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

Carvedilol in Heart Failure

Study Objective

• To determine if the β-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

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

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

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

r-MSSD (msecs\(^2\))

Baseline Carvedilol

pNN50 (%)

Baseline Carvedilol

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

\[ \Delta \ln [\text{HFP}] \text{ (ms}^2) \]

\[ r = 0.73 \]

\[ P < 0.05 \]

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

\[ \Delta \ln [HFP] \text{ (ms}^2 \text{)} \]

\[ 100 \ 200 \ 300 \ 400 \ 500 \ 600 \]

\[ 0.0 \ 0.5 \ 1.0 \ 1.5 \ 2.0 \ 2.5 \ 3.0 \]

\[ r = 0.60 \]

\[ P < 0.07 \]

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**

![Graph showing heart rate and high frequency power changes over time with cocaine and lidocaine]

*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

The CAST RR Interval Sub-Study Database

1. Introduction

2. RR Interval Data
   - Description of the datasets
   - Dataset (T) for subjects who were randomly assigned to receive Flecainide
   - Dataset (F) for subjects who were randomly assigned to receive Flecainide
   - Dataset (M) for subjects who were randomly assigned to receive Moricizine

3. References

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