CARDIAC RESYNCHRONISATION THERAPY IN HEART FAILURE

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Hacettepe University, Ankara, Turkey
Pacing for heart failure

- **DDD pacing w/ short AV delay**
- **DDD pacing AV Delay optimization**
- **Biventricular pacing CRT**
- **Expanded CRT indications**
- **Added functions to CRT devices**
- **CRT + ICD**
WHAT IS CARDIAC DYSSYNCHRONY?

• Cardiac dyssynchrony means that the heart’s contraction is not occurring in its usual orderly sequence.

• The three components of dyssynchrony that may impair cardiac efficiency:
  1. Atrio-ventricular dyssynchrony
  2. Interventricular dyssynchrony
  3. Intraventricular dyssynchrony
Electromechanical Delay in End Stage Heart Failure Patients With Conduction Delay

- AV DELAY
- INTERVENTRICULAR DELAY
- INTRAVENTRICULAR DELAY
- INTRAMURAL DELAY
The prevalence of ventricular dyssynchrony

Aaronson et al, Circ 95: 2660-7, 1997 1, derivation sample; 2, validation sample
Schoeller et al, AJC 71: 720-26, 1993
NEGATIVE HEMODYNAMIC EFFECTS OF LEFT VENTRICULAR ACTIVATION DELAY: Concept of dyssynchrony

- Altered LV contraction and relaxation intervals (↑ PEP, ↑ IVRT)
- Shortening of diastolic filling time
- Reduced systolic function (Global & Regional EF)
- Induction or worsening of mitral regurgitation
CRT: ACUTE HEMODYNAMIC EFFECTS

- Increase in cardiac index
- Increase in differential arterial pressure
- Increase in systolic arterial pressure and in left ventricular dp/dt max
- Increase in biventricular EF
- Decrease in systemic vascular resistance
- Decrease in pulmonary capillary pressure
- Decrease in amplitude of V wave in MR
IMPROVED HEMODYNAMICS BY CRT IN CHF PATIENTS

- Optimization of AV contraction sequence
- Resynchronization of right and left ventricular contraction sequence
- Prolongation of diastolic filling time
- Septal motion resynchronization
- Reduction of severity or duration of mitral regurgitation
Improvement In Atrioventricular Synchrony

Before AVD Adjustment

After AVD Adjustment

E/A = 2.09
Diastolic filling time = 359ms

E/A = 1.3
Diastolic filling time = 450ms
Improvement in Interventricular Synchrony

BEFORE CRT

QRS Ao = 180ms
DELAY: 180 - 70ms = 110ms

QRS P = 70

3 DAYS AFTER CRT

QRS Ao = 124ms
DELAY: 124 - 115ms = 9ms

QRS P = 115 ms
Improvement in Intraventricular Synchrony

Baseline

Synchrony $r = 0.40$

6 months BiV Pacing

Synchrony $r = 0.87$

- Lateral wall
- Septum
This slide summarizes these improvements showing tissue Doppler cine-loops with a corresponding mitral annular time velocity curves from baseline and 6 months. A dyssynchronous rocking motion of the mitral annulus was seen at baseline. This improved at 6 months, showing a more synchronous motion of the mitral annulus. In addition, you can see an improvement in global LV function.
Cardiac Resynchronisation Therapy

Intraventricular synchronisation

Atrioventricular Synchronisation

Interventricular Synchronisation

↑ dP/dt, ↑ EF, ↑ CO (↑ pulse pressure)

↓ LVESV

↓ LVEdV

↓ MR

↓ LA Pressure

↑ LV diastolic filling

→ Reverse Remodeling

↑ RV stroke V

Evidence of LV Resynchronization by Spectral Doppler

**MIRACLE Study**

**LV Filling Time**

- Baseline
- 3mo
- 6mo

**IVC Time**

- Baseline
- 3mo
- 6mo

*:* p<0.05

*Sutton et al. Circulation 2003;107:1985*
Echocardiographic Evidence of LV Reverse Remodeling in Responders to CRT

- End diastolic diameter
- End diastolic volume
- End systolic diameter
- End systolic volume
- Ejection fraction
- Sphericity
LV Reverse Remodeling by CRT
*MIRACLE Study*

**LVEDV**

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**LVESV**

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*: p<0.05

LV Reverse Remodeling by CRT

MIRACLE Study

**LVEF**

- **CONTROL**
- **CRT**

**CARDIAC INDEX**

- **CONTROL**
- **CRT**

*:* p<0.05

*Sutton et al*  *Circulation* 2003;107:1985
LV Reverse Remodeling by CRT

**MIRACLE Study**

### MR Jet Area

- **CONTROL**
- **CRT**

<table>
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<th>Time</th>
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<th>p-value</th>
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<tr>
<td>3 mo</td>
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<tr>
<td>6 mo</td>
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### LV MASS

- **CONTROL**
- **CRT**

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<th>Time</th>
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<th>p-value</th>
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<tr>
<td>6 mo</td>
<td>330</td>
<td>300</td>
<td>0.05</td>
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</table>

*: p<0.05

*Sutton et al. Circulation 2003;107:1985*
CARE HF
Mechanistic Outcomes
At 18 months, compared to the control group, patients randomized to CRT had:

- Shorter Interventricular Mechanical delay  $P < 0.0001$
- Higher LVEF (by about 7%)  $P < 0.0001$
- Less mitral regurgitation  $P = 0.003$
- Lower ventricular volumes  $P < 0.0001$
- Higher systolic blood pressure  $P < 0.0001$
- Lower NT-pro-BNP  $P < 0.0016$

The biological hypothesis behind the study was also proven. With CRT, both at 3 and 18 months there was powerful evidence that resynchronisation had occurred, LV function had improved, mitral regurgitation was less severe, ventricular volumes were reduced, blood pressure had increased and NT-BNP had fallen.
Resynchronization and Reduction in Mitral Regurgitation

- **AV delay optimization**
  - Reduction in presystolic MR

- **Septal to free wall resynchronization**
  - Improved coaptation of the valve leaflets

- **LV reverse remodeling**
  - Decreased LV end systolic volume

- **Acute decrease in mitral regurgitation**
  - Raise in mitral valve closing force by LV $+dP/dt_{max}$
Reduction in Mitral Regurgitation by a Raise in LV $+dP/dt_{\text{max}}$

Acute Effects of Cardiac Resynchronization Therapy on Functional Mitral Regurgitation in Advanced Systolic Heart Failure

Ole A. Breithardt, MD,* Anil M. Sinha, MD,* Ehud Schwammenthal, MD, FESC,† Nadin Bichou, BSc,* Kai U. Markus, MD,* Andreas Franke, MD,* Christoph Stellbrink, MD, FESC*

Aachen, Germany; and Tel Hashomer, Israel

We studied the acute effects of cardiac resynchronization therapy (CRT) on functional mitral

![Graph showing the correlation between ΔΔ $+dP/dt_{\text{max}}$ and ΔΔ EROA.](image)

Raise in mitral valve closing force

EROA: effective regurgitant orifice area

$\Delta$ $+dP/dt_{\text{max}}$ (% increase)

$\Delta$ EROA (% decrease)

$r=-0.83$

$p<0.0001$
Geometric changes alter the balance between tethering and closing forces and impede effective mitral valve closure. The accelerated rise transmitral pressure during isovolumic contraction phase effectively counteracts the increased tethering forces that impair midsystolic mitral leaflet tenting area. CRT increase LV contraction efficacy thereby generates effective transmitral closing force
Reduction in Mitral Regurgitation by AV Delay Optimization

BEFORE CRT

3 DAYS AFTER CRT

Presystolic MR

No presystolic MR, Decreased MR time, Decreased MR
Reduction in Mitral Regurgitation by Coordinated Timing of Mechanical Activation of Papillary Muscles

Echocardiography and Resynchronization

A Mechanism for Immediate Reduction in Mitral Regurgitation After Cardiac Resynchronization Therapy
Insights From Mechanical Activation Strain Mapping

Hideaki Kanzaki, MD, Raveen Bazaz, MD, David Schwartzman, MD, FACC, Kaoru Dohi, MD, L. Elif Sade, MD, John Gorcsan III, MD, FACC

Pittsburgh, Pennsylvania

Improved coaptation of the valve leaflets
Mechanical Activation Maps in Bull’s Eye Projection

LBBB

AFTER CRT

Time delay between papillary muscle insertion sites
LBBB: 106±74ms   AFTER CRT: 39±43ms   Normal: 12±8ms

Kanzaki H et al. JACC 2004; 44:1619
CRT improves myocardial metabolism

Septal/Lateral-Ratio

Baseline CRT

% Baseline 91

62

Nowak et al., JACC 2003
LV ENERGETICS BY CRT

CRT increases efficacy of LV at low energy cost
Evolution of CRT TRIALS

PILOT STUDIES

SAFEETY EFFICACY STUDIES

MORTALITY STUDIES

1995

PATH-CHF

French Pilot Trial

InSync Trial

1996

Italian InSync Registry

1997

PATH-CHF II

CONTAK

MIRACLE

1998

PACMAN

1999

InSync ICD Study

2000 ...

PAVE

COMPANION

RELEVENT

CARE-HF
Evolution of CRT TRIALS

1999  2000  2005....

STUDIES FOR EXPANDED INDICATIONS

PATH-CHF II
MIRACLE
InSync ICD Study

MORTALITY STUDIES

CARE-HF
PAVE
COMPANION
RELEVENT
CRT IMPORTANT CLINICAL TRIALS

Completed

- French Pilot
- InSync
- In Sync III
- MUSTIC
- CONTAC-CD
- InSync ICD
- MIRA CLE

Ongoing

- PACMAN
- BELIEVE
- PROSPECT
- REVERSE
- PAVE
- COMPANION
- CARE-HF
- BIOPACE
- BLOCK-HF
- MADIT CRT
- RELEVENT
Functional Benefits of CRT

- 6 - minute walking distance
- Health related QOL score
- Peak oxygen consumption
- Hospitalizations for decompensated heart failure
- NYHA functional class

*AHA Science Advisory* Circulation 2005;111:2146-50
COMPANION: Primary Endpoint
Time to first all cause mortality or all cause hospitalization

CRT vs. OPT: RR = 19%, p = 0.014 (Adjusted p-value = 0.015)
CRT-D vs. OPT: RR = 20%, p = 0.010 (Adjusted p-value = 0.011)

Days from Randomization

12-month Event Rates
OPT: 68%
CRT: 56% (AR=12%)
CRT-D: 56% (AR=12%)

OPT
CRT HR 0.81 (CI: 0.69-0.96)
CRT-D HR 0.80 (CI: 0.68-0.95)
COMPANION
Death or CV
Hospitalization

Death or HF
Hospitalization

12-month Event Rates
OPT: 60%
CRT: 45% (AR=15%)
CRT-D: 44% (AR=16%)

12-month Event Rates
OPT: 45%
CRT: 31% (AR=14%)
CRT-D: 23% (AR=16%)

CRT vs. OPT: RR = 25%, p=0.002
CRT-D vs. OPT: RR = 28%, p<0.001

CRT vs. OPT: RR = 34%, p=0.002
CRT-D vs. OPT: RR = 40%, p<0.001

Endpoint Components:
OPT: Mortality 24%
HF Hospitalization 72%
iv Medications 4%
COMPANION: Secondary Endpoint of All-Cause Mortality

CRT vs. OPT: RR = 24%, p=0.059 (Adjusted p-value = 0.060)
CRT-D vs. OPT: RR = 36%, p=0.003 (Adjusted p-value = 0.004)

12-month Event Rates
- OPT: 19%
- CRT: 15% (AR=4%)
- CRT-D: 12% (AR=7%)

Days from Randomization

% of Patients Event-Free

OPT: HR 0.76 (CI: 0.58-1.01)
CRT: HR 0.64 (CI: 0.48-0.86)
## Meta-Analysis of CRT Trials

**All cause mortality**

<table>
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<td>CONTAK CD</td>
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<td>InSync ICD</td>
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<tr>
<td>MIRACLE</td>
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<td>MUSTIC</td>
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<tr>
<td><strong>Total</strong></td>
<td>1426</td>
<td>1133</td>
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Odds Ratio (95% Confidence Interval)

*Int J Cardiol 2004;93:101-103*
Need for a mortality trial to test the effect of CRT alone on mortality in pts with chronic heart failure

The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure

John G.F. Cleland, M.D., Jean Claude Daubert, M.D., Erland Erdmann, M.D., Nick Frejmanne, Ph.D., Daniel Gras, M.D., Lukas Kappenberger, M.D., and Luigi Tavazzi, M.D., for the Cardiac Resynchronization in Heart Failure (CARE-HF) Study Investigators*
CARE-HF: Main Inclusion & Exclusion Criteria

- Heart failure for at least 6 weeks requiring loop diuretics
- Currently in NYHA class III/IV
- A high standard of pharmacological therapy
- LV systolic dysfunction and dilation
  - EF ≤35%; EDD ≥30mm/height in metres
- QRS ≥120 ms
  - Dyssynchrony confirmed by echo if QRS 120-149 ms
    - Aortic pre-ejection delay >140 ms
    - Interventricular mechanical delay >40 ms
    - Delayed activation of postero-lateral LV wall
- Patients with AF or requiring pacing excluded
This slide shows the main inclusion/exclusion criteria. A full list of these criteria has been published (J.G.F. Cleland, J.C. Daubert, E. Erdmann et al. The CARE-HF study [CArdiac REsynchronisation in Heart Failure] study: rationale, design and end-points. Eur J Heart Fail 2001;3:481-9).

Patients with NYHA III/IV heart failure were selected because these patients have a heavy burden of symptoms and a high morbidity and mortality. Therefore, if intervention was effective in improving well-being and prognosis it should be obvious in this group of patients. Also, patients with few symptoms and a relatively good prognosis may have been unwilling to have a device implanted. Congestive signs and symptoms requiring control with diuretics is a bad prognostic sign. The higher the dose required the worse the prognosis. Requiring patients to be on loop diuretics excluded patients with few symptoms and a good prognosis.

A 6 week rather than 12 week duration of persistent symptoms was required because the prognosis of this group of patients is poor. Shortening the period of symptoms meant that more high-risk patients would be enrolled and any benefit might be observed sooner. A low LVEF is a marker of a poor prognosis and cardiac dyssynchrony occurs predominantly in patients with severe LVSD and LV dilatation.

The following trials of pharmacological therapy guided recommendations for pharmacological therapy (CONSENSUS and SOLVD for ACE inhibitors, US Carvedilol trial, MERIT and CIBIS-II for beta-blockers and RALES for Spironolactone). The following trials were reported only AFTER recruitment had started (COPERNICUS, COMET, CHARM and EPHESUS). Patients were therefore required to be on ACE inhibitors and beta-blockers and Spironolactone was strongly recommended for more severe patients. Investigators were encouraged to review medications frequently during the study to maintain and increase appropriate pharmacological therapy.

The MUSTIC trial (a positive trial) used a QRS cut-off >150msec, MIRACLE (a positive trial) a cut-off of >130msec and CONTAK (a neutral trial) used a cut-off of >120msec. The prevalence of cardiac dyssynchrony increases as QRS becomes longer as noted previously. Accordingly, patients with QRS >150msec did not require additional validation of dyssynchrony but patients with a QRS 120-149msec required additional echocardiographic evidence as shown on the slide.

Patients with AF were excluded as there was little evidence of benefit with CRT in this group of patients when CARE-HF was designed. Also, these patients could not benefit from atrio-ventricular resynchronisation.
Primary & Principal Secondary
Endpoints

Primary composite endpoint
• All-cause mortality or unplanned hospitalisations for a major CVS event (time to first event analysis)

Principal secondary endpoint
• All-cause mortality
Device implantation is a substantial procedure for patients to undergo and therefore the events that the device can prevent should be of sufficient severity to warrant device therapy. It was considered that the major effect of CRT would be to improve LV function and symptoms leading to a reduction in hospitalisations for heart failure. It was thought possible that CRT could reduce arrhythmias and possibly other CVS events. Moreover, many patients are hospitalised for a combination of arrhythmias, ischaemic events and heart failure and it becomes difficult to classify patients accurately. However, improved LV function, a reduction in worsening heart failure and in other major CVS events would also be expected to reduce mortality.

Accordingly, the primary endpoint of the study was all-cause mortality or an unplanned (i.e. emergency) admission to hospital for a major CVS event. Emergency heart transplants were counted as deaths (and would have been part of the composite primary endpoint anyway). Elective heart transplants were censored 7 days after transplant, as deaths after this time are more likely to reflect complications of the transplant than the patients pre-operative state. Patients randomised to device implantation were admitted to hospital for the procedure and during this time cannot be admitted for another CVS problem (since they are already in hospital). This could have biased the trial in favour of the device. Therefore, only death and not hospitalisation could count towards the primary endpoint in the first 10 days because most patients randomised to a device would spend a few days in hospital for the procedure during this period. Planned admissions were defined as ones where there was at least 24 hours between the decision to admit and admission. All others were considered unplanned. Two expert cardiologists, blinded to randomisation, independently adjudicated all admissions (unless they were definitely planned) and decided whether the admission was cardiovascular or non-cardiovascular. Cardiovascular hospitalisations were then classified as admission for symptoms without a major event (e.g.: chest pain without evidence of myocardial infarction, palpitations without syncope or evidence of arrhythmia), admission for ‘minor’ cardiovascular events (e.g.: transient ischaemic attack, new onset well tolerated atrial fibrillation) or ‘major’ cardiovascular events (e.g.: myocardial infarction, stroke, pulmonary oedema).

All-cause mortality was the principal secondary endpoint. It is the most robust outcome measure in an unblinded study.
Primary Endpoint
(All-cause Mortality or Unplanned Hosp. for Major CVS Event)

HR 0.63 (95% CI 0.51 to 0.77)

No statistical significant heterogeneity in subgroups

CRT
P < .0001

Medical Therapy

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<th>Number at risk</th>
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<td>118</td>
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There was no heterogeneity in effect in any of the pre-specified subgroups. In particular, benefit was observed in older patients, women, patients with ischaemic heart disease, in patients above and below median LVEF and in patients receiving or not receiving beta-blockers and Spironolactone (there were too few patients not receiving an ACE inhibitor or ARB and therefore this analysis was not included in the statistical analysis plan).
All-Cause Mortality

HR 0.64 (95% CI 0.48 to 0.85)

P = .0019

CRT

Medical
Therapy
There was a striking reduction in mortality in the CRT group. The absolute difference between control and CRT was 10%. Again, there was no early hazard and the curves begin to separate within the first 6 months of randomisation. A reduction in both sudden deaths and deaths due to worsening heart failure was observed. There were only 29 sudden deaths out of 82 in the CRT group.

The benefits of CRT are in addition to those of the above pharmacological therapy. The absolute difference in mortality at 2 years was 7.1%. This compares to 5.2% with Enalapril in the SOLVD-treatment study and is similar to the estimated two-year mortality difference between placebo and Bisoprolol in the CIBIS-II study or the 8.8% difference between placebo and Carvedilol in COPERNICUS (which using the method of trial duration used in our study had a duration of about 15 months).

The hazard ratio of the effect of CRT in CARE-HF (0.64; 95% confidence interval 0.48 to 0.85; p=0.0019) was similar to that of CRT-D compared to control in the COMPANION trial (0.64, 95% confidence interval, 0.48 to 0.86; P=0.003). The absolute estimated difference at 2 years in the COMPANION study between CRT-D and control was about 8% with CRT and CRT-D having similar effects in that study.
CRT-Established benefits

- Improvement in global synchronization (Hemodynamically)
- Organized ventricular activation sequence (EF)
- Improvement in cardiac efficiency (peak VO2)
- Symptomatic improvement (QOL)
- Improved exercise tolerance (NYHA)
- Decreased sympathetic activity and myocardial energy consumption

- IMPROVED SURVIVAL
Characteristics of patients in whom CRT is strongly supported by randomized trials

- Sinus rhythm
- LVES<0.35
- Ischemic or non-ischemic cardiomyopathy
- QRS complex duration>120 msc
- NYHA functional class III or IV
- Maximal pharmacological therapy for heart failure

*AHA Science Advisory. Circulation 2005;111:2146-50*
Resynchronization therapy using biventricular pacing can be considered in patients with reduced EF and ventricular dyssynchrony (QRS width > 120 ms) and who remain symptomatic (NYHA III and IV) despite optimal medical therapy to improve symptoms (Class I, Level of evidence A), hospitalizations (Class I, level of evidence A), and mortality (Class I, Level of evidence B).

Eur Heart J 2005;26:1115-40
CRT in End Stage Heart Failure

*MIRACLE Study*

- Improved: 67%
- No change: 17%
- Worsened: 16%

High number of non-responders!
QRS Duration and LV Dyssynchrony in End-Stage HF

Some heterogeneity between electrical and mechanical dyssynchrony!

LV Dyssynchrony in Patients with Narrow QRS

Quantification of Radial Mechanical Dyssynchrony in Patients With Left Bundle Branch Block and Idiopathic Dilated Cardiomyopathy Without Conduction Delay by Tissue Displacement Imaging

L. Elif Sade, MD, Hideaki Kanzaki, MD, Donald Severyn, MS, Kaoru Dohi, MD, and John Gorcsan III, MD

As a group, patients with IDC without electrical conduction delay had diminished and delayed regional wall displacement compared with normal controls (Table 2 and Figure 5). Significant delays were noted in all segments except for the septum. Two anteroseptal peaks were observed in most patients (83%), with S2 occurring 164 ± 64 ms after aortic valve closure. Evaluation of individual patients revealed heterogeneous patterns of regional dyssynchrony.

with anteroseptal to posterior wall displacement delays of 169 ± 56 ms (p <0.001 vs normal) (Figures 5 to 7).
Long-Term Effectiveness of Cardiac Resynchronization Therapy in Patients With Refractory Heart Failure and “Narrow” QRS

Augusto Achilli, MD,* Massimo Sassara, MD,* Sabina Ficili, MD,* Daniele Pontillo, MD,* Paola Achilli, MD,* Claudio Alessi, MD,* Stefano De Spirito, MD,* Roberto Guerra, MD,* Nicolin Patruno, MD,† Francesco Serra, MD#

Viterbo and Albano Laziale, Italy

OBJECTIVES The aim of the study was to evaluate the effectiveness of cardiac resynchronization therapy (CRT) in patients with refractory heart failure (HF) and incomplete left bundle branch block.

Pacing therapy was effective in the significant reduction of IVD and Q-LW in the entire patient population. The QRS duration does not alter the impact of CRT on the IVD. In fact, IVD significantly improved in all groups after CRT with no statistically significant difference between the groups. Moreover, whereas a significant reduction in the Q-LW interval was observed after CRT only in group 1, the difference between groups 1 and 2 was not statistically significant.

A regression analysis of the asynchrony patterns and the echocardiographic outcome in both groups showed a sig-

DISCUSSION

The major finding of our paper is that this amelioration is comparable to that obtained in patients who are currently selected by means of current indications for CRT (QRS duration >120 to 150 ms) (1–5).

Current study rationale. To date, CRT has been reserved for patients with refractory HF and a consistent prolongation of the QRS (>120 to 150 ms), as suggested by previous studies (1–5). This assumption is based on epidemiologic
“The degree of intraventricular dyssynchrony evaluated by tissue Doppler imaging and not the baseline QRS duration, is predictive of the effectiveness of CRT.”
New imaging modalities to identify the candidates for CRT

- Standard 2D and spectral Doppler
  - Global EF, dimensions, volumes, mass, transvalvular flows
- Tissue Doppler Imaging
  - Regional systolic and diastolic function
  - Regional timing of mechanical events
- 3D echocardiography
- MRI
Echocardiography is a *Must* for the Success of CRT

- Evaluates the mechanical effects of CRT
- Helps predicting responders and non-responders – *evaluation of mechanical dyssynchrony*
- Helps avoiding site of delay- site of pacing mismatch - *optimal lead positioning*
Quantification of Septal To Free Wall Delay in LBBB by Different Tissue Doppler Imaging Modalities

**DISPLACEMENT**
- **CONTROL**
  - Time (ms) vs. Displacement (mm)
- **LBBB**
  - Time (ms) vs. Displacement (mm)

**VELOCITY**
- **CONTROL**
  - Time (ms) vs. Velocity (mm/s)
- **LBBB**
  - Time (ms) vs. Velocity (mm/s)

**STRAIN**
- **CONTROL**
  - Time (ms) vs. Strain (%)
- **LBBB**
  - Time (ms) vs. Strain (%)

**STRAIN RATE**
- **CONTROL**
  - Time (ms) vs. Strain rate
- **LBBB**
  - Time (ms) vs. Strain rate

*Sade LE Eur J Echocardiography 2003;4:S67*
LV mechanical dyssynchrony in LBBB can also be identified by using angle corrected tissue velocity, strain and strain rate.
Quantification of Regional Dysynchrony
Angle-corrected Tissue Displacement Imaging

Sade LE Am J Cardiol 2004; 94:514
Tissue Synchronization Imaging (TSI)

Time to peak velocity delay

- Significant delay in the posterior and lateral walls
  - Responder
- No delay
  - Non-responder
- Reversed delay in the anterior septum
  - Non-responder

Algorhytm to Predict Responders to CRT by TSI

TSI of 2D images (A4C, A2C, ALAX)

Most severe delay at the lateral wall?

Yes

Proceed to quantitative TSI: Ts-SD- 12 ejection

> 34.4ms

Likely responder

≤ 34.4 ms

Likely non-responder

No

Yu CM et al. JACC 2005; 45:677
## Cut-off Values of Systolic Dyssynchrony Measured by TSI

<table>
<thead>
<tr>
<th></th>
<th>Cut-off (ms)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ts-SD-12 ejec</td>
<td>34.4</td>
<td>87</td>
<td>81</td>
</tr>
<tr>
<td>Ts-SD-6 ejec</td>
<td>34.5</td>
<td>70</td>
<td>92</td>
</tr>
<tr>
<td>Ts-12 ejec</td>
<td>105</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>Ts-6 ejec</td>
<td>78</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td>Ts-SD-12 PSS</td>
<td>70</td>
<td>70</td>
<td>46</td>
</tr>
<tr>
<td>Ts-SD-6 PSS</td>
<td>40</td>
<td>87</td>
<td>61</td>
</tr>
<tr>
<td>Ts-12 PSS</td>
<td>250</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>Ts-6 PSS</td>
<td>102</td>
<td>87</td>
<td>61</td>
</tr>
</tbody>
</table>

Yu CM et al. JACC 2005; 45:677
Quantification of Regional Dyssynchrony

Tissue Velocity Imaging

Apical 4 Chamber  Apical Long Axis  Apical 2 Chamber

End-stage HF patient with QRS>140ms

Yu CM et al Circulation 2002;105:438
Tissue Synchronization Imaging (TSI)

Color coded display of time to peak velocity

- **Green**: 20-150ms  Normal timing
- **Yellow-orange**: 150-300ms  Moderate delay
- **Red**: 300-500ms  Severe delay

Baseline

Apical 4 Chamber  Apical 2 Chamber  Apical long axis

CRT for 3 months

Apical 4 Chamber  Apical 2 Chamber  Apical long axis

Yu CM JACC 2005; 45:677
Tissue sync imaging is a parametric imaging tool derived from 2D TDI images. It automatically calculates and color-codes the time to peak tissue velocity (Ts) in every position in the image with reference to the QRS onset. The TSI algorithm detects positive velocity peaks within a specified time interval, and the color coding ranges from green to yellow, orange to red within this interval. Herein, a TSI example set up to measure the time to peak myocardial systolic velocity at ejection. This patient had severe delay over the basal to mid-lateral wall and the whole septal wall, severe delay over the whole inf wall and moderate to severe delay over the posterior wall. 3 mo after crt a dramatic improvement of these delays was noticed with some residual delay over the lateral and inf walls.
Echocardiographic Dyssynchrony Index

Dyssynchrony index (Ts-SD) (ms) = Standard deviation of segmental time to peak myocardial systolic contraction

Cut-off: Ts-SD > 32.6 ms

Predictive Value of Ts-SD For Reverse Remodeling

<table>
<thead>
<tr>
<th>QRS</th>
<th>Sen</th>
<th>Spes</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;120</td>
<td>94</td>
<td>83</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>120-150</td>
<td>100</td>
<td>78</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>&gt;150</td>
<td>83</td>
<td>86</td>
<td>83</td>
<td>86</td>
</tr>
</tbody>
</table>

Yu CM Am J Cardiol 2002; 91:684
Yu CM J Cardiovasc Electrophysiol 2004 15:1058
Echocardiographic Dyssynchrony Index

- Yu Index (Ts-SD)
- Septal to free wall delay

Parasternal M-mode
Septum-Posterior Wall
time to peak wall motion
Cut-off ≥ 130ms

Parasternal Short Axis
Septum-Posterior Wall
time to peak
strain/displacement delay

Apical views
Opposing wall
time to peak velocity delay
Cut-off ≥ 60ms

Yu CM J Cardiovasc Electrophysiol 2004 15:1058
Regional Dyssynchrony by 3D Volumetric Curves

CRT OFF

CRT ON

Tmsv: time to minimum systolic volume

Zhang Q et al, AJC 2005; 95: 126
Upper panel: Regional volumetric curves of 6 basal and mid segments in a study patient showing asynchronous LV contraction in CRT off mode: Scattered timings to minimal regional volume, with a Tmsv 12 SD=52 ms and Tmsv 12 dif 136 ms

Lower panel:
Pre-Implantation Mechanical Dyssynchrony is Predictive for Event Free Survival

SPWMD ≥ 130ms
SPWMD < 130ms

p = 0.005

SPWMD : septum-posterior wall motion delay

Pitzalis V et al JACC 2005; 45:65
RISKS AND COMPLICATIONS OF CRT

- Bleeding 1%
- Infection 1%
- Hematoma 1%
- Pneumothorax 1%
- Pericardial effusion 1%
  w/wo tamponade
- MI/Stroke/death 1/500
- Coronary sinus dissection/perforation 1%
- LV lead dislodgement 5%

AHA Science Advisory Circulation 2005;111:2146-50
Long-term retention of CRT

• CRT is interrupted in 36 % of pts after successful implantation of a CRT device
• Most common causes of interruption of CRT are development of AT’s (18 %) and loss of LV capture (10 %)
• CRT can be reinstated in majority of patients and only 5 % of pts permanently lose CRT
• Long-term retention of CRT in 2.5 yrs is 83 % (Intention to treat )

JACC 2004;44:72-7
UNCERTAINTIES ABOUT CRT

1. Does CRT improve outcomes of all patients with advanced CHF regardless of their QRS width or NYHA Class?
2. Does CRT improve outcomes of patients with chronic AFib or RBBB?
3. Is definition of rehospitalization in the clinical trials of CRT adequate?
4. Under what circumstances does CRT provide benefit in patients who would not derive a survival benefit from ICD?

AHA Science Advisory  Circulation 2005;111:2146-50
Major Causes of Death in CHF

- NYHA II (n=103)
  - Other: 12%
  - Sudden Death: 64%
  - CHF: 24%

- NYHA III (n=232)
  - Other: 26%
  - Sudden Death: 59%
  - CHF: 15%

- NYHA IV (n=27)
  - Other: 56%
  - Sudden Death: 33%
  - CHF: 11%

**Deaths**

- NYHA II (n=103)
- NYHA III (n=232)
- NYHA IV (n=27)

*Am J Cardiol 2003;91(Suppl):62F-73F*
• Does every patient who needs CRT also needs ICD?
• Does every patient who needs an ICD also needs CRT?
ELIGIBILITY FOR CRT IN PATIENTS WITH AN ICD

Etiology of Cardiac Disease in 79/390 (Appr 20 %) ICD Patients Eligible For CRT

- ischemic 72%
- idiopathic DCMP 8%
- congenital 5%
- miscellaneous 5%

Eur J Heart Failure 2003;5:315-17
COMPANION and CARE-HF

Eligibility criteria

**COMPANION**

- NYHA III or IV
- SR, QRS $\geq 120$ ms, PR $>150$ ms
- LVEF $\leq 35\%$
- LVEDD $\geq 60$ mm

**CARE-HF**

- NYHA class III or IV
- QRS $\geq 120$ msec
- LV EF $\leq 35\%$
- LVEDD $\geq 30$ mm (indexed to height)

Bristow et al., NEJM 2004; 350: 2140-50
JGF Cleland et al., NEJM 2005; 352: 1539-49
Primary Endpoint
(All-cause Mortality or Unplanned Hosp. for Major CVS Event)

HR 0.63 (95% CI 0.51 to 0.77)

No statistical significant heterogeneity in subgroups

CARE- HF

Number at risk

<table>
<thead>
<tr>
<th>CRT</th>
<th>409</th>
<th>323</th>
<th>273</th>
<th>166</th>
<th>68</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Therapy</td>
<td>404</td>
<td>292</td>
<td>232</td>
<td>118</td>
<td>48</td>
<td>3</td>
</tr>
</tbody>
</table>
There was no heterogeneity in effect in any of the pre-specified subgroups. In particular, benefit was observed in older patients, women, patients with ischaemic heart disease, in patients above and below median LVEF and in patients receiving or not receiving beta-blockers and Spironolactone (there were too few patients not receiving an ACE inhibitor or ARB and therefore this analysis was not included in the statistical analysis plan).
HR 0.64 (95% CI 0.48 to 0.85)  
P = .0019
There was a striking reduction in mortality in the CRT group. The absolute difference between control and CRT was 10%. Again, there was no early hazard and the curves begin to separate within the first 6 months of randomisation. A reduction in both sudden deaths and deaths due to worsening heart failure was observed. There were only 29 sudden deaths out of 82 in the CRT group.

The benefits of CRT are in addition to those of the above pharmacological therapy. The absolute difference in mortality at 2 years was 7.1%. This compares to 5.2% with Enalapril in the SOLVD-treatment study and is similar to the estimated two-year mortality difference between placebo and Bisoprolol in the CIBIS-II study or the 8.8% difference between placebo and Carvedilol in COPERNICUS (which using the method of trial duration used in our study had a duration of about 15 months).

The hazard ratio of the effect of CRT in CARE-HF (0.64; 95% confidence interval 0.48 to 0.85; p=0.0019) was similar to that of CRT-D compared to control in the COMPANION trial (0.64, 95% confidence interval, 0.48 to 0.86; P=0.003). The absolute estimated difference at 2 years in the COMPANION study between CRT-D and control was about 8% with CRT and CRT-D having similar effects in that study.
COMPANION: Secondary Endpoint of All-Cause Mortality


CRT vs. OPT: RR = 24%, p=0.059 (Adjusted p-value = 0.060)
CRT-D vs. OPT: RR = 36%, p=0.003 (Adjusted p-value = 0.004)

12-month Event Rates
OPT: 19%
CRT: 15% (AR=4%)
CRT-D: 12% (AR=7%)

Days from Randomization

% of Patients Event-Free

OPT
CRT HR 0.76 (CI: 0.58-1.01)
CRT-D HR 0.64 (CI: 0.48-0.86)
Subgroup Hazard Ratios (univariate) Mortality

NOTE: The study was not statistically powered to evaluate subgroups

COMPANION

• CRT alone was associated with a trend ($p = .06$) for reduction (by 24%) in mortality

• The addition of an ICD to CRT enhanced the mortality reduction by an additional ~ 50% (from 24% to 36%) which was significant ($p = .003$)

• The CRT-D mortality benefit appeared higher in non-ischemic pts than in ischemic pts

• No difference in morbidity between CRT alone vs CRT-D

CLASS II a (Level of evidence B)

Implantation of an ICD in combination with biventricular pacing can be considered in patients who remain symptomatic with severe heart failure NYHA Class III-IV with LVEF >35% and QRS>120ms to improve morbidity and mortality.

The selection criteria

The limited FU

Increased morbidity associated with ICD implantation

Low cost-effectiveness prevent to extend the findings into general population with CHF

Eur Heart J 2005;26:1115
Optimal pharmacologic therapy

PROGRESSION OF HF
(PUMP FAILURE )

SCD

CRT

CRT+ICD

ICD

CRT-D
Pacing for heart failure

DDD Pacing

DDD pacing w/ short AV delay

DDD pacing AV Delay optimization

Biventricular pacing CRT

FUTURE

Expanded CRT indications

CRT-D&Gene Based therapy

Added functions to CRT devices

CRT + ICD
CONCLUSIONS

• CRT REDUCES MORBIDITY AND MORTALITY IN ADVANCED HEART FAILURE

• MORE DATA IS NEEDED FOR CERTAIN PATIENT GROUPS (MILDLY SYMPTOMATIC, Pts w AF,N QRS)

• The answer to the question ‘Does every patient with CRT needs ICD?’ is not clear yet.