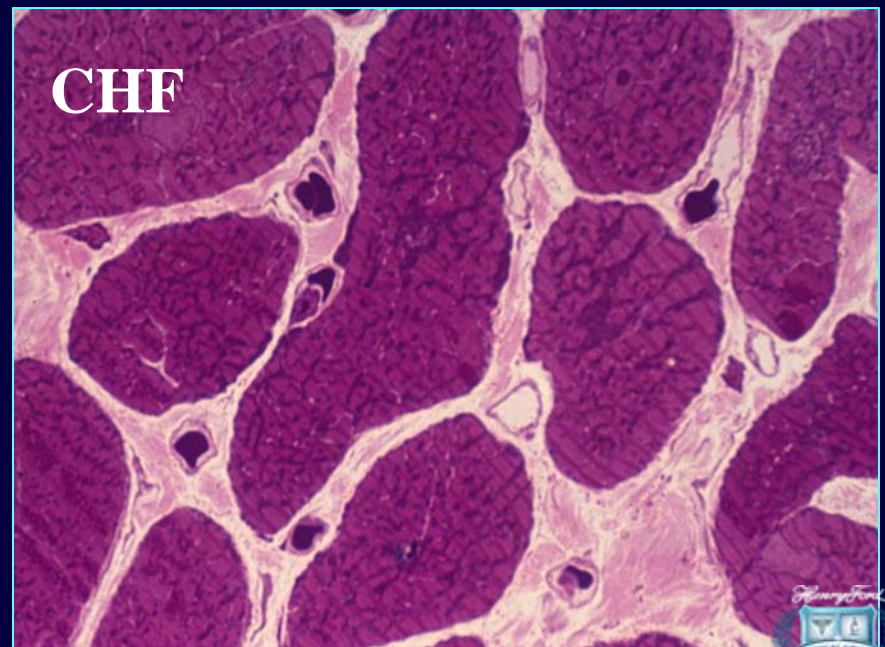
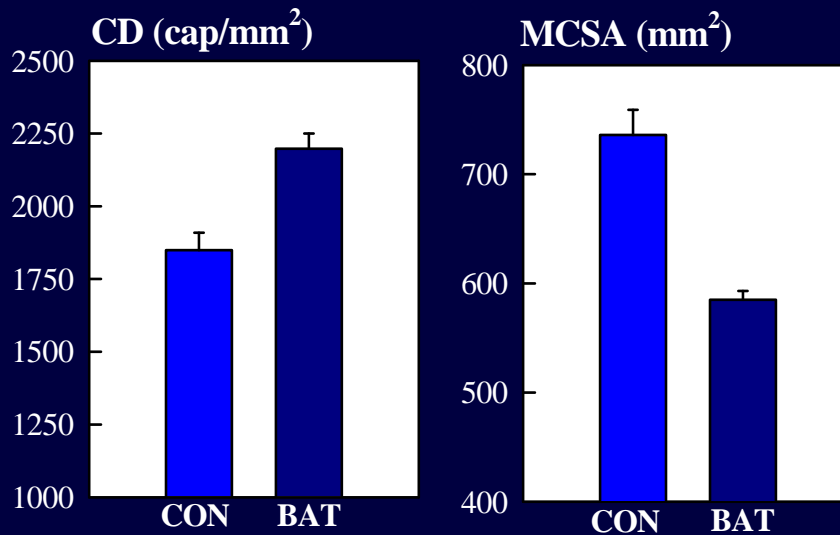
# △ LV Diastolic Indexes Treatment Effect



## LV Histomorphometry



## LV Histomorphometry



# BAT in Dogs With Chronic Heart Failure: Effects on Ventricular Arrhythmias

## Objective

Assess the effects of chronic therapy with BAT on the induction of VT or VF in dogs with coronary microembolization-induced HF (EF~20%).

## Methods

- Study conducted in 14 dogs: active group (n = 7), sham-operated control group (n = 7)
- EP studies performed at pre-therapy and at 3 and 6 months of therapy and at 6 weeks after withdrawal of therapy.

*Wang...Sabbah et al, Circulation 2008*



# BAT in Dogs With Chronic Heart Failure: EP Stimulation Protocol

Programmed ventricular stimulation was performed from the right ventricular apex and included delivery of up to 4 extra-stimuli at progressively shorter coupling intervals (in steps of 10 msec).

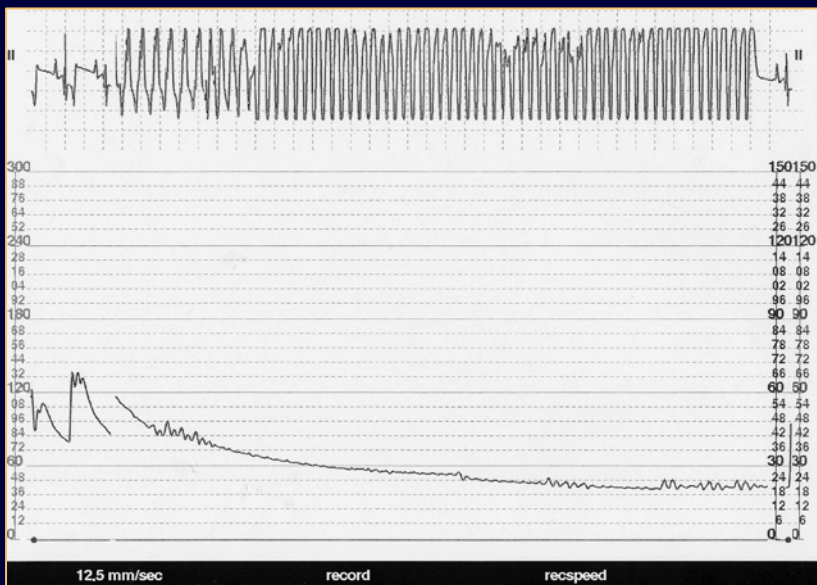
Extrastimuli delivered following 8 ventricular paced beats with a drive cycle length of 600 to 200 msec.

If a sustained monomorphic VT or VF could not be induced, isoproterenol infusion was initiated to increase the sinus rate by ~30% and the EP stimulation protocol was repeated.

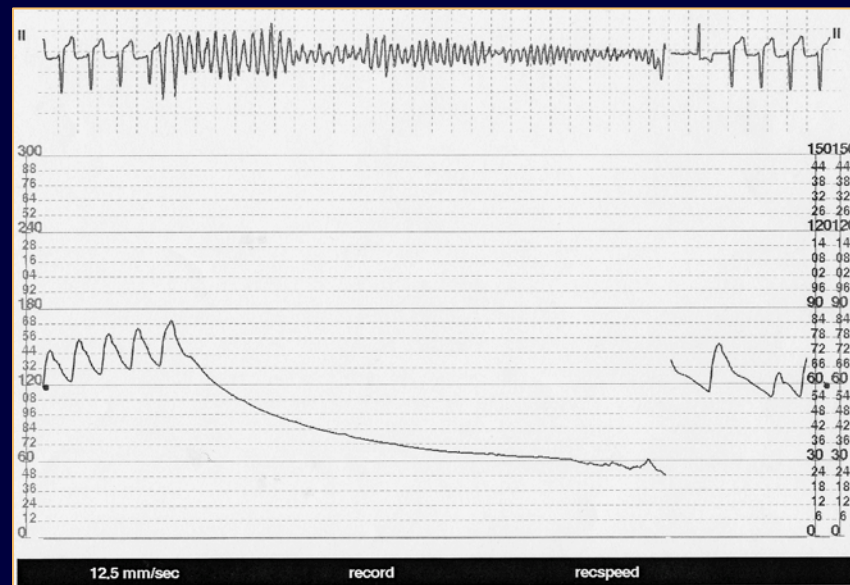
*Wang...Sabbah et al, Circulation 2008*



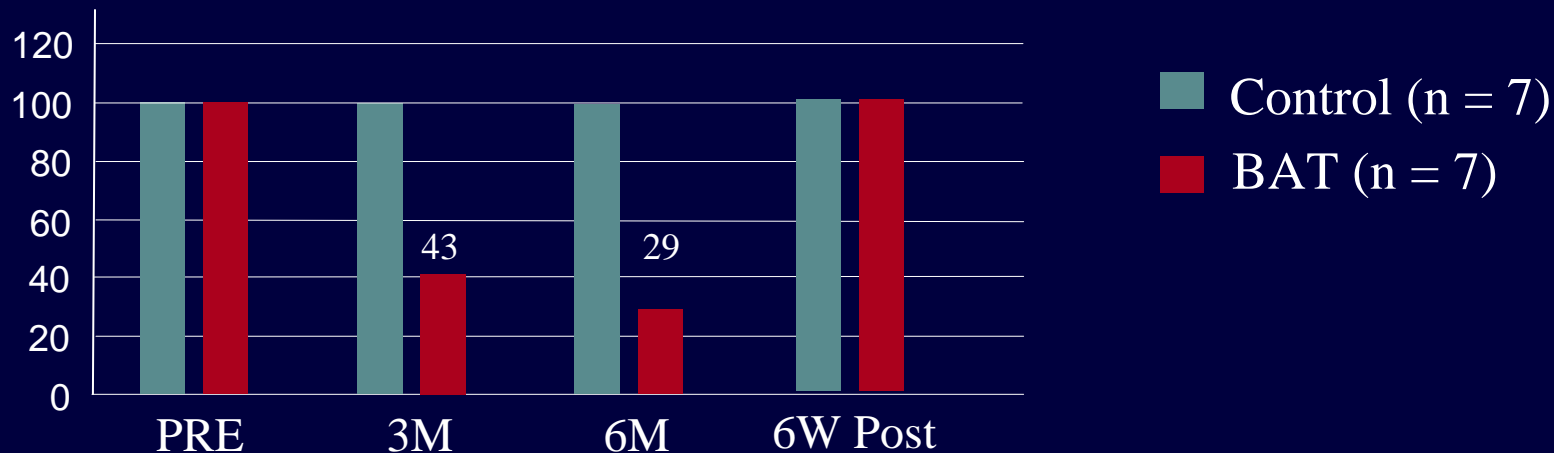
## Control



## BAT-Treated



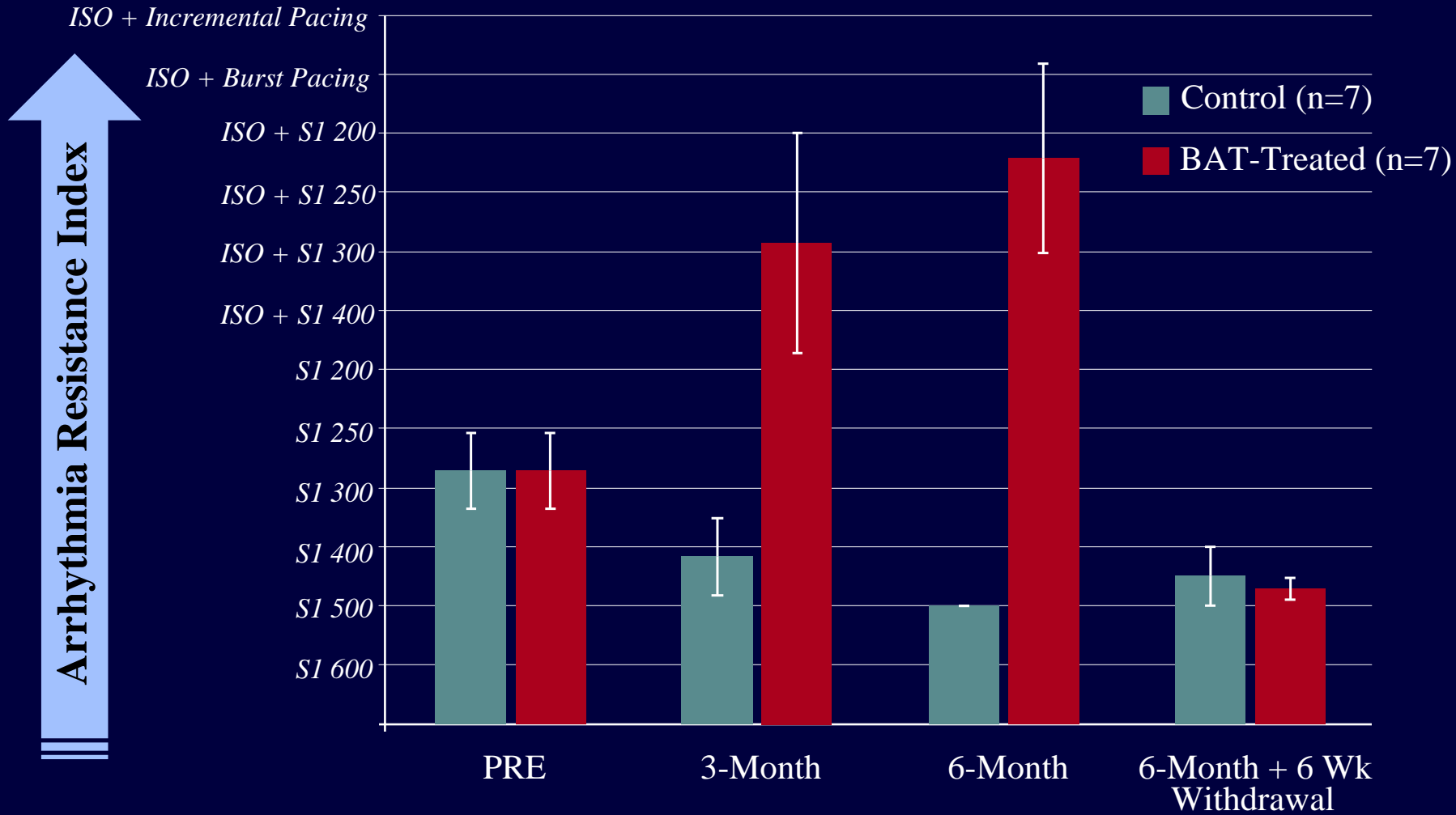
## Percent of Dogs Induced into VT or VF



Wang...Sabbah et al, Circulation 2008



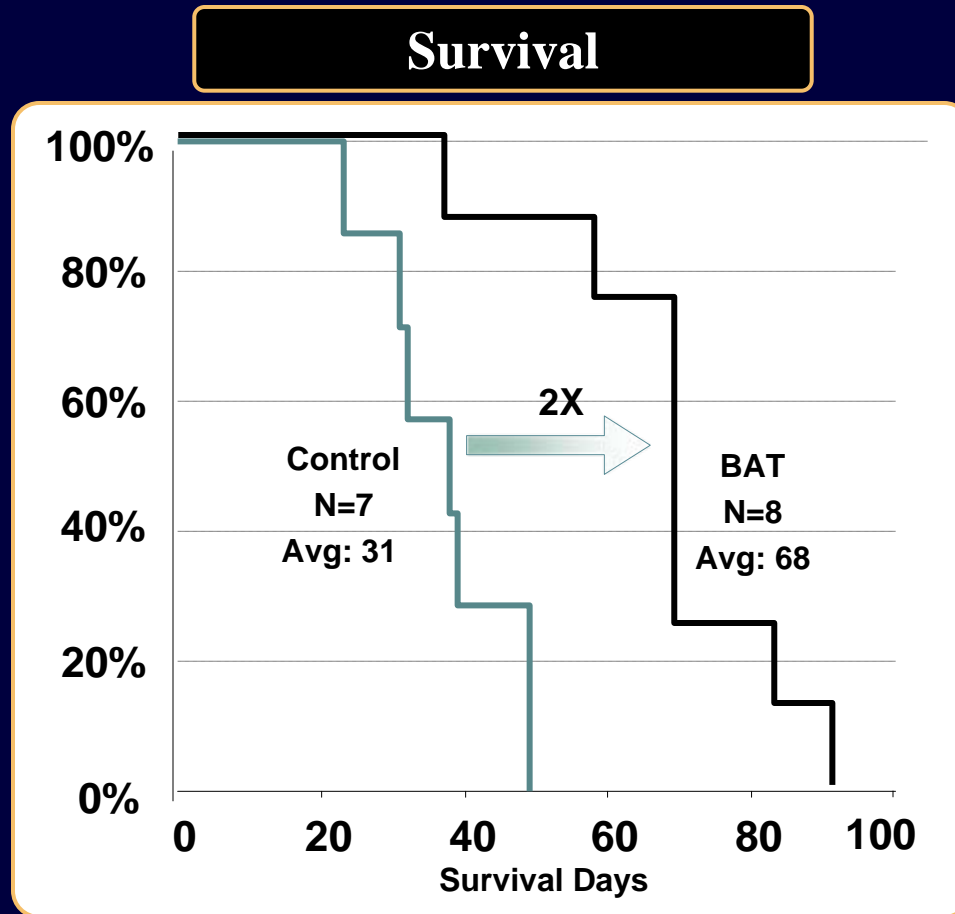
# Effects of BAT on Arrhythmia Resistance in Experimental Heart Failure



Wang...Sabbah et al, *Circulation* 2008



# Effects of BAT in Experimental Heart Failure Produced by Rapid Pacing

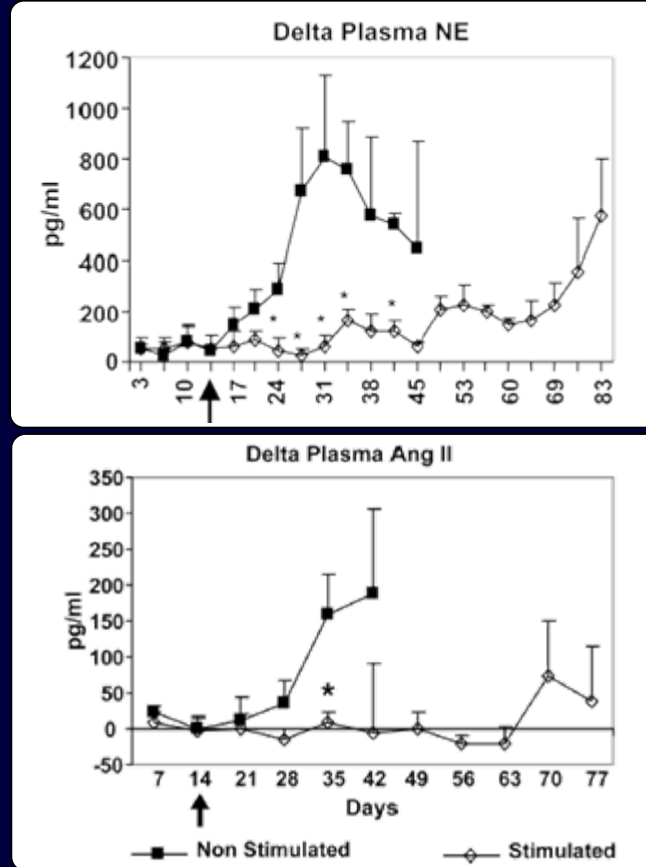


*Zucker et al, Hypertension 2007*

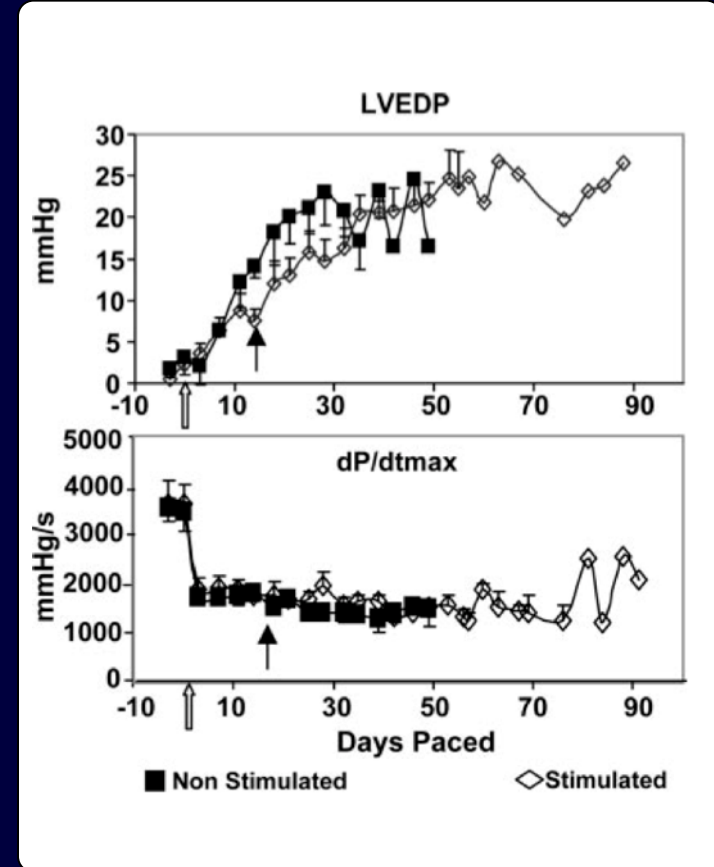


# Effects of BAT in Experimental Heart Failure Produced by Rapid Pacing

## Plasma Neurohormones



## Pressures



Zucker et al, Hypertension 2007

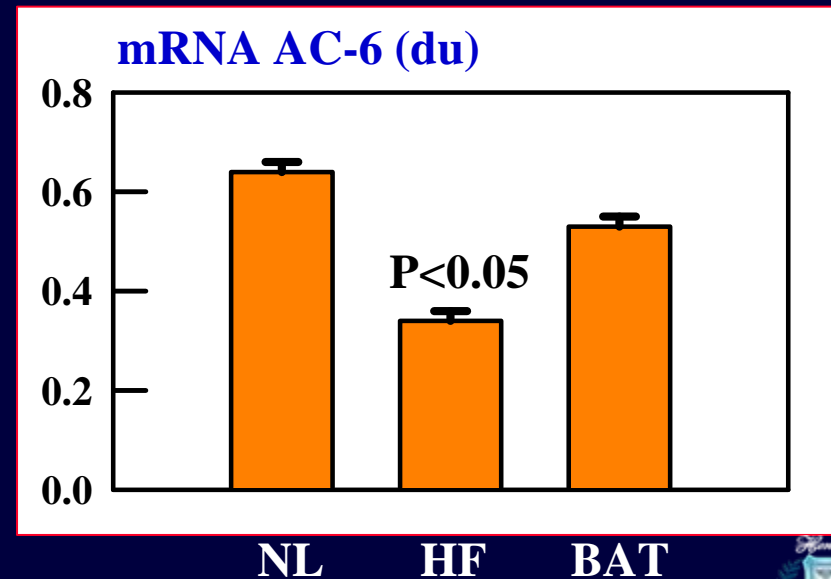
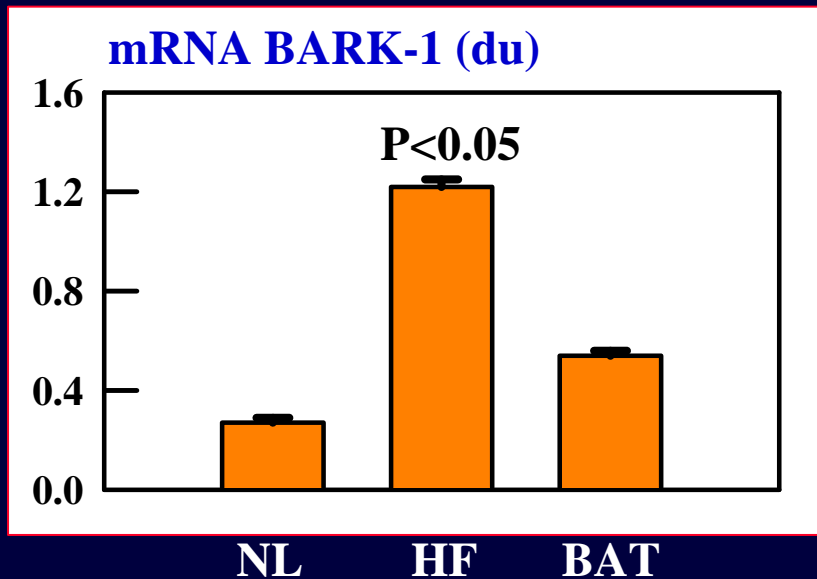
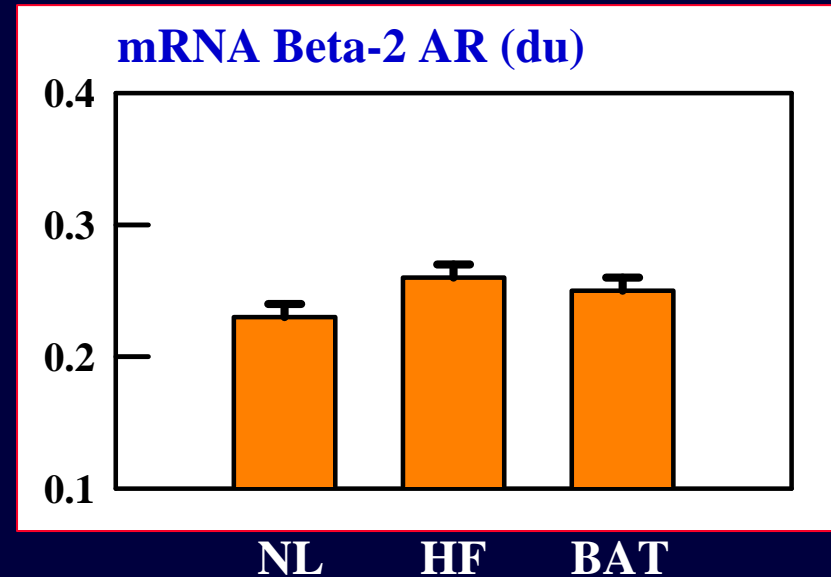
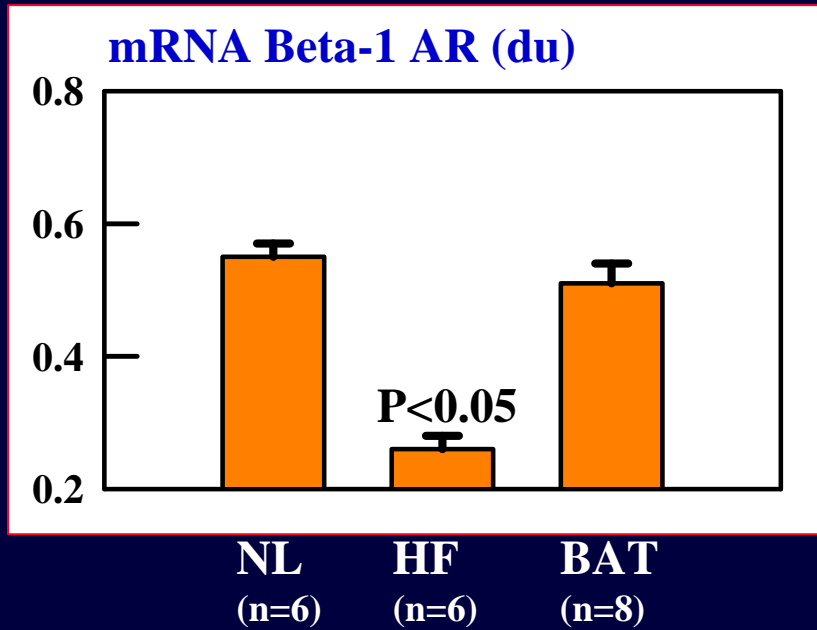


# Adrenergic Pathway






In heart failure (HF), cardiac  $\beta$ -adrenergic receptor ( $\beta$ -AR) signaling is impaired leading to desensitization of the myocardium to catecholamines. This is associated with reduced gene expression for  $\beta$ 1-AR and adenylyl cyclase and increased expression of  $\beta$ -adrenergic receptor kinase.

# Beta-Adrenergic Receptor Signal Transduction Pathway



# Nitric Oxide Synthases

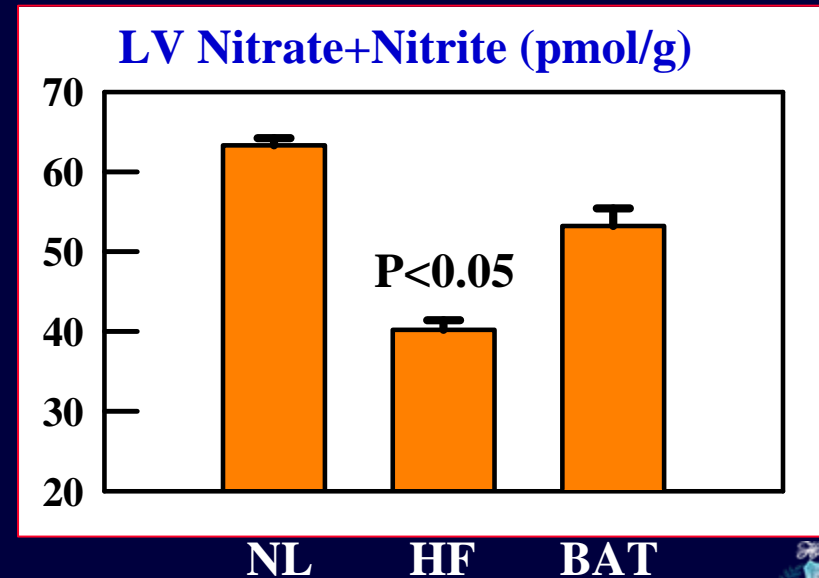
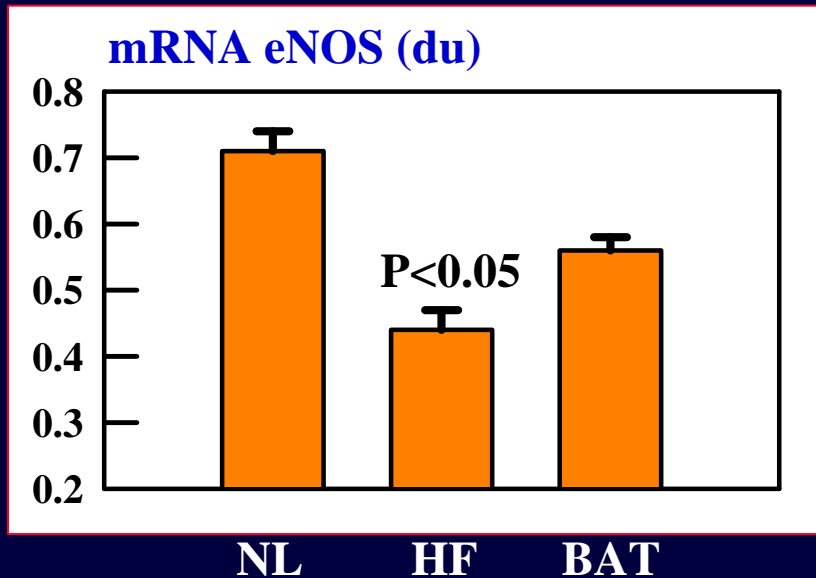
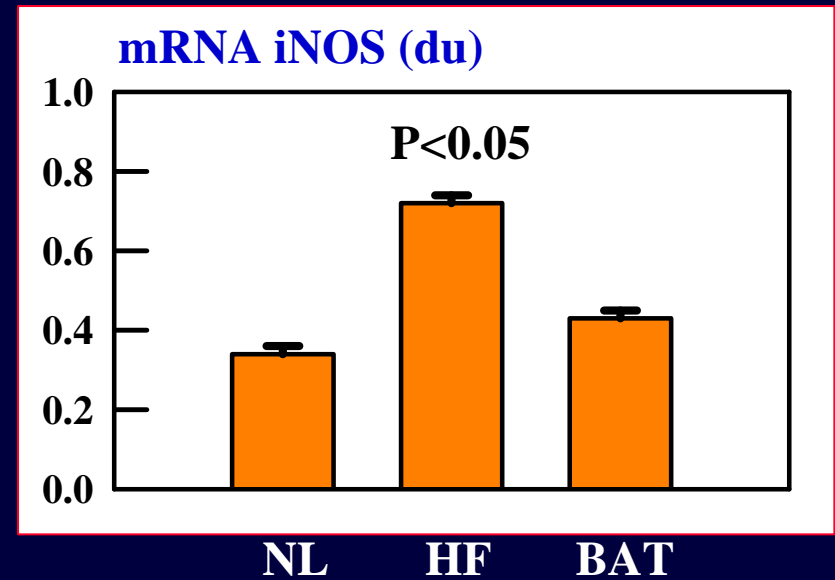
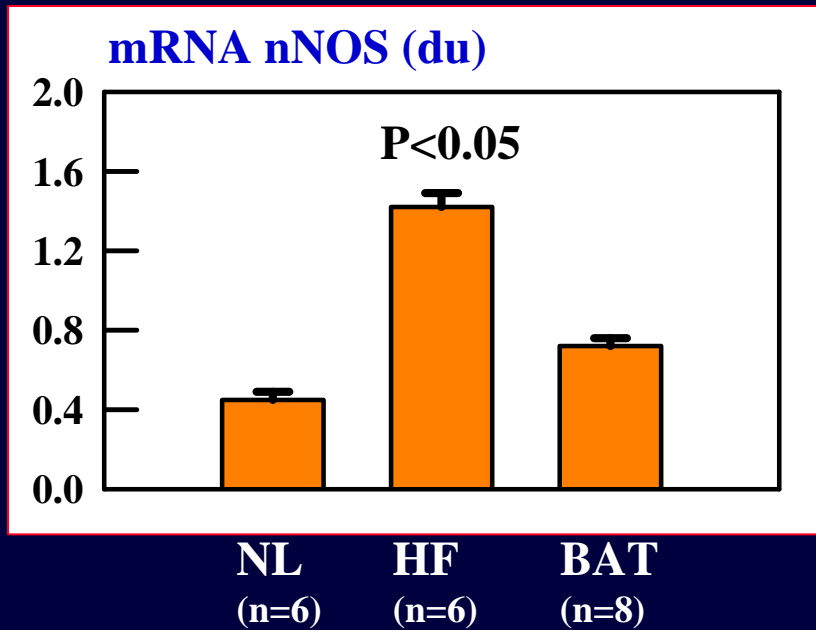
-  **eNOS:** (Reduced in CHF). Enhances relaxation; regulates contractility; regulates cell growth and apoptosis.
-  **iNOS:** (Increased in CHF). Overexpression leads to apoptosis, increased fibrosis, hypertrophy, heart block, sudden cardiac death.
-  **nNOS:** (Increased in CHF). Can modulate calcium cycling and contractility. Inhibition results in increased sensitivity of myocardium to  $\beta$ -adrenergic stimulation.

Kelly et al. *Circ. Res.* 79:363-380, 1996  
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# Nitric Oxide Pathway



# SUMMARY & CONCLUSIONS

- ♥ Long-term BAT improves LV systolic and diastolic function in dogs with chronic advanced HF and partially reverses LV remodeling.
- ♥ BAT normalizes mRNA expression of key components of the  $\beta$ -AR signal transduction pathway. Reversal of this maladaptive gene expression is likely to restore sensitivity of the failing myocardium to catecholamines and explains, in part, the improvement of LV function seen following chronic BAT.
- ♥ BAT also normalizes mRNA expression of eNOS, nNOS and iNOS in LV myocardium of dogs with HF. This finding provides additional insights into the possible mechanisms of action of this form of therapy.

# SUMMARY & CONCLUSIONS

-  In addition to improving LV function, long-term monotherapy with BAT markedly increases the threshold for lethal ventricular arrhythmias in dogs with chronic HF, prolongs survival in dogs with pacing-induced HF and attenuates heart rate variability in patients with drug-resistant severe arterial hypertension.
-  These benefits of BAT support the continued exploration of this therapeutic modality for the treatment of patients with chronic HF and increased risk of sudden cardiac death.