Electrophysiology

Gender and cardiac resynchronization therapy

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Gender and Cardiac Resynchronisation Therapy

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Disclosure/Warning

• I am male.
• I am a descendant of Emmeline Pankhurst, leader of the British Suffragette movement.
• Like my ancestor I struggle to accept the status quo.
• My family genetics seem to lean towards forthright speech and sometimes militancy when addressing injustice.

Cardiac Resynchronisation Therapy
CRT

- Simultaneous pacing of RV & LV = Biventricular pacing
- RA, RV & LV
- LV paced via coronary sinus
Patient Selection

- Not all patients respond to CRT therapy.
- Expensive devices.
- Labour intensive.
- Which patients will get the most benefit from therapy?
- How do we get the best value for money with this resource allocation?
Non Responders

- **Reasons for CRT nonresponse**
- There are several reasons why a patient may not benefit from CRT after implantation:
  - The implanted system is not working properly due to electrode dislocation or inhibition of ventricular stimuli;
  - The LV pacing lead position is not optimized for CRT use;
  - Lack of viable myocardium for resynchronization therapy, for example, after myocardial infarction;
  - Endstage of dilative cardiomyopathy with a loss of capability for reverse remodeling.
European(ESC 2016) Guidelines

- Recommendations for cardiac resynchronization therapy implantation in patients with heart failure
- Recommendations Class a Level b Ref c
  - CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration \( \geq 150 \) msec and LBBB QRS morphology and with LVEF \( \leq 35\% \) despite OMT in order to improve symptoms and reduce morbidity and mortality.
  - IIa B 261–272
  - CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration \( \geq 150 \) msec and non-LBBB QRS morphology and with LVEF \( \leq 35\% \) despite OMT in order to improve symptoms and reduce morbidity and mortality.
  - IIb 261–272
  - CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF \( \leq 35\% \) despite OMT in order to improve symptoms and reduce morbidity and mortality.
  - IIa B 266, 273
  - CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF \( \leq 35\% \) despite OMT in order to improve symptoms and reduce morbidity and mortality.
  - IIb 266, 273
  - CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).
  - III A 274–277
  - CRT should be considered for patients with LVEF \( \leq 35\% \) in NYHA Class III–IVd despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration \( < 130 \) msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.
  - IIa B
  - IIb
  - IIb
  - CRT rather than RV pacing is recommended for patients with HF\(\text{EF} \) who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.
  - IIb B 282
  - CRT is contra-indicated in patients with a QRS duration \( < 130 \) msec. III A
  - III A
  - IIb B

Criteria predicting good response to CRT

- MADIT CRT identified 6 predictors of super response:
- Female sex
- Non Ischaemic
- QRS duration \( \geq 150\text{ms} \)
- Left Bundle Branch block (LBBB)
- BMI \( < 30 \)
- Smaller left atrial volume
<table>
<thead>
<tr>
<th>Study/Design</th>
<th>Number of Subjects</th>
<th>Enrolment Criteria</th>
<th>Randomisation</th>
<th>HR for Events (95%; p Value)</th>
</tr>
</thead>
</table>
| **COMPANION** | Men: 1,025 (67%)  
  Women: 495 (33%) | LVEF ≤35%  
  NYHA class III–IV  
  QRS ≥120 ms | OMT versus OMT  
  + CRT-D | HR for death – men: 0.63  
  (0.4–0.9)  
  women: 0.58 (0.25–1.13) |
| **CARE-HF** | Men: 597 (73%)  
  Women: 216 (27%) | LVEF ≤35%  
  NYHA class III–IV  
  QRS ≥120 ms  
  LVEDD ≥30 mm | OMT versus OMT  
  + CRT | HR for death or cardiac hospitalisation –  
  men: 0.62 (0.49–0.79)  
  women: 0.64 (0.42–0.97) |
| **MADIT-CRT** | Men: 1,367 (75%)  
  Women: 453 (25%) | LVEF ≤30%  
  NYHA class I–II  
  QRS ≥120 ms  
  LVEDD ≥30 mm | ICD versus CRT-D | HR for HF event or death –  
  men: 0.71 (0.59–0.97)  
  women: 0.57 (0.22–1.46) |
| **RAFT** | Men: 1,490 (83%)  
  Women: 308 (17%) | LVEF ≤30%  
  NYHA class I–II  
  QRS ≥120 ms | ICD versus CRT-D | HR for death or HF admission –  
  men: 0.82 (0.7–0.95)  
  women: 0.52 (0.35–0.85) |
| **REVERSE** | Men: 479 (78.5%)  
  Women: 131 (21.5%) | LVEF <40%  
  NYHA class I–II  
  QRS >120 ms | CRT-ON versus CRT-OFF | HF composite end-points –  
  men: 0.65 (0.43–1.11)  
  women: 0.75 (0.26–2.19) |
| **MIRACLE** | Men: 216 (67%)  
  Women: 107 (33%) | LVEF ≤35%  
  NYHA class III–IV  
  QRS >130 ms | CRT-ON versus CRT-OFF | NYHA class, quality of life, exercise capacity:  
  women but not men with CRT experienced longer  
  times to first HF hospitalisation or death  
  (p=0.157) |

**Under-representation of Women in CRT Trials**

- Complex issue.
- There may be selection bias.
- Perhaps this reflects a difference in the way that heart failure presents between men and women.
- Perhaps the indication criteria should be gender dependent.
CRT therapy: do women benefit more than men?

- Xu et al, Journal Cardiovascular Electrophysiology, 2012
- Retrospective evaluation of 728 patients receiving CRT.
- Women had a significant improvement in NYHA class which was not seen in men.
- Greater improvement in EF was also seen in women.

Female Gender is associated with a better outcome after CRT

- Leyva et al, Pacing Clin Electrophysiology, 2011
- Female sex was an independent predictor of survival regardless of age, EF, QRS duration, type of CRT device and NYHA class.
- Women had better survival, longer event free survival from death/HF hospitalisation and also significantly better improvements in NYHA class, EF and LV reverse remodelling.
LBBB predicts better survival in women than men receiving CRT

- Loring et al, JACC Heart Failure, 2013
- Long term follow up of 145,000 patients.
- LBBB was associated with a significantly better survival rate in women compared to men treated with CRT

CRT in women vs men

- Zusterzeel et al, Circoutcomes, 2015
- Looked at sex specific outcomes in data registry patients with class III and IV who had CRT-D vs ICD.
- Among patients receiving CRT, with LBBB and QRS >120, both sexes had lower relative death risk to those receiving ICD.
- Women had a more significant reduction than men.
CRT in women: FDA meta-analysis

• Zusterzeel et al, JAMA, 2014
• Looked at whether women with LBBB benefit from CRT-D at a shorter QRS duration than men with LBBB do.
• Pooled data from 3 CRT-D vs ICD trials (MADIT CRT, RAFT and REVERSE) including 4076 patients with predominantly class II heart failure.
• In patients with LBBB and QRS 130-149 women had a significant reduction in heart failure or death and death alone. For the same QRS duration men did not have benefit
• Both sexes benefited from CRT-D with QRS duration 150ms or longer.

Further Meta Analysis
Cipriani et al, Int J Cardiology, 2015
Response to CRT according to QRS duration and gender in NICM and LBBB

- Varma et al, HeartRhythm, 2014
- Retrospective Study involving 212 non ischaemic patients with class III/IV receiving CRT and looking at improvement in EF on echo.
  - 86% of women vs 36% of men with QRS duration <150ms.
  - 83% of women vs 69% of men with QRS duration ≥ 150ms.

Gender Differences in CRT and outcome in patients aged 75 and older

- Wang et al, Am J Cardiol, 2017
- Women were more likely to receive CRT-P than men.
- Men with CRT-P were significantly older than women with CRT-P and both men and women with CRT-D.
- Women had lower all cause mortality compared with men.
Conclusion

- Women are under represented in CRT trials and probably also in clinical practice.
- Women appear to get greater benefit overall from CRT.
- Women probably get greater benefit in the QRS duration range from 130-150ms.
- Current guidelines may be doing women a disservice by moving towards longer QRS duration criteria for indication for CRT.