CRT in Heart Failure: Emerging Concepts and Clinical Insights into Reverse Remodeling

Katherine Fan
Consultant Cardiologist
Grantham Hospital
HK SAR
Pathogenesis of Heart Failure

Dynamic complex cascade

Myocardial Insult → Myocardial Dysfunction → Reduced System Perfusion

Sympathetic System Activation → Renin-Angiotensin-Aldosterone System Activation

Altered Gene Expression → Apoptosis → Remodeling
Pathophysiology of Ventricular Remodeling

Myocyte Death
- Decreased CO
- TGF-β1 release
  - Macrophage & fibroblast chemotaxis
  - Fibroblast proliferation
  - Macrophage transformation

Juxtaglomerular Apparatus Activation of RAAS
- Increased ANP, BNP
  - Increased Na⁺, Water excretion

ET-1 release
- Decreased Volume SVR

Myocyte Hypertrophy
- Transient Improvement LV function
- Local Ang II & Aldosterone production
- Fibroblast transformation into myo/fibroblast
- TGF-β1 expression
  - Activation of TIMPs

Wall thinning
- Ventricular Dilatation
- Increased wall stress
- Mechanical stretch
- Local Ang II release
  - Activation of fetal gene program
  - Increased contractile proteins

Early Remodeling (<72 hours)

Fibrosis
- Late Remodeling

Sutton MG SJ. Circ 2000;101:2981-8
Processes Occurring in Ventricular Remodeling: Adaptive vs Maladaptive Processes

- Cardiomyocyte lengthening
- Ventricular wall thins
- Infarct expansion rather than extension occurs
- Inflammation and re-absorption of necrotic tissue
- Scar formation
- Continued expansion of infarct zone
- Dilation and reshaping of the left ventricle
- Myocyte hypertrophy
- Ongoing myocyte loss
- Excessive accumulation of collagen in the cardiac interstitium
LV Remodeling - A Dynamic Process

- Characterized by
  - Progressive chamber dilatation
  - Distortion of cavity shape
  - Disruption of mitral valve geometry with MR
  - Deterioration in contractile function

LV Remodeling Post Anteroseptal MI

1 week
- EDV 137ml ESV 80ml
  - EF 41%

3 months
- EDV 189ml ESV 146ml
  - EF 23%

Apical 4 Chamber View
End-diastole
Reverse Remodeling

Reversal of maladaptive remodeling mechanism in HF patients by both pharmacological and non-pharmacological interventions is viewed as a surrogate of improved outcome.
Myocardial Asynchrony

- Atrio-Ventricular
- Intra-Ventricular
- Inter-Ventricular
Electrical dyssynchrony leads to mechanical dyssynchrony...
Prolonged AV Conduction Delay

- Sub-optimal contribution of atrial systole
- Limited LV filling period
- Mitral regurgitation
Optimal AV Delay Improves AV synchrony

Intrinsic
- Aortic pressure
- Peak atrial systole
- Left ventricular (LV) pressure

Paced
- Diastolic mitral regurgitation
- Start of LV systole
- Synchronized LV and atrial systoles
- Maximum effective preload

PP
Delayed Inter-ventricular Activation

- Delayed LV lateral wall contraction
- Disorganized ventricular contraction
- Decreased pumping efficiency
Abnormal Wall Motion
Interventricular Resynchronization

- Intraventricular Activation
- Organized ventricular activation sequence
- Coordinated septal and free-wall contraction
- Improved pumping efficiency
Issues Associated with Heart Failure

**CRT–global synchrony**

Baseline

DCM - CRT

Courtesy of C. Stellbrink, MD.
Intra-ventricular Activation Delay

- Delayed segmental contraction within LV
- Disorganized ventricular contraction
- Decreased pumping efficiency
Intra-LV Electromechanical Asynchrony
A New Independent Predictor of Severe Cardiac Events in Heart Failure Patients
Bader et al JACC 2004; 43: 248-56

- 104pts with stable HF (EF 31% & non-ischemic)
- 57pts (55%) has QRS<120ms

Distribution of ECG characteristics according to different type of electromechanical asynchrony in study population

<table>
<thead>
<tr>
<th>ECG Characteristics</th>
<th>Inter-V Asynchrony Alone (%)</th>
<th>Intra-LV Asynchrony Alone (%)</th>
<th>Inter-V and Intra-LV Asynchrony (%)</th>
<th>Total Asynchrony (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete LBBB</td>
<td>7</td>
<td>55*</td>
<td>29</td>
<td>91</td>
</tr>
<tr>
<td>Complete RBBB</td>
<td>0</td>
<td>56*</td>
<td>27</td>
<td>82</td>
</tr>
<tr>
<td>Incomplete LBBB</td>
<td>2</td>
<td>44</td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>Left anterior hemiblock</td>
<td>0</td>
<td>40</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>QRS width &gt;120 ms</td>
<td>6</td>
<td>56*</td>
<td>28</td>
<td>90</td>
</tr>
<tr>
<td>QRS width &gt;140 ms</td>
<td>8</td>
<td>51*</td>
<td>38</td>
<td>97</td>
</tr>
<tr>
<td>QRS width &lt;120 ms</td>
<td>2</td>
<td>46</td>
<td>10</td>
<td>58</td>
</tr>
</tbody>
</table>

*p < 0.05 by multivariate analysis of variance between the four types of asynchrony. Data are presented as the percentage of patients.
Intraventricular asynchrony

Multivariate Cox regression analysis for identifying pts with rehospitalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>Hazard Ratio (95% CI)</th>
<th>t Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primitive cardiomyopathy</td>
<td>0.209</td>
<td>1.19 (0.75–1.74)</td>
<td>0.927</td>
<td>0.353</td>
</tr>
<tr>
<td>QRS width &gt;120 ms</td>
<td>0.091</td>
<td>1.03 (0.65–1.63)</td>
<td>0.198</td>
<td>0.842</td>
</tr>
<tr>
<td>QRS width &gt;140 ms</td>
<td>0.819</td>
<td>1.86 (1.11–3.21)</td>
<td>2.284</td>
<td>0.022</td>
</tr>
<tr>
<td>Complete LBBB</td>
<td>0.346</td>
<td>1.21 (0.71–1.68)</td>
<td>0.880</td>
<td>0.378</td>
</tr>
<tr>
<td>Aortic pre-ejection interval</td>
<td>0.514</td>
<td>1.34 (0.91–1.84)</td>
<td>0.987</td>
<td>0.185</td>
</tr>
<tr>
<td>Inter-V asynchrony</td>
<td>0.215</td>
<td>1.18 (0.71–1.86)</td>
<td>0.783</td>
<td>0.433</td>
</tr>
<tr>
<td>Intra-LV asynchrony</td>
<td>1.469</td>
<td>3.39 (2.12–6.05)</td>
<td>5.776</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF &lt;25%</td>
<td>1.340</td>
<td>3.27 (1.96–5.86)</td>
<td>5.275</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Proposed Mechanisms of Action of CRT

- **Increased LV filling time**
  - $\uparrow$AV and/or IVCD with delayed LV activation
  - Simultaneous atrial “kick” and early LV passive filling
  - Decreased total transmitral flow and $\downarrow$preloading of LV
  - With CRT, LV is able to complete contraction and begin relaxation earlier thus $\uparrow$filling time

- **Decreased septal dyskinesia**
  - Corrects paradoxical septal wall motion
  - Allow ventricular ejection to occur before relaxation of septum
  - $\downarrow$MR and $\uparrow$stroke volume

- **Reduced mitral regurgitation**
  - Diastolic MR occurs because of improperly timed atrial and ventricular systole
MIRACLE
Effect of CRT on composite clinical response end point

Composite end-points: death, HF hospitalization, worsening of NYHA functional class, global assessment score
Who is a Responder to CRT?

- Clinical parameters
  - NYHA functional class
  - QOL
  - Peak Vo2
  - 6 mins walk
  - Hospitalization
  - Mortality

- Subjective/ Substantial placebo effects (up to 40%)

- ECHO parameters
  - LV systolic function (EF)
  - Mitral regurgitation
  - LV dimensions/volumes- “reverse LV remodeling” has been reported consistently and used as an indicator of response

- More objective
Reverse Remodeling is a CRT-dependant, Immediate Dynamic Process....

LV Filling time

EF

*p<0.05 vs baseline

Circulation 2002;105:438-45
LVED

LVES

P<0.05

Left ventricular end-diastolic volume (ml)

Circulation 2002;105:438-45
MR area

6-min Hall Walk

*p<0.05 vs baseline

Circulation 2002;105:438-45
Effect of CRT on LV size and function in chronic heart failure - substudy of MIRACLE

Circulation 2003;107:1985-90
CRT produces reverse remodeling regardless of HF etiology or use of $\beta$-blockers.
135 pts who were CRT responders. LVESV $< 15\%$ after 6 months of CRT.

Beneficial effects of LV reverse remodeling is pacing dependent, and that continuous pacing is warranted.
Differential change in LV mass and regional wall thickness after CRT for HF

Zhang et al. Eur Heart J 2006;27:1423-30
Differential increase in regional wall thickness – both septal and lateral walls at baseline and in non-responders

Septum
- Early depolarization
- Hyperactive contraction
- Extra wall stress during late systole & isovolumetric relaxation

Lateral
- Exerts extra stress on relaxed orthogonal wall
- Delayed contraction
Reverse LV Remodeling

- Significant reduction in LV linear diameters and LV cavity volumes
  - ↓ LV loading condition and wall stress
  - LV mass regression
  - ↑ LV contractile function
- Progressive reverse remodeling is time dependent and is sustained by continuous CRT pacing
- Mechanical advantageous alteration in LV architectures- evidenced by reduction in severity of MR
  - Changes in geometry of LV shape and mitral subvalve apparatus
  - Restoration of temporal co-ordination of mechanical activation of papillary muscle insertions with better MV coaptation
Mechanism of MR Reduction

- CRT can reduce MR by
  - Improved temporal coordination of mechanical activation of papillary muscles
  - Improved co-ordination of papillary muscle forces on mitral chordae- ↑area of MV leaflet co-aptation
  - Improved LV size and geometry due to reverse remodeling
Acute effects of initiation and withdrawal of CRT on papillary muscle dyssynchrony and mitral regurgitation

Ypenburg et al JACC 2007;50-2071-7

Acute improvement in MR attributed to resynchronized contraction of papillary muscle. Acute interruption resulted in acute deterioration of MR indexes.
Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after CRT

Yu et al. Circulation 2005;112:1580-6

- 141 HF pts with mean age 64 yrs; 73% men
- CRT implanted with mean FU 695 days
- ECHO demonstrated LV reverse remodeling 3-6 mths

Findings:
- Pts whose LVESV decreased by at least 10% at 3-6 months had a more favorable long-term outcome

7% vs 31% (p=0.0003)
12% vs 33% (p=0.0032)
14% vs 39% (p =0.0016)
The Magnitude of Reverse Remodeling Irrespective of Aetiology Predicts Outcome of Heart Failure Patients Treated with CRT

Di Biase et al EHJ 2008;29:2497-2505

- Prospective observational study
- 398 pts with CRT (9/98-8/07)
  - 179 ischemic; 219 non-ischemic
  - ECHO at baseline and mean 4.6mths post CRT
  - FU median 4.4 yrs
- ΔLVEF was dichotomized at median of its distribution (</=6 absoulte point) and its upper tertile (</=11 absolute points)
• Once reverse remodeling occurred (either defined as change of LVEF ≥6pts or change in LVESV at least 10%), aetiology of underlying cardiac disease does not impact outcome anymore.

• Up to certain change in LVEF, outcome will not greatly change.
Left ventricular dyssynchrony predicts right ventricular remodeling after CRT

Bleeker et al. JACC 2005;46:2264-69

- Reverse remodeling after CRT with reduction in TR and decrease in PA pressure
- Acute septal-lateral delay after CRT but was not accompanied by reduction in RV dimension
- Possibly sustained improved LV performance led to reduction in PA pressure (rather than coordinated motion of interventricular septum)
Effects of cardiac resynchronization on disease progression in pts with left ventricular dysfunction, an indication for an ICD and mildly symptomatic chronic HF


- Randomized double blind, parallel-controlled trial
- Total 186pts (CRT=85/ control 101) with NYHA class II HF, EF<35%, LVEDD >55mm, QRS>130ms & indication for ICD/ FU 6 mths
- Results:
  - ↑ 6 mins hall walk and peak VO2 but not statistically significant
  - ECHO: significant reduction of LVEDV/ LVESV & improvement of EF

? Prophylactic CRT
Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms reverses remodeling in systolic left ventricular dysfunction.

Study Group

Linde C, Abraham WT, Gold MR et al.

JACC 2008 52;1834-43
Multicenter (n=73) randomized, double-blind trial in NYHA class I or II pts with SR with QRS >120ms, EF <40%, LVdd>55mm

684 enrolled- 91% (n=621) received successful CRT implants

1° end-point: HF clinical composite response
- Improved
- Worsened
- Unchanged

2° end-point: left ventricular end-systolic volume index (LVESVI)
.. But must balanced against risks eg LV lead dislodgement requiring re-operation at 1 yr = 8%
Electrical and Mechanical Components of Dyssynchrony in Heart Failure Patients with Normal QRS Duration and Left Bundle-Branch Block


- 22 HF pts [13 LBBB (mean QRS 171ms)/9 normal QRS (mean 100ms)] implanted with resynchronization pacemakers
- LV free wall activation occurred earlier in normal QRS than in LBBB gp (65±25 vs 155±23 ms after onset of QRS ;p<0.001)
Despite different electrical activation pattern between HF pts with normal QRS duration and LBBB- BIV or LV pacing can resynchronize mechanical function of LV in both gps.

HF pts with normal QRS duration had late LV free wall activation & mechanical dsysynchrony which improved with CRT.

Timing of LV free wall electrical activation may help to identify those who will be resynchronized.

*Garc 2004; 109: 2544-49*
Cardiac Resynchronization Therapy in Heart Failure with Narrow QRS Complexes

RethinQ Study

*NEJM 2007;357:2461*

- N=172pt: ICD indicated; EF <35%, NYHA class III, QRS <130ms, mechanical dyssynchrony on ECHO/ Double blinded study
- CRT did not improve peak oxygen consumption, QoL, 6 min hall walk or LV reverse remodeling in QRS<120ms
- More comprehensive quantification of LV dyssynchrony based on myocardial imaging necessary to dientify responder to CRT in selecting patients with narrow QRS
Energetics Data

Cost of increased systolic function

- Drugs that increase systolic function typically increase energetic demand and historically result in adverse chronic outcomes
- What is the energetic cost of CRT?


CRT decreasing O2 consumption vs dobutamine

LV mechanical dyssynchrony is responsible for regional heterogenous mechanical load and LV wall stress

CM with intraventricular conduction delay

Septal wall activation first

Posterolateral wall early systolic stretch (↑ local preload)

Energy waste

Early / vigorous shortening against low regional preload

Posterolateral wall activation last

Aortic valve opening

Energy waste

Late systolic contraction against high LV cavity pressure (↑ afterload and wall stress)

Regional blood flow & myocardial oxygen demand ↑

Regional hypertrophy

Disruption of myocardial cellular integrity

Vicious cycle of LV remodeling begins…
Abnormal Local Wall Strain/ Stress

Healthy

DCM

Longer

Relaxed

Shorter

SEPTUM

BASE

APEX

TF: 0
time = 47.3 ms

TF: 1
time = 98.3 ms
Dysregulation of myocardial proteins in late-activated high stress lateral wall

- Mechanical dyssynchrony spatially polarizes ventricular protein expression especially in the late-activated lateral wall
CRT reduces interstitial remodelling, apoptotic death and TNF-α expression

Before CRT

After CRT

CVF (collagen volume fraction)

TNF-α immuno-reaction

Apoptosis detection:
→ Activated caspase-3
→ Apoptotic nuclei

Eur Heart J 2006 27(2):201-6
Effect of CRT on global and regional oxygen consumption and myocardial blood flow in patients with non-ischemic and ischemic cardiomyopathy

Lindner et al Eur Heart J 2005;26:70-76

11C-acetate PET study before and 4 mths after CRT in 42 pts

No improvement in overall global MBF but a more homogenous flow distribution as evidence by increase in septal/ lateral wall ratio.
Cost of increased systolic function

Ventricular conduction delay

Positive inotropic agent

CRT

An Epidemic of Dyssynchrony
What are we really looking for?
Systolic Improvement and Mechanical Resynchronization does not Require Electrical Synchrony in Dilated Failing Heart with LBBB
Different Mechanisms for Generating Cardiac Dyssynchrony

- Causes of dyssynchrony
  - Temporal delay
    = Delay in electrical activation
  - Results of heterogeneity of contractile properties in the ventricular wall

Kass JACC 2008;51:12-17
3D ECHO

Longitudinal Strain

Speckled Tracking
### Overview of different ECHO techniques to assess dyssynchrony to consider CRT as beneficial

<table>
<thead>
<tr>
<th>Methods</th>
<th>Measures</th>
<th>Dyssynchrony cutoff values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Doppler</td>
<td>Difference between aortic and pulmonary pre-ejection time</td>
<td>≥ 40ms</td>
</tr>
<tr>
<td>Conventional Doppler</td>
<td>Aortic pre-ejection interval during spontaneous rhythm</td>
<td>≥140ms</td>
</tr>
<tr>
<td>M-mode</td>
<td>Septal to posterior wall motion delay</td>
<td>≥130ms</td>
</tr>
<tr>
<td>TDI</td>
<td>Max delay between peak systolic velocities of any 2 of 12 LV segments</td>
<td>≥100ms</td>
</tr>
<tr>
<td>TDI</td>
<td>Max delay between peak systolic velocities in 4 LV segments</td>
<td>≥65ms</td>
</tr>
<tr>
<td>TDI</td>
<td>Standard deviation of time to peak systolic velocity of 12 LV segments</td>
<td>≥33ms</td>
</tr>
<tr>
<td>TDI</td>
<td>Maximal delay in time to peak systolic velocity from anterior to posterior wall</td>
<td>≥65ms</td>
</tr>
<tr>
<td>TSI</td>
<td>Time to peak velocities of opposing ventricular walls</td>
<td>≥65ms</td>
</tr>
<tr>
<td>Longitudinal strain</td>
<td>Temporal difference in septal-lateral peak systolic strain</td>
<td>≥50ms</td>
</tr>
<tr>
<td>Radial strain</td>
<td>Time difference of peak radial strain in septum vs posterior wall</td>
<td>≥130ms</td>
</tr>
<tr>
<td>Real time 3D</td>
<td>Systolic dyssynchrony index</td>
<td>≥14.7%</td>
</tr>
</tbody>
</table>
All offline analyses were conducted in the same apical 4-chamber view. For velocity measurement, the time to systolic peak (and also the peak velocities) is highly consistent (arrow) when the sampling windows were placed in the basal septal (yellow curve) and basal lateral (green curve) segments (a), when compared with a slightly lower position (b) or slightly inward motion towards endocardium (c). However, for strain assessment, variance in the same position resulted in dramatic changes in the shape and size of the curves resulting in significant changes in time to peak strain, their values and even directions. Note also significant beat-to-beat variation of the strain curves, but not the velocity curves.
Strain Dyssynchrony Index Correlates with Improvement in LV Volume after CRT Better Than Tissue Velocity Dyssynchrony Indexes

Miyazaki et al. Circ Cardiovas Imaging 2008;1:14-22
### Table 4. Primary End-Point Results

<table>
<thead>
<tr>
<th>Echocardiography Type</th>
<th>Dyssynchrony Method/Cutoff</th>
<th>Cutoff Met?</th>
<th>Total</th>
<th>n</th>
<th>%</th>
<th>p</th>
<th>Total</th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>M mode</td>
<td>SPWMD ≥30 ms</td>
<td>Yes</td>
<td>426</td>
<td>294</td>
<td>69</td>
<td>0.44</td>
<td>286</td>
<td>161</td>
<td>56</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>135</td>
<td>91</td>
<td>67</td>
<td></td>
<td>98</td>
<td>48</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Pulsed Doppler</td>
<td>RVMD ≥40 ms</td>
<td>Yes</td>
<td>194</td>
<td>143</td>
<td>74</td>
<td>0.045</td>
<td>148</td>
<td>92</td>
<td>62</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>182</td>
<td>116</td>
<td>64</td>
<td></td>
<td>126</td>
<td>62</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LVFT/FR ≥40%</td>
<td>Yes</td>
<td>112</td>
<td>87</td>
<td>75</td>
<td>0.015</td>
<td>88</td>
<td>59</td>
<td>67</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>235</td>
<td>153</td>
<td>65</td>
<td></td>
<td>168</td>
<td>85</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPEI ≥140 ms</td>
<td>Yes</td>
<td>239</td>
<td>175</td>
<td>73</td>
<td>0.013</td>
<td>185</td>
<td>113</td>
<td>61</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>146</td>
<td>99</td>
<td>66</td>
<td></td>
<td>97</td>
<td>44</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>M mode + Doppler</td>
<td>LLWC any overlap</td>
<td>Yes</td>
<td>17</td>
<td>11</td>
<td>65</td>
<td>0.58</td>
<td>16</td>
<td>10</td>
<td>66</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>230</td>
<td>164</td>
<td>71</td>
<td></td>
<td>174</td>
<td>95</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>TDI published</td>
<td>Ts Lat-Sep ≥60 ms</td>
<td>Yes</td>
<td>95</td>
<td>64</td>
<td>67</td>
<td>1.00</td>
<td>74</td>
<td>50</td>
<td>68</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>128</td>
<td>87</td>
<td>66</td>
<td></td>
<td>99</td>
<td>45</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ts-SD ≥22 ms</td>
<td>Yes</td>
<td>119</td>
<td>86</td>
<td>72</td>
<td>0.27</td>
<td>98</td>
<td>55</td>
<td>56</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>48</td>
<td>30</td>
<td>63</td>
<td></td>
<td>35</td>
<td>16</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVD ≥110 ms</td>
<td>Yes</td>
<td>179</td>
<td>123</td>
<td>69</td>
<td>0.42</td>
<td>143</td>
<td>80</td>
<td>56</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>93</td>
<td>59</td>
<td>63</td>
<td></td>
<td>71</td>
<td>28</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>TDI + SAR, published</td>
<td>DLC ≥2 segments</td>
<td>Yes</td>
<td>111</td>
<td>75</td>
<td>68</td>
<td>0.79</td>
<td>90</td>
<td>51</td>
<td>57</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>160</td>
<td>105</td>
<td>66</td>
<td></td>
<td>123</td>
<td>66</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>TDI, medium value used as cutoff</td>
<td>Ts peak displacement ≥120 ms</td>
<td>Yes</td>
<td>64</td>
<td>46</td>
<td>72</td>
<td>0.34</td>
<td>49</td>
<td>29</td>
<td>59</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>61</td>
<td>38</td>
<td>62</td>
<td></td>
<td>45</td>
<td>21</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ts peak basal ≥83 ms</td>
<td>Yes</td>
<td>137</td>
<td>95</td>
<td>69</td>
<td>0.44</td>
<td>105</td>
<td>62</td>
<td>59</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>137</td>
<td>88</td>
<td>64</td>
<td></td>
<td>111</td>
<td>57</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ts onset basal ≥67 ms</td>
<td>Yes</td>
<td>135</td>
<td>99</td>
<td>73</td>
<td>0.029</td>
<td>110</td>
<td>63</td>
<td>57</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td>139</td>
<td>84</td>
<td>60</td>
<td></td>
<td>106</td>
<td>56</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>
PROSPECT Study

- Study site selection/
  Training of dyssynchrony
  assessment
- ECHO issues:
  - Inter-observer and intra-
    observer variations++
    (retrospective)
  - “low-end machine”
- Other determinants of CRT
  response
  - Presence of scars
  - LV lead position
- “CRT in the Real World”-limited feasibility of
  techniques/ training/
  equipment from multiple
  vendors etc
Although a number of echocardiographic dyssynchrony methods have suggested superiority to ECG QRS width for predicting response to CRT, evidence from large scale clinical trials and current practice guidelines do not include an echocardiographic Doppler dyssynchrony study for patient selection.

Accordingly, this writing group currently does not recommend that patient who meet accepted criteria for CRT should have therapy withheld because of results of an echocardiographic Doppler dyssynchrony study.

Emerging Imaging Techniques

MRI
Timings in maximal wall thickening

SPECT gated myocardial perfusion
Mechanical disco-ordination rather than dyssynchrony predicts reverse remodeling upon cardiac resynchronization
Kirn et al. Am J Physiol Heart Circ Physiol 2008 295 (2); H640-6

- MRI tagging image
- Internal stretch fraction [ISF] = ratio of stretch to shortening during ejection as index of mechanical discooordination
“Internal Stretch Fraction”

- ISF- mechanical discoordination is better predictor of reverse remodelling after CRT than differences in time to onset and time to peak shortening.

*Combination of mechanical imaging with 3D electrical analyses to reveal the substrate...*
Conclusions

- LV reverse remodeling has been consistently showed in most non-controlled and multicenter randomized trials of CRT
- Reduction of LVESV as most important predictor for long-term outcome (mortality and rehospitalization for HF)
- Several different mechanisms may be involved in CRT-induced reverse remodeling
- Best patient selection method may require several combined and/or stepwise approach other than a single dyssynchrony index
- An effort to standardize the ECHO protocols +/- new imaging tools to assess asynchrony remains to be performed