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Drugs and HRV

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Objectives

- Review basis of drug effects on HRV
- Describe confounding factors
- Present selected examples: e.g., beta-blockers post-MI; carvedilol in CHF; cocaine; omega-3 fatty acids/fish oil supplements; psychotropics
- Discuss future priorities: need for open-access data

Background Notions

- Drugs with direct or indirect neuroautonomic effects will affect HRV (esp. atropine-like agents!)
- HRV changes may provide useful way to assay for potential beneficial and harmful effects on integrative neuroautonomic function
- Pharmacology also useful to probe HRV mechanisms

HRV and Drugs: Background

- Many studies in literature (and probably more not published!)
- Results sometimes apparently in conflict

HRV & Drug Effects: Caveats and Conflicts

- Confounders: age, gender, health vs pathology (type/severity), activity, etc
- Data length
- Measures used (and not used)
- Dosage: amount, timing, route, etc
- Acute vs. chronic administration
- Drug interactions
- Species differences

Some Interesting Cardiac Findings

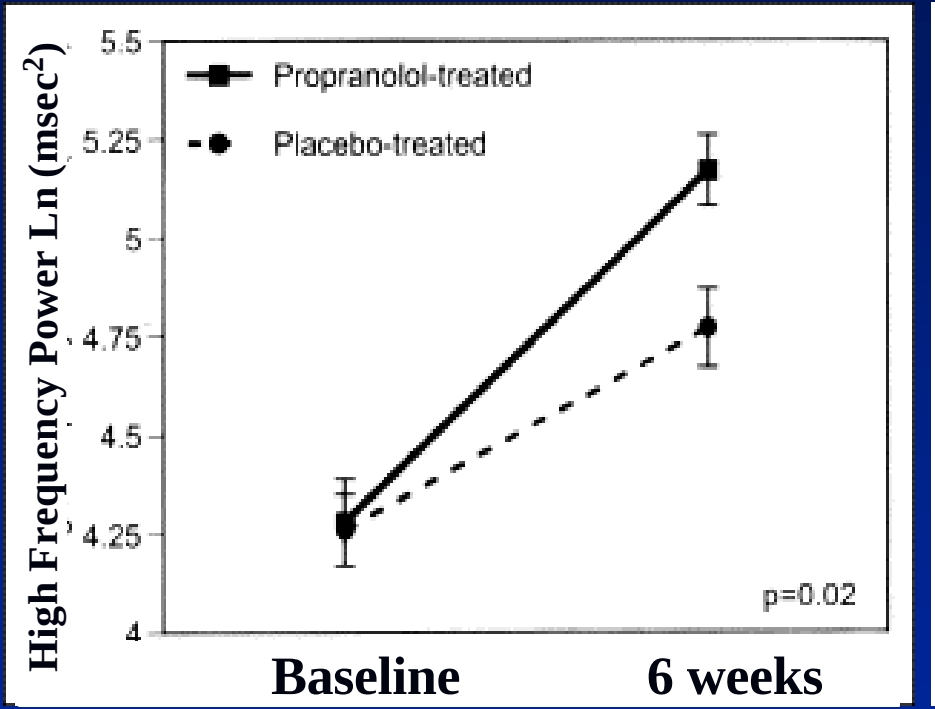
- Drugs that increase vagal/decrease sympathetic effects tend to be salutary (e.g., low dose scopolamine, low dose digoxin or pyridostigmine in CHF; ACEI in CHF
- Drugs that decrease vagal/increase sympathetic effects may have harmful/proarrhythmic effects (oral milrinone, cocaine, higher dose digoxin, quinidine, disopyramide, etc)

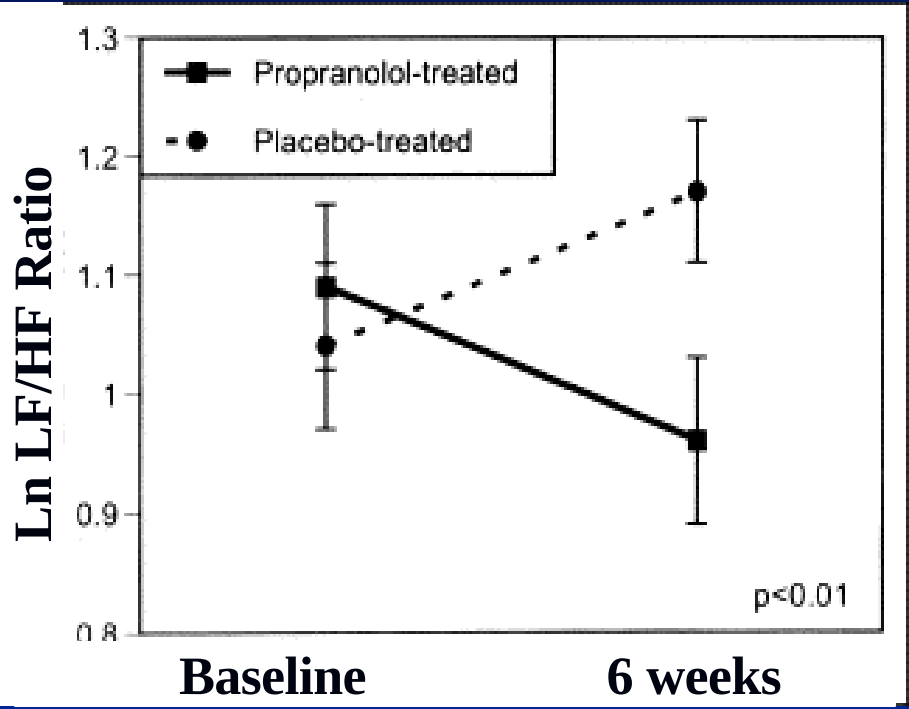
Voodoo Autonomics

- Good vagus vs b-adrenergic

Beta-blocker post-MI

Enhanced Recovery of Cardiac Vagal Tone Modulation





From: Lampert R, et al: Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. Am J Cardiol 2003:91:137

Carvedilol in Heart Failure

Study Objective

- To determine if the ß-blocker (and alpha-1 blocker) carvedilol increases the cardiac modulatory activity of the parasympathetic nervous system in patients with heart failure treated with digoxin and ACE inhibitors

Goldsmith RL, Bigger JT, Bloomfield DM, et al. Long-term carvedilol therapy increases parasympathetic nervous system activity in chronic heart failure. Am J Cardiol; 1997; 80:1101.

Patient Population

10 patients (8 males; 38-68 yrs) with CHF

- NYHA class III heart failure
- LV ejection fraction: 6-34 % (mean 18 %)
- VO_2 max (ml/kg/min) 14.8 ±1.2
- Cause of heart failure
  - Ischemic heart disease 4
  - Dilated cardiomyopathy 6

Goldsmith RL, Bigger JT, Bloomfield DM, et al. Am J Cardiol 1997; 80:1101

Methods

- Clinically stable, receiving constant dose of digoxin, diuretics and ACE inhibitor for 2 weeks
- Baseline evaluation of exercise capacity, LV function, and HRV
- Carvedilol 25 mg BID for 4 months
- Continued digoxin, diuretics & converting enzyme inhibitors in unchanged doses
- Repeat assessment of exercise capacity, LV function and HRV at end of treatment period

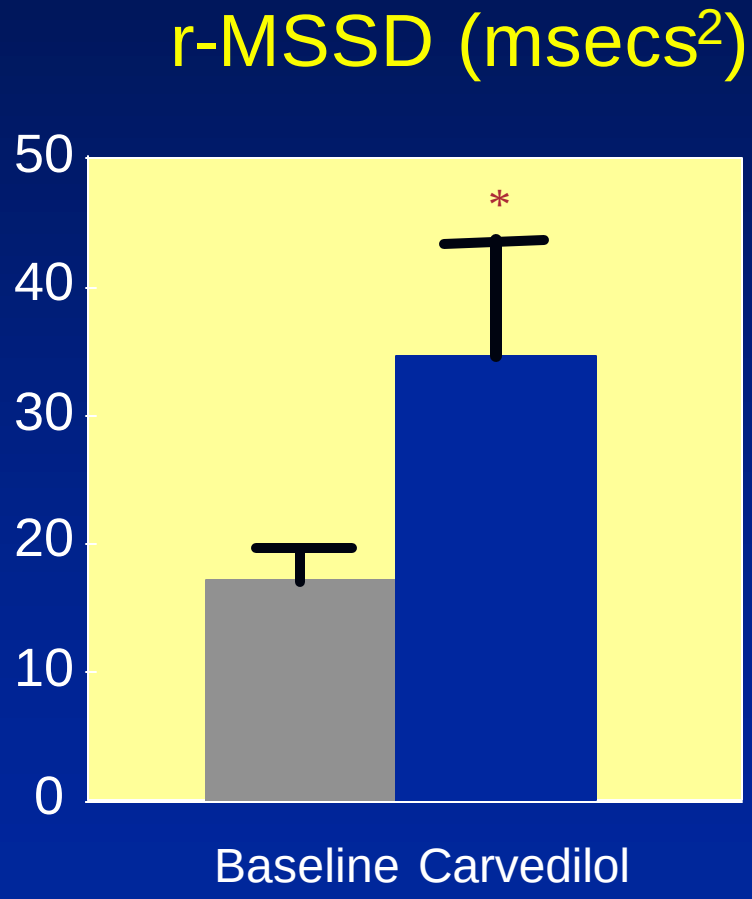
Goldsmith RL, Bigger JT, Bloomfield DM, et al. Am J Cardiol 1997; 80:1101

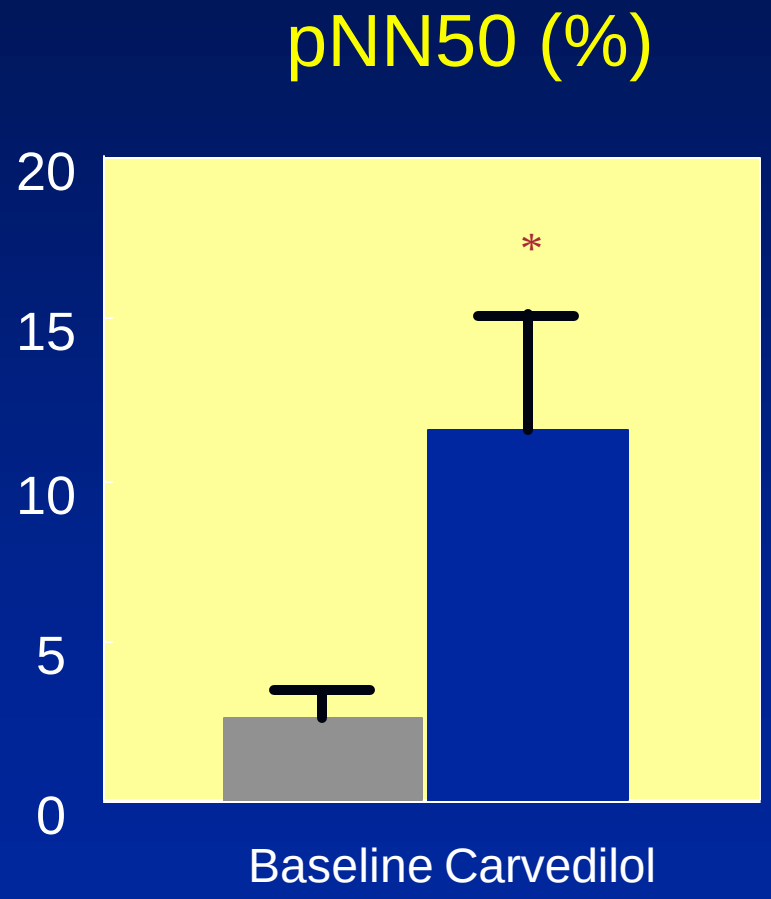
Methods (con't)

- 24 hour Holter recordings
- Measures of parasympathetic function
  - Time Domain
    - rMSSD (root mean square successive difference)
    - pNN50 (proportion of successive normal RR intervals greater than 50 msec)
  - Frequency Domain

Goldsmith RL et al. Am J Cardiol 1997; 80:1101

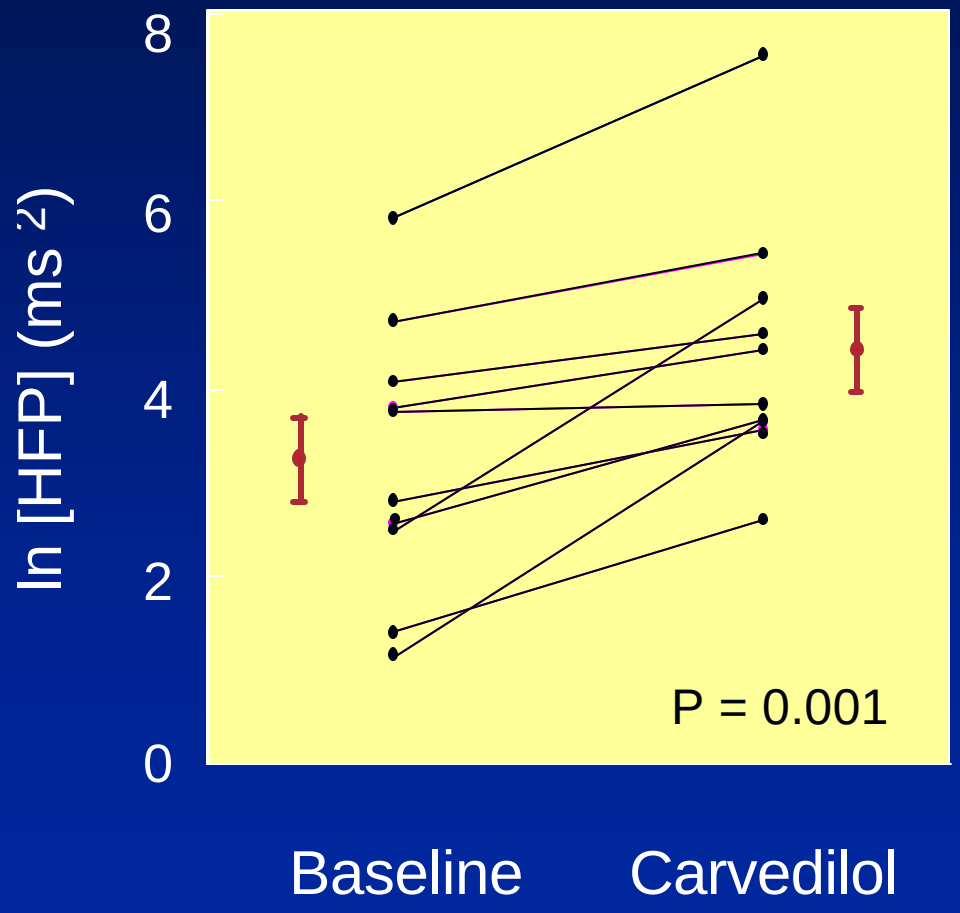
Carvedilol in CHF: Time Domain





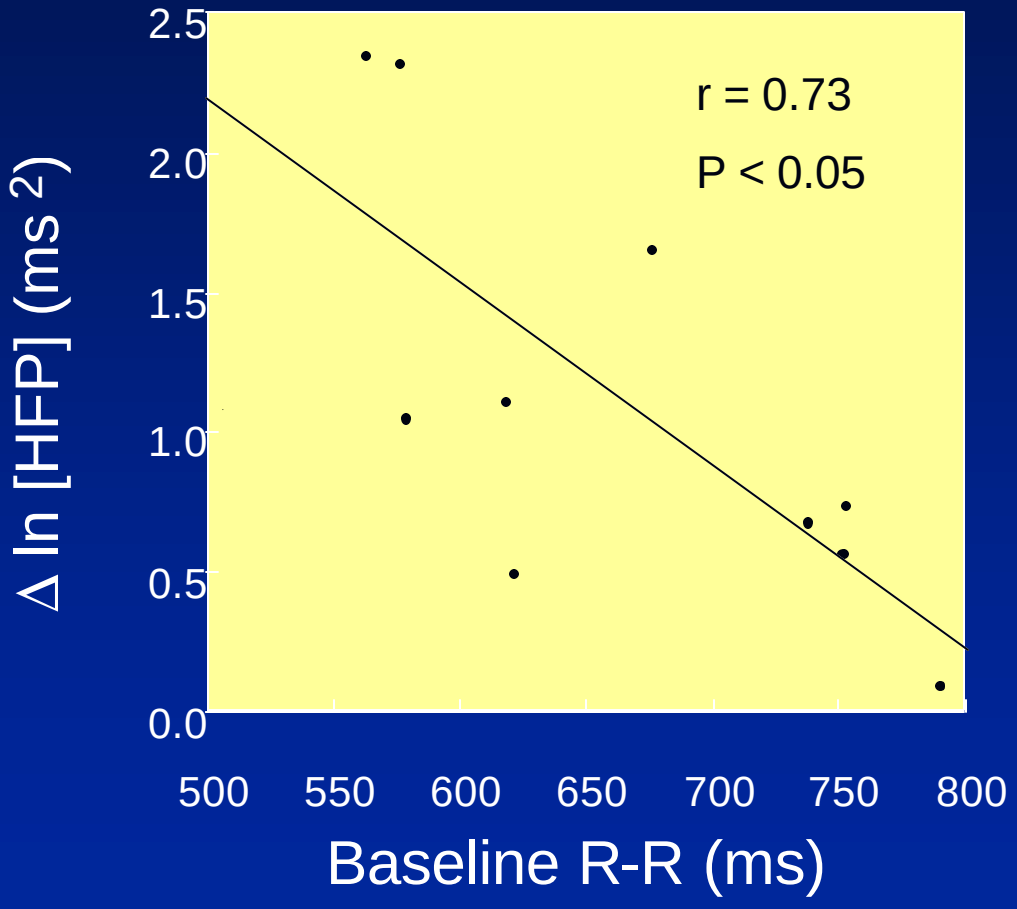
Goldsmith RL, Bigger JT, Bloomfield DM, et al. Am J Cardiol; 1997; 80:1101

Carvedilol in CHF: Frequency Domain



Goldsmith RL et al. Am J Cardiol 1997; 80:1101

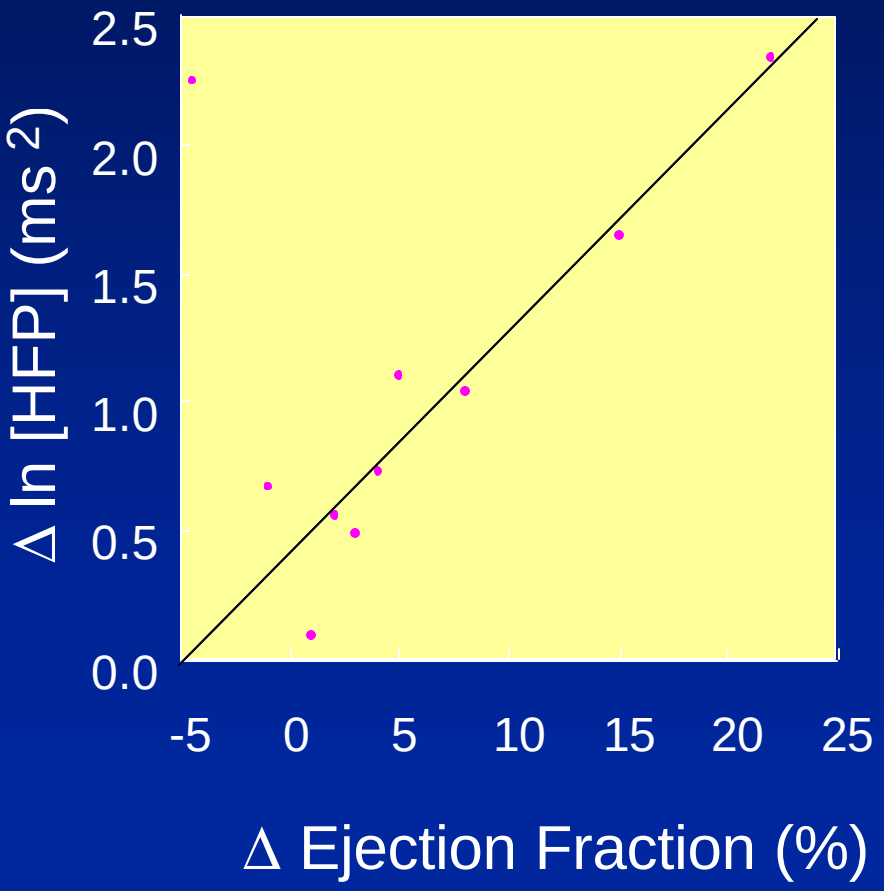
Relation of Baseline Heart Rate and Change in High Frequency Power

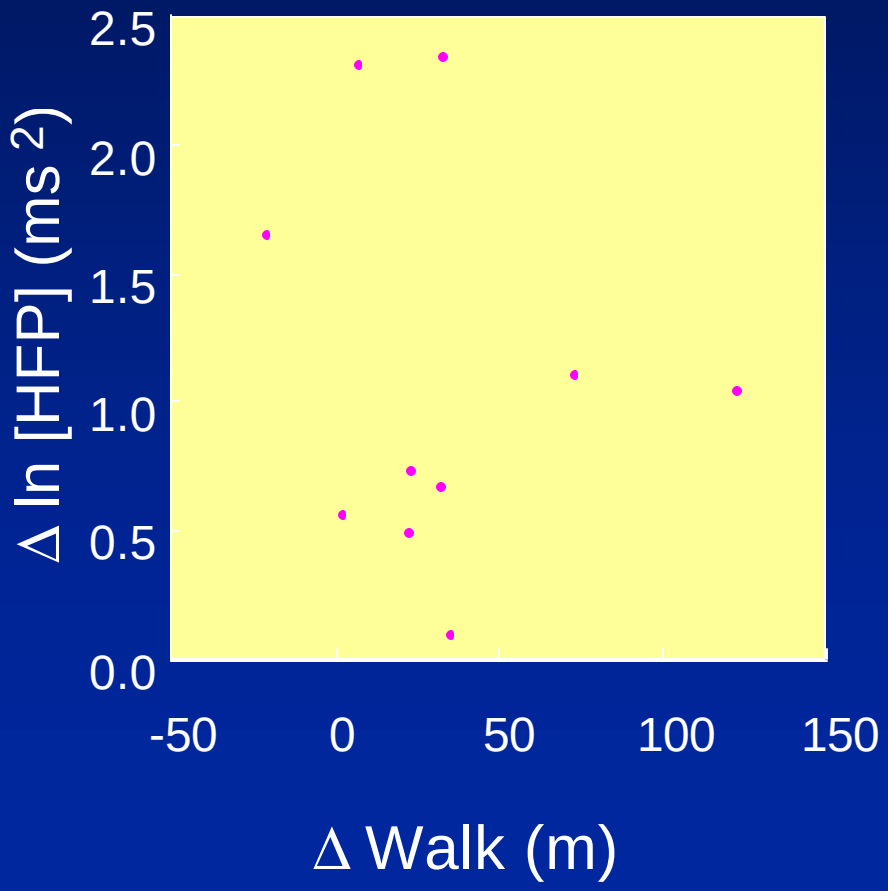


Goldsmith RL et al. Am J Cardiol 1997; 80:1101

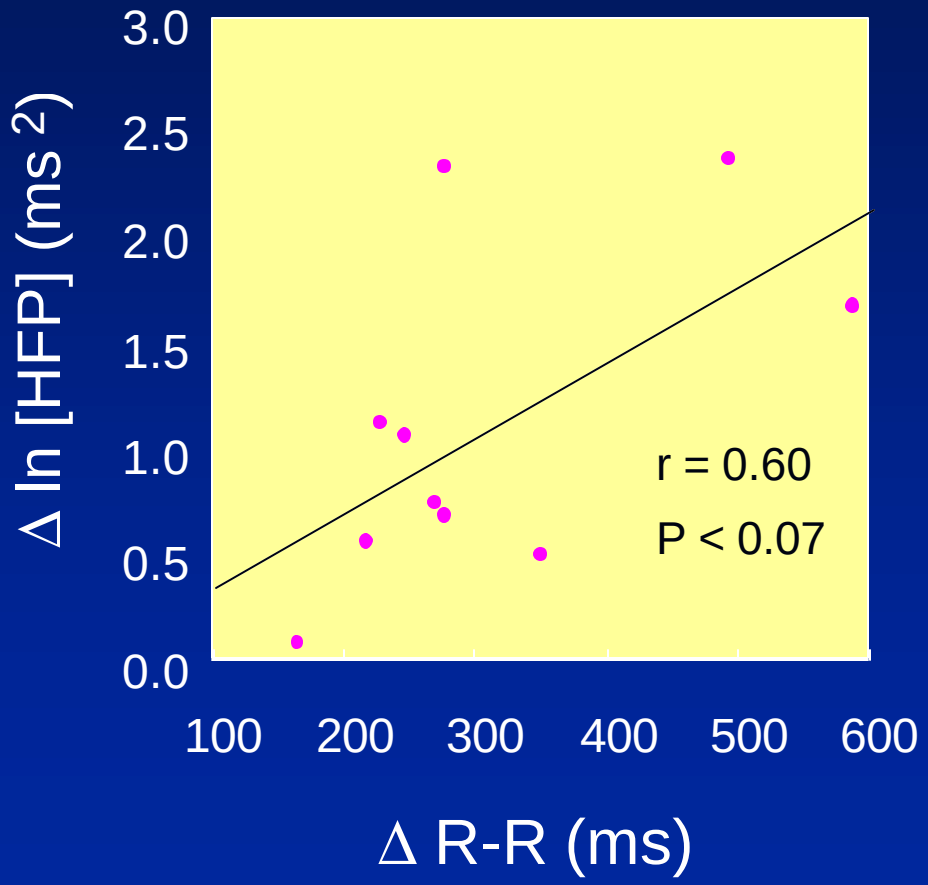
Relation of Change in High Frequency Power to Hemodynamic and Clinical Effects of Carvedilol

Goldsmith RL et al. Am J Cardiol 1997; 80:1101





Relation of Change in High Frequency Power to Change in Heart Rate



Goldsmith RL et al. Am J Cardiol 1997; 80:1101

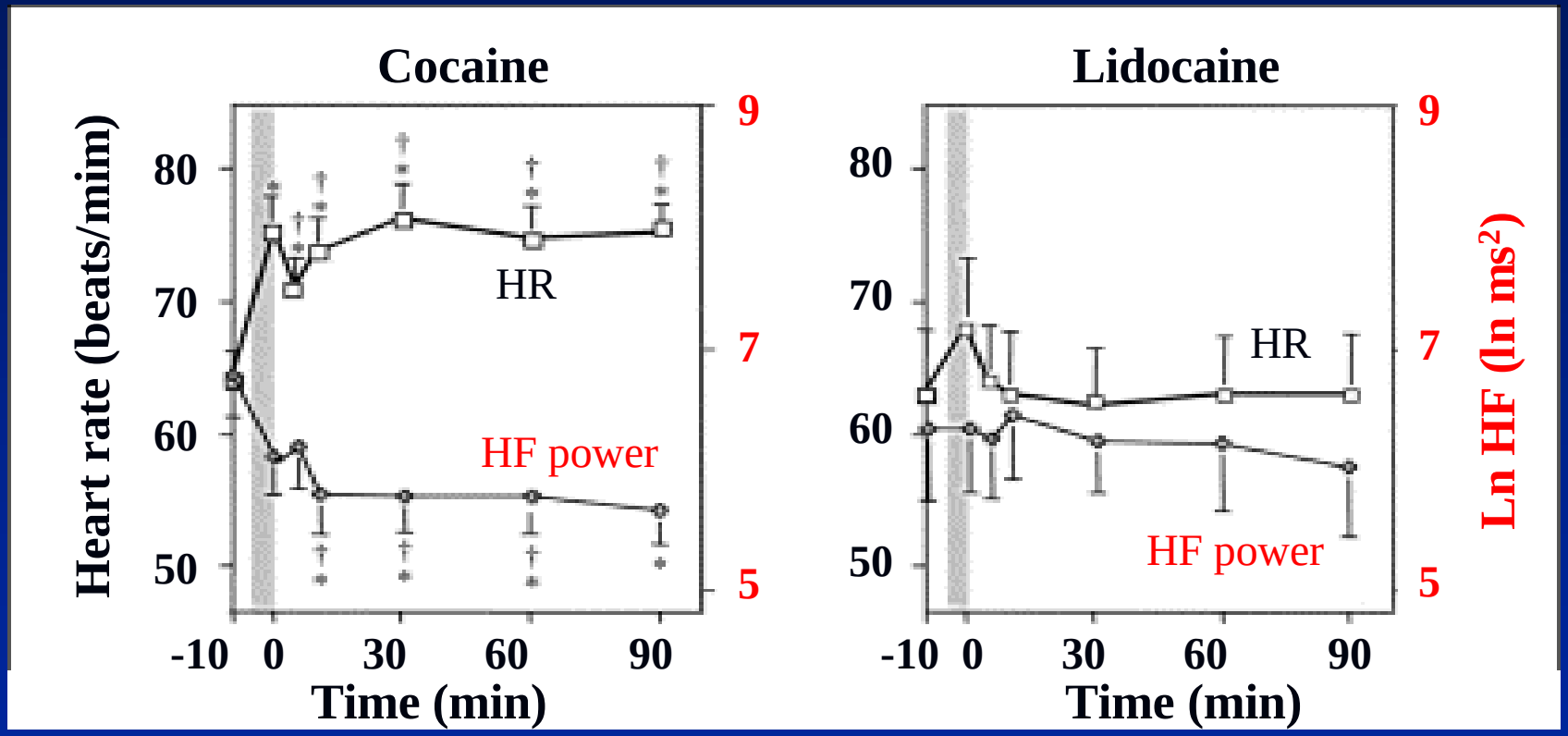
Carvedilol/CHF: Conclusions

Carvedilol increases the activity of the parasympathetic nervous system in patients with moderate to severe chronic heart failure treated with digoxin and ACE inhibitors

Goldsmith RL et al. Am J Cardiol 1997; 80:1101

Acute (Intranasal) Cocaine Effects in Healthy Humans

Loss of High Frequency Power



Adapted from: Vongpatanasin W, Taylor JA, Victor, RG. Am J Cardiol 2004;93:385

HRV and Psychotropics

Decrease reported with a number of agents:

- Tricyclics
- Clozapine
- Thioridazine

SSRIs: variable but usually not prominent effects reported

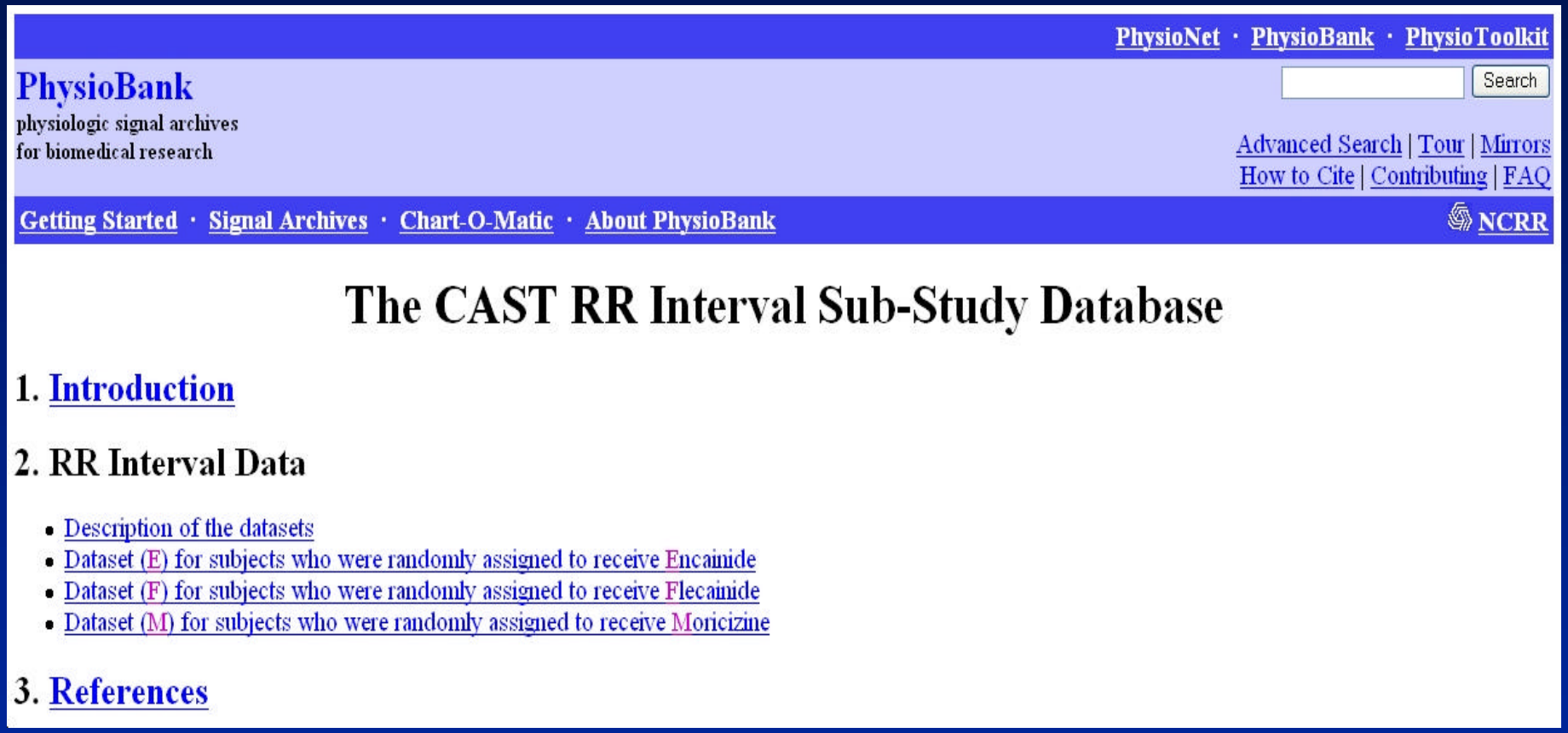
HRV and Fish Oil Supplements

- Omega-3 fatty acid supplements reported to increase physiologic HRV in some, but not all groups
- Intriguing results: more data/analyses needed in different subsets; doses
- Possible relationship to antiarrhythmic and other reported salutary cardiovascular effects

Future/Current Needs

- Open-access databases of drug effects on heart rate dynamics
- Only current example: CAST RR-interval subset database on PhysioNet
- Ideally, need continuous ECG with detailed metadata: please contribute!

PhysioNet CAST Sub-Study Database



http://www.physionet.org/database/crisdb