Breaking the toxic cycle of CHF-AF-CHF
CHF begets AF and vice versa
CHF increases mortality in AF patients (and vice versa)

<table>
<thead>
<tr>
<th></th>
<th>Men (RR)</th>
<th>Women (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact of CHF incident</td>
<td>2.7 (1.9-3.7)</td>
<td>3.1 (2.2-4.2)</td>
</tr>
<tr>
<td>on AF patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact of AF incident</td>
<td>1.6 (1.2-2.1)</td>
<td>2.7 (2.0-3.6)</td>
</tr>
<tr>
<td>on CHF patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Prevalence of AF Increases with CHF Severity

- SOLVD
- SOLVD
- V-HeFT
- CHF-STAT
- DIAMOND
- GESICA
- CONSENSUS

Legend:
- Black
- Pink
- Blue
- Gray

Percent
Why AF worsens CHF

- Poor rate control results in cardiomyopathy
- Atrial fibrillation causes increased sympathetic tone
- Lack of atrial systole
- Irregularity results in decreased cardiac output and mitral regurgitation
- More rapid rates result in shorter diastolic filling times
Increased sympathetic activity in AF

- Recordings of SNA during NSR and AF
- Recordings of SNA during AV synchronous irregular and regular rhythm
- Sympathetic activity is increased in AF and irregular rhythm
Atrial Fibrillation Causes Worsening CHF

- Study of 54 patients with CHF
  - 36 maintained NSR
  - 18 developed AF
  - Followed for 19 months
- Mean NYHA Score
  - AF patients: 2.3 to 2.9
  - NSR patients: 2.2 to 2.6
- Peak VO₂ (ml/kg/min)
  - AF patients: 16 to 11
  - NSR patients: 14 to 14
- Mitral Regurgitation Score:
  - AF patients: 1.4 to 2.4
  - NSR patients: 1.4 to 1.6
Why AF worsens CHF

- Rapid atrial rates in excess of 150% of resting rate predicted for age
- More than 10-15% of the day
- Associated with dilation of the left ventricle
- Mechanism has not been fully elucidated
Why AF worsens CHF

- Canine model with complete AV block.
- Paced at the same rates either regularly or irregularly
- Cardiac output measurement
- Angiography measurement

Naito M, Am Heart J 1983;106:284
<table>
<thead>
<tr>
<th></th>
<th>Regular</th>
<th>Irregular</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output</td>
<td>2.3</td>
<td>2.1</td>
<td>.03</td>
</tr>
<tr>
<td>(L/M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral Regurg</td>
<td>Absent</td>
<td>Present</td>
<td></td>
</tr>
</tbody>
</table>

Naito M, Am Heart J 1983;106:284
• 24 patients with cardiomyopathy and tachyarrhythmia
  – Atrial fibrillation: 14
  – Atrial flutter: 4
  – Atrial tachycardia: 3
  – PJRT: 2

• Mean follow up after tachycardia treatment: 26 months
Resumption of NSR

- 506 patients with CHF and atrial fibrillation or flutter randomized to:
  - Dofetilide
  - Placebo

- Conversion to NSR:
  - Dofetilide: 44%
  - Placebo: 14%

- Maintenance of NSR:
  - Dofetilide: 79%
  - Placebo: 42%

- Heart failure hospitalizations:
  - Dofetilide: 29%
  - Placebo: 40%
Resumption of NSR

- 103 patients with atrial fibrillation
  - Amiodarone: 51
  - Placebo: 52
- 20 patients converted to NSR
  - Amiodarone: 16
  - Placebo: 4
- Rate control better in amiodarone group
- No difference in mortality between the groups
• 1376 patients with a history of AF and CHF with an LVEF of ≤ 0.35.
• Randomized to rate control versus rhythm control (with amiodarone (82%), sotalol (<1%), dofetilide (<1%))
• Mean follow up: 37 ± 19 months
No difference in Mortality

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Rate control</th>
<th>Rhythm control</th>
<th>Rate control</th>
<th>Rhythm control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of Follow-up</td>
<td>0</td>
<td>12</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>593</td>
<td>514</td>
<td>378</td>
<td>228</td>
</tr>
<tr>
<td></td>
<td>604</td>
<td>521</td>
<td>381</td>
<td>219</td>
</tr>
</tbody>
</table>

P = 0.59
No difference in Worsening Heart Failure

Hazard ratio, 0.87 (95% CI, 0.72–1.06)
P=0.17

No. at Risk
Rhythm control  523  436  311  174  63
Rate control  509  419  289  165  54
Limitations

- Amiodarone was the predominant antiarrhythmic medication
- Not all rhythm control patients were in NSR and vice versa
- 10% crossover rate to rhythm control
Increased risk of amiodarone in Class III CHF

B. NYHA Class III

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio (97.5% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs. placebo</td>
<td>1.44 (1.05–1.97)</td>
<td>0.010</td>
</tr>
<tr>
<td>ICD therapy vs. placebo</td>
<td>1.16 (0.84–1.61)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Amiodarone
(5-yr event rate, 0.528)

ICD therapy
(5-yr event rate, 0.484)

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0-yr</th>
<th>12-yr</th>
<th>24-yr</th>
<th>36-yr</th>
<th>48-yr</th>
<th>60-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>244</td>
<td>209</td>
<td>179</td>
<td>106</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>Placebo</td>
<td>253</td>
<td>234</td>
<td>202</td>
<td>138</td>
<td>86</td>
<td>17</td>
</tr>
<tr>
<td>ICD therapy</td>
<td>263</td>
<td>228</td>
<td>202</td>
<td>130</td>
<td>68</td>
<td>23</td>
</tr>
</tbody>
</table>
Methods of rate control

• Drug therapy
  – Beta blockers are the treatment of choice
  – Digoxin is less effective in settings of enhanced sympathetic activity and has a slow onset of action.
  – Calcium channel blockers are relatively contraindicated because of negative inotropy
  – Amiodarone can be used for rate control

• His bundle ablation and permanent pacing
  – Biventricular pacing is superior to RV pacing in patients with CHF with respect to 6 minute walk test and LVEF (PAVE trial 2005)

• Maintenance of sinus rhythm is an excellent rate control mechanism
Rate Control Targets

- Target resting heart rate: \( \leq 80 \text{ BPM} \)
- 24 hour Holter average: \( \leq 100 \text{ BPM} \)
- 24 hour Holter: no individual heart rate > 110\% of age predicted
- Heart rate \( \leq 110 \text{ BPM} \) on 6 minute walk test.
His Bundle ablation compared to PVAI

- Symptomatic drug refractory patients with Class II-III CHF (LVEF < 0.40) randomized to:
  - AV node ablation and biventricular pacing
  - Pulmonary vein isolation for cure of AF
- Follow up: 6 months
- PVAI success: 88% of those on AA drugs, 71% of those not on AA drugs
  - Complications: Pericardial effusion (1), pulmonary vein stenosis (2), pulmonary edema (1)
- Bi-V implant complications: lead dislodgement (1), pneumothorax (1)
Improved ejection fraction

A Ejection Fraction

Ejection Fraction (%)

Months

PVI

P=0.03

AV-node ablation + BiV

P<0.001
Improved 6 minute walk test

B 6-Minute Walk

Distance (m)

0  260  280  300  320  340  360

0  3  6

Months

PVI

P=0.003

AV-node ablation + BiV

P<0.001
Why CHF worsens AF

- Atrial remodeling
  - Elevated LA pressures
    - Mitral regurgitation
    - Increased LVEDP
- Increase in sympathetic nervous system
  - Increased sympathetic nerve activity in AF
- Activation of the Renin-Angiotensin system
  - Increased atrial fibrosis
  - Possible direct ion channel effects
Effects of the Renin Angiotensin System

LV Hemodynamics
Enalapril reduces atrial fibrosis in AF

**P < 0.01 vs CTL

## P < 0.01 vs 5W and 5W+E**

[Images of histological sections showing connective tissue with annotations for control (CTL) and experimental conditions (5W, 5W+E, 5W+HI)]
# Reduction in AF with Angiotensin Blockade

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow Up</th>
<th>Treatment</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF &lt; 0.30</td>
<td>2.9 years</td>
<td>Enalapril (5.4%)</td>
<td>Placebo (24%)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Post MI EF&lt; 0.35</td>
<td>2-4 years</td>
<td>Trandolapril (2.8%)</td>
<td>Placebo (5.3%)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>EF &lt; 0.40</td>
<td>23 months</td>
<td>Valsartan (5.12%)</td>
<td>Placebo (7.95%)</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>
Atrial Stretch Increases AF

Sustained AF

P=10 cm H₂O

AF → Sinus Rhythm

P=0 cm H₂O

AF INTERVAL (ms)

Number of AF cycles

P=10 cm H₂O

P=0 cm H₂O

Number of AF cycles

Last beat of AF
Sympathetic Activity

- Subset analysis of US Carvedilol Heart Failure Trial.
  - 136 patients with AF analyzed.
  - 55% of patients had Class III
- Improvement in LVEF
  - Carvedilol: 0.23 to 0.33
  - Placebo: 0.24 to 0.27
- Trend to improvement in hospitalization/death
  - Carvedilol: 7%
  - Placebo: 19% (p = 0.55)
How to break the cycle

- Aggressive rate control
- Treatment with beta blockers
- Treatment with ACE inhibitors or ARBs
- When is conversion to Sinus Rhythm essential:
  - When rate control cannot be achieved by standard therapy
  - When patients are not responding to appropriate medical therapy