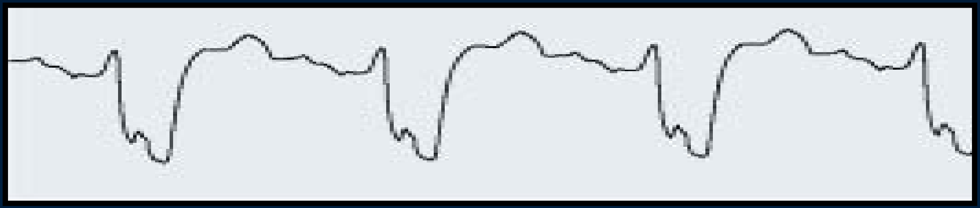
Cardiac Resynchronization Therapy for Heart Failure

Ventricular Dyssynchrony vs Resynchronization

Ventricular Dysynchrony



Ventricular Dysynchrony[1]

Electrical: Inter- or Intraventricular conduction delays typically manifested as left bundle branch block

Structural: disruption of myocardial collagen matrix impairing electrical conduction and mechanical efficiency

Mechanical: Regional wall motion abnormalities with increased workload and stress—compromising ventricular mechanics

Elements of Cardiac Dyssynchrony [2]

Atrio-ventricular

Intra-ventricular

Inter-ventricular

[1] Tavazzi L. *Eur Heart* J 2000;21:1211-1214

2.Cazeau, et al. *PACE* 2003; 26[Pt. II]: 137–143

Deleterious Effects of Ventricular Dyssynchrony on Cardiac Function

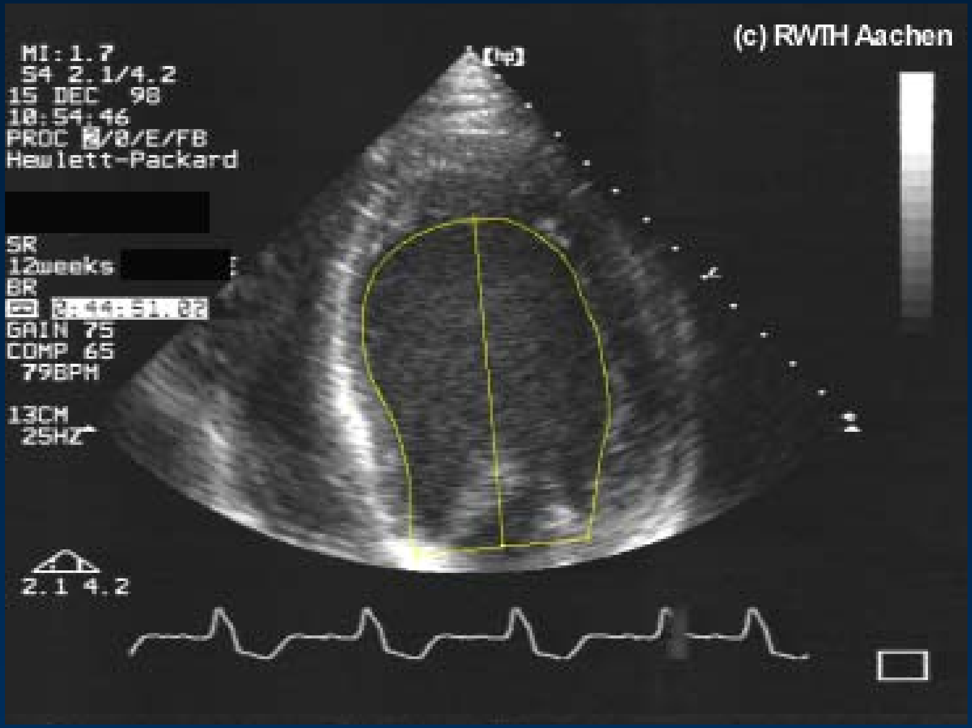
Reduced diastolic filling time [1]

\+ Weakened contractility [2]

\+ Protracted mitral regurgitation [2]

\+ Post systolic regional contraction [3]

= Diminished stroke volume

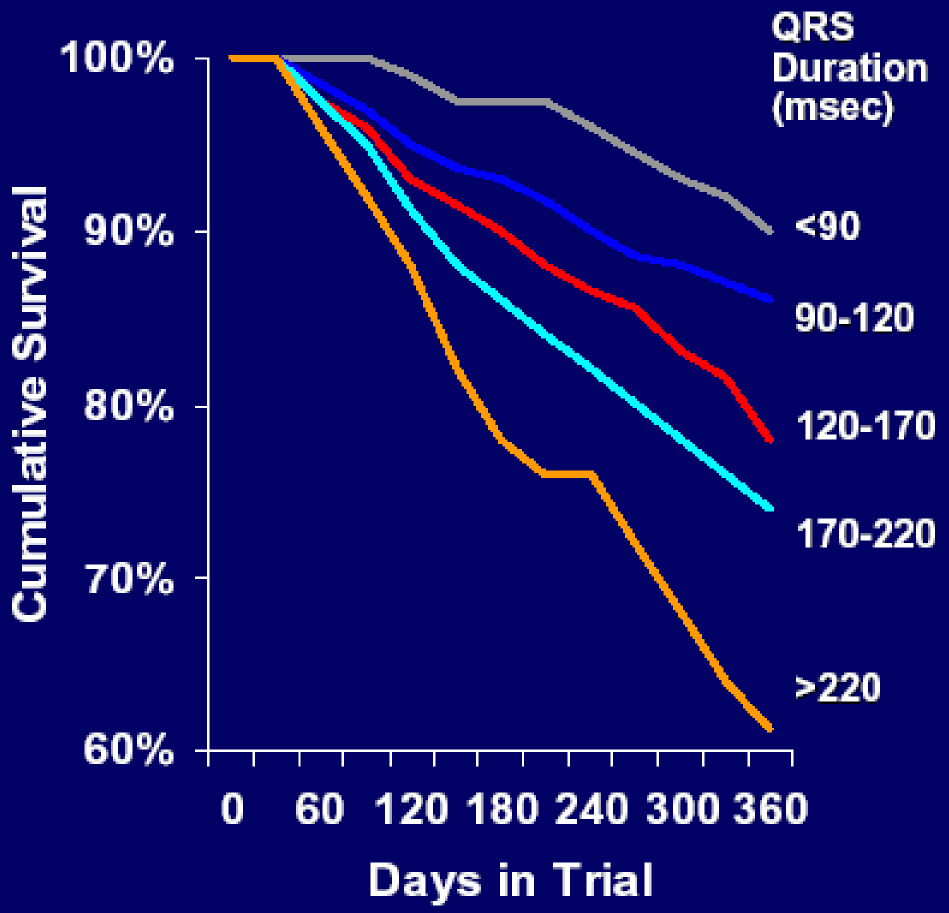


1. Grines CL, et al *Circulation* 1989;79: 845-853
2. Xiao HB, et al *Br Heart J* 1991;66: 443-447
3. Søgaard P, et al. *J Am Coll Cardiol* 2002;40:723–730

CHF Mortality : Impact of QRS Duration

Vesnarione Study [1]
(VEST Study Analysis)

NYHA Class II-IV patients



1. Gottipaty V, Krelis S, Lu F et al. JACC 1999;33(2):145

Deleterious Effects of QRS Prolongation

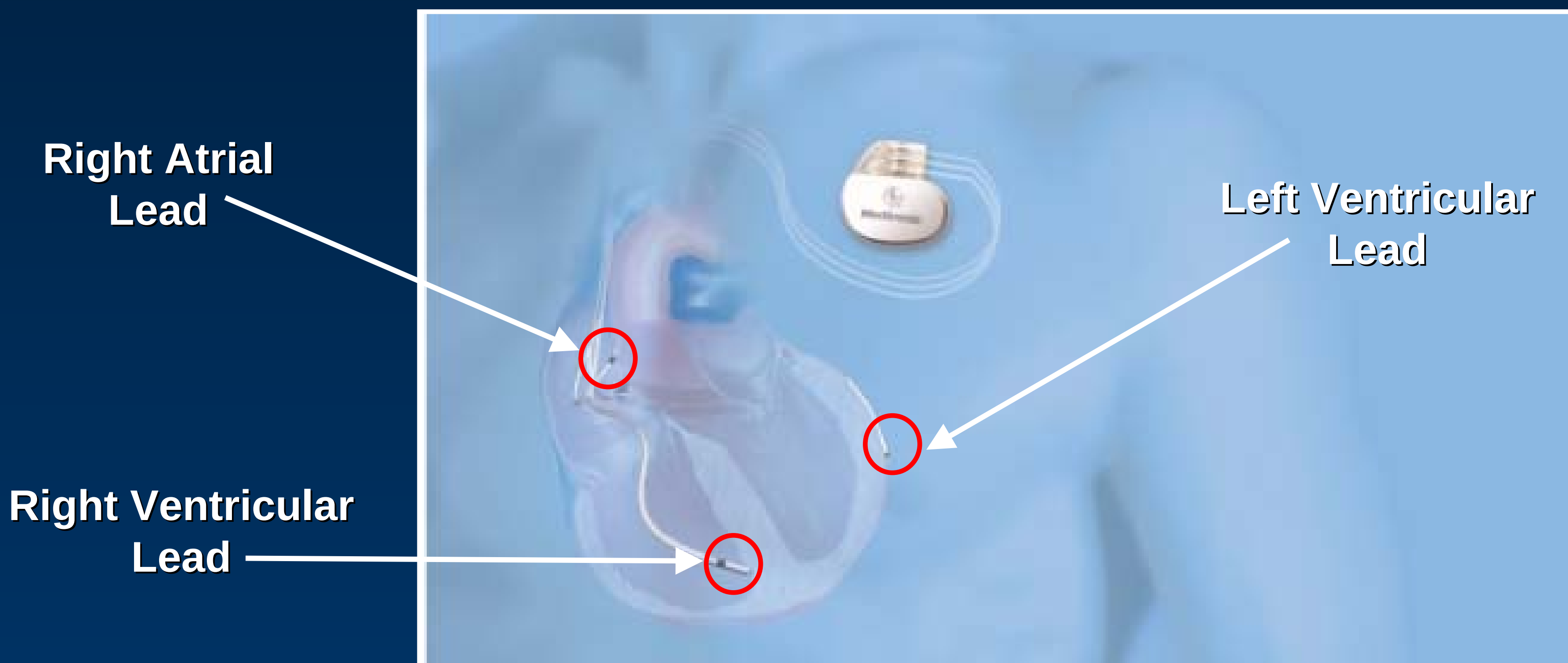
- Increased Mortality[1]
- Increased VT/VF PES[2,3]
- Increased Arrhythmic Death[4,5]
- Inefficient dyssynchronous LV contraction[6]

1. Xiao HB, et al *Br Heart J* 1991;66: 443-447
2. Horwith T, et al Am J Cardiol 2003; 92:804-809
3. Lieberman R, et al J. Am Coll Cardiol 2001 89; 330
4. Michaels A, et al Am J Cardiol 2005:95:394-397
5. Juliano S, et al Am H J 2002;143:1085-1091
6. Søgaard P, et al. *J Am Coll Cardiol* 2002;40:723–730

Achieving Cardiac Resynchronization

Mechanical Goal: Atrial-synchronized bi-ventricular pacing

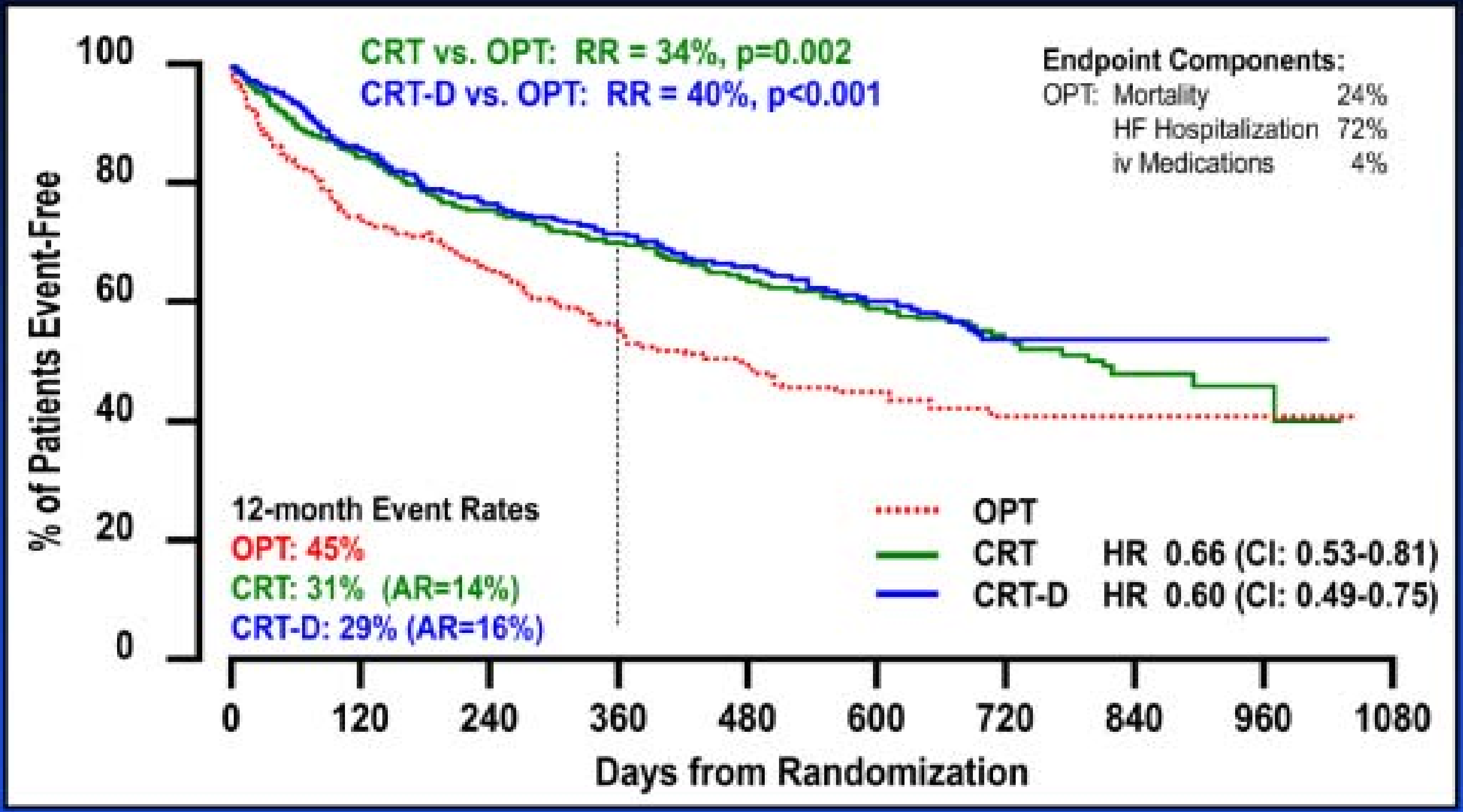
- **Transvenous Approach**
  - Standard pacing lead in RA
  - Standard pacing or defibrillation lead in RV
  - Specially designed left heart lead placed in a left ventricular cardiac vein via the coronary sinus



Cardiac Resynchronization Therapy (Bi-V Pacing)

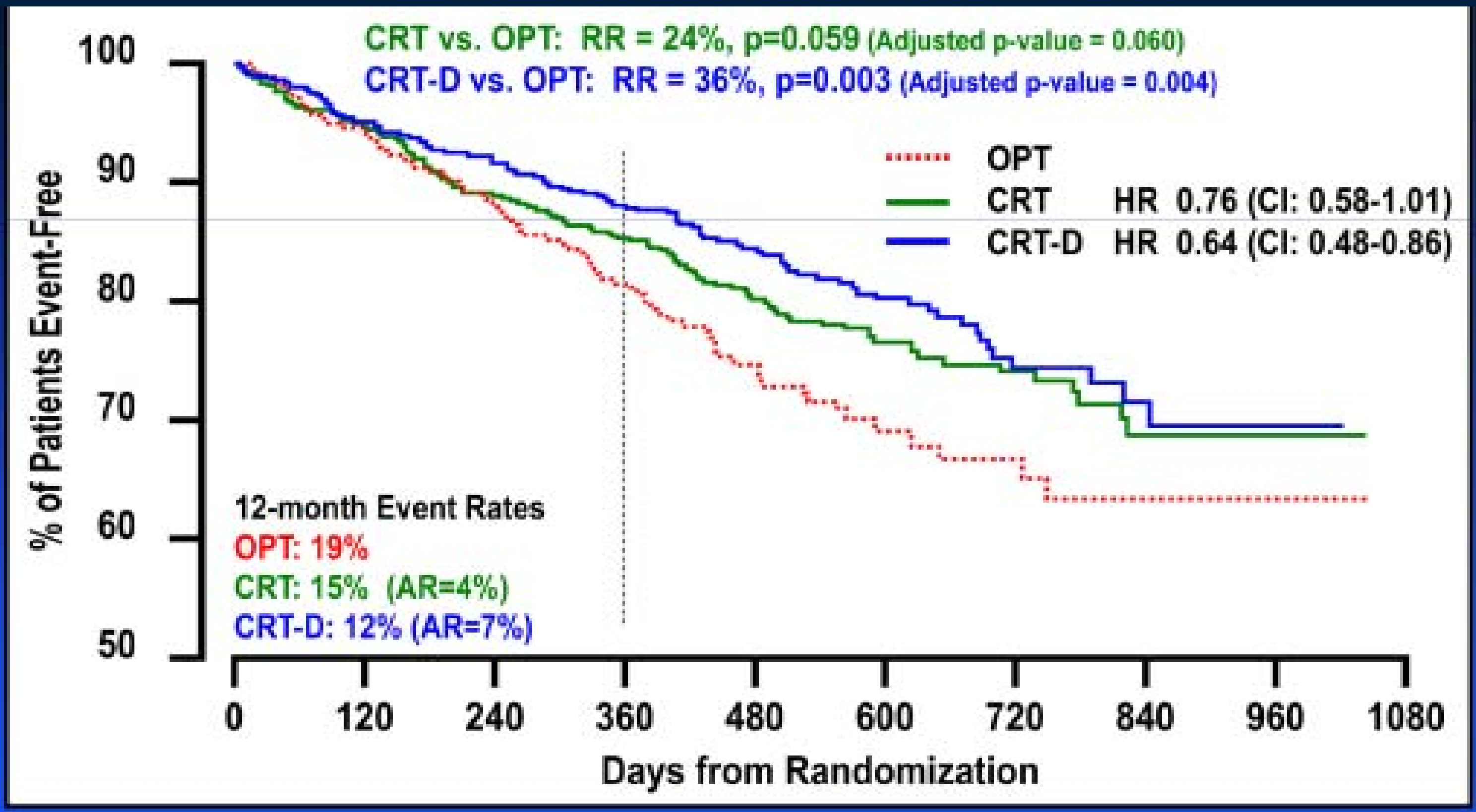
- Restore Electrical Mechanical Synchrony
  - Improves QOL, 6 min Hall Walk, NYHA CHF
  - Improves LV Efficiency without increasing energy consumption
- Does CRT do more that improve CHF symptoms?
  - promote “reverse” LV remodeling?
  - reduces Overall Mortality?
  - prevent SCD?

COMPANION:Death or HF Hospitalization



Bristow MR. N Eng J Med 2004;350:2140-50

COMPANION:Secondary Endpoint
CRT-D improves All-cause Mortality



COMPANION:Conclusions

When added to optimal pharmacological therapy in patients with moderate-severe LV dysfunction, NYHA Class III or IV symptoms and QRS lengthening:

- CRT or CRT-D reduces mortality + hospitalizations
- CRT-D reduces mortality
  - 2/3 of the effect size can be attributed to CRT

Bristow MR. N Eng J Med 2004;350:2140-50

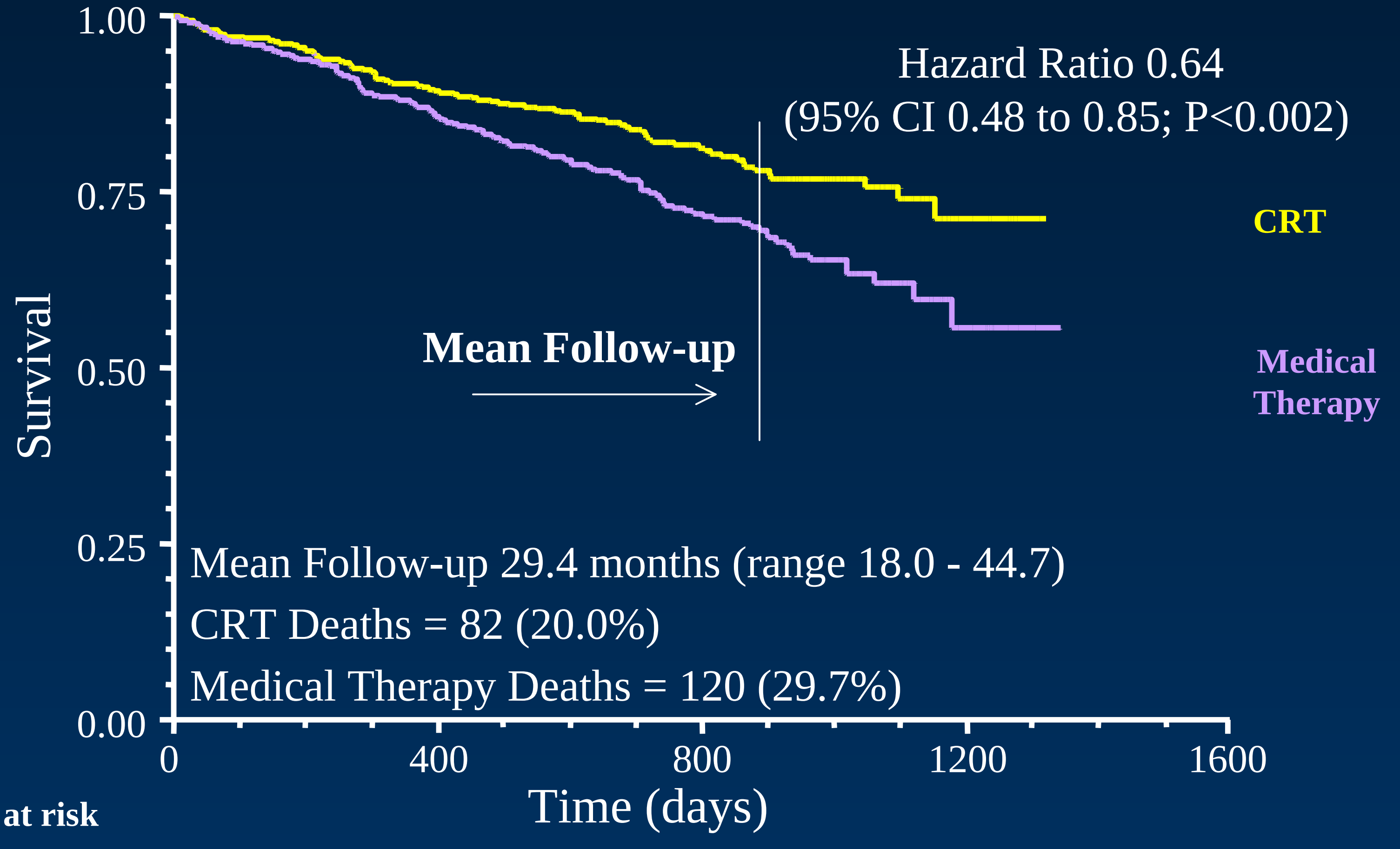
The CARE-HF Study
CArdiac REsynchronisation in Heart Failure
Main Inclusion & Exclusion Criteria

- 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

NEJM 2005:352(15): 1539-49

Care - HF

CARE-HF Main Study
Effect of CRT on All-Cause Mortality
(Emergency heart transplant included in definition)



Number at risk

CRT	**409**	**376**	**351**	**213**	**89**	**8**
Medical therapy	**404**	**365**	**321**	**192**	**71**	**5**

Results of Main Study

	Medical Therapy	CRT	Hazard/ Odds Ratio	P value
Primary EP	224 (55%)	159 (39%)	0.63* (0.51- 0.77)	<0.001
Mortality	120 (30%)	82 (20%)	0.64 (0.48 - 0.85)	<0.002
Death or HF Hosp	191 (47%)	118 (29%)	0.54 (0.43 - 0.68)	<0.001
NYHA I/II at 90 Days	144# (40%)	270# (71%)	4.1 (2.9 - 5.8)	<0.001

* Consistent effect across subgroups including IHD/non-IHD

\# Patients (n) and % of survivors in NYHA I/II when NYHA class reported

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	$P < 0.0016$

Care - HF

CARE-HF Conclusions

- CRT should be considered as part of routine therapy for patients with moderate to severe HF due to LVSD with evidence (ECG supported by Echo) of cardiac dyssynchrony to:
  - Improve cardiac function and efficiency
  - Improve symptoms and QoL
  - Reduce morbidity
  - Prolong survival
- These benefits are in addition to those of pharmacological therapy

NEJM 2005:352(15): 1539-49

ACC/AHA/NASPE 2002 Indications for Cardiac Resynchronization Therapy

- Class I indications for sinus node dysfunction or AV block (Level of Evidence: C)
- Class IIa Indication for Permanent Pacing in Idiopathic Dilated Cardiomyopathy
  - —Biventricular pacing in

    Medically refractory, symptomatic NYHA Class III/IV Idiopathic dilated or ischemic cardiomyopathy, Prolonged QRS interval ($\geq$130 msec,)

    LV end diastolic diameter $\geq$55mm

    and LVEF $\leq$35% (Level of Evidence A)

Gregoratos G. et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. Circulation. 2002;106:2145-2161

2005ACC/AHA Heart Failure Guidelines

CRT Class I Recommendations

Level of Evidence	Indication
A	• Patients with LVEF ≤35%, NYHA Class III or ambulatory Class IV and QRS ≥120ms Sinus Rhythm • For CRT-D, patients must meet criteria for CRT therapy and also have an ICD indication

CRT – Responders*

Criteria : QOL, 6 min walk, NYHA

1 Criteria > 50% CRT Patients

2 Criteria ~ 30 - 50% CRT Patients

3 Criteria < 30% CRT Patients

* All patients Echo AV optimized

MIRACLE Trial : NEJM 2002

Problem of Non-responder

- Non-responder (20-30%)

1. Which indication is better?
2. Optimal LV pacing site
   - LV epicardial lead implantation

Predicting CRT Responders

1. Ischemic Vs Non ischemic cardiomyopathy

    Lieberman AHA 2000, Leclercq Circ 2002

2. QRS Duration, RBBB vs LBBB,

    Lieberman AHA 2001, Grau Circ 2002

3. Inter-Ventricular Electrical Dysynchrony

    Alfonso AJC 2001

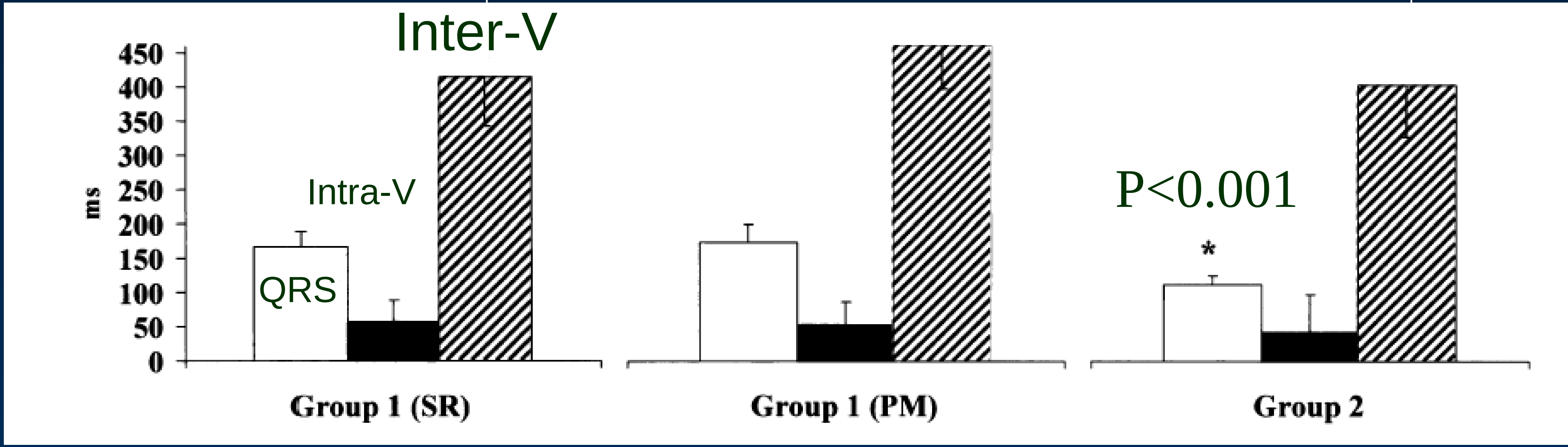
4. Intra-LV Mechanical Dysnchrony

    Tissue Doppler Imaging: Sogaard JACC 2003

NYHA Class III CHF Patients

QRS Duration a Does Not Predict Intra-LV Dysynchrony

Inter-V: P=NS vs Group 1
Intra-V: P=NS vs Group 1



QRS >120ms

QRS <120ms

Electrical Dysynchrony≠ Mechanical Dysynchrony

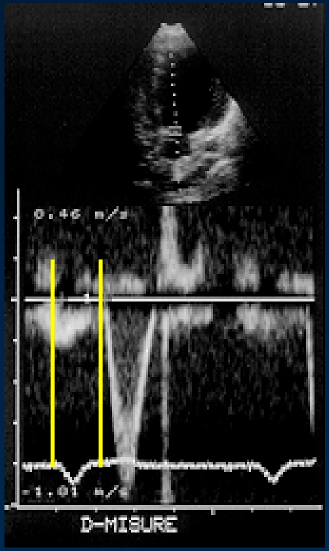
Achilli JACC 2003

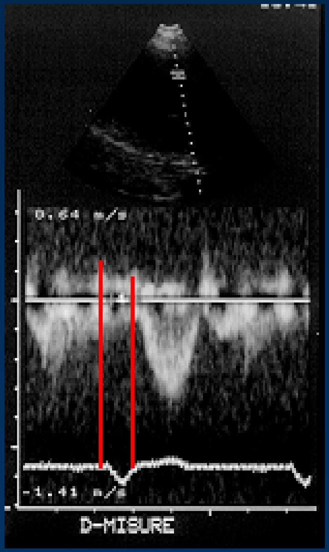
Measuring Mechanical Dyssynchrony

	+ Pros	- Cons
ECG	• simple, widely available • defined (120 ms) • > 3000 in RCT	• may lack specificity • QRS duration non-specific
MRI (tagged)	• 3-D • accurate	• resolution/frame rate/#cycles used • no post-implant data • expensive
Radionuclide venography	• improved border detection	• invasive • few tissue movement algorithms
Echo-based	**• widely available/clinical** **• simplicity** **• time-dependent algorithms**	**• accuracy and reproducibility** **• varying techniques, not all available**

Aortic Pre-ejection Interval and Interventricular Mechanical Delay

- **Aortic Pre-ejection interval (APEI)** measured from Q-wave on ECG to aortic valve opening (Figure at right)
  - ✓ Normal = 93 ± 14 ms[1]
  - ✓ Dyssynchronous = ?; 133 ± 30 ms in presence of LBBB,[1] 140 ms proposed[2]
- **Interventricular mechanical delay (IVMD)**
  - ✓ IVMD = APEI less time from Q-wave on ECG to pulmonary valve opening (figure below right)
  - ✓ Normal ≅ 8 ms[1]
  - ✓ Dyssynchronous = ?; 40 ms [2] and 20 ms[3] proposed

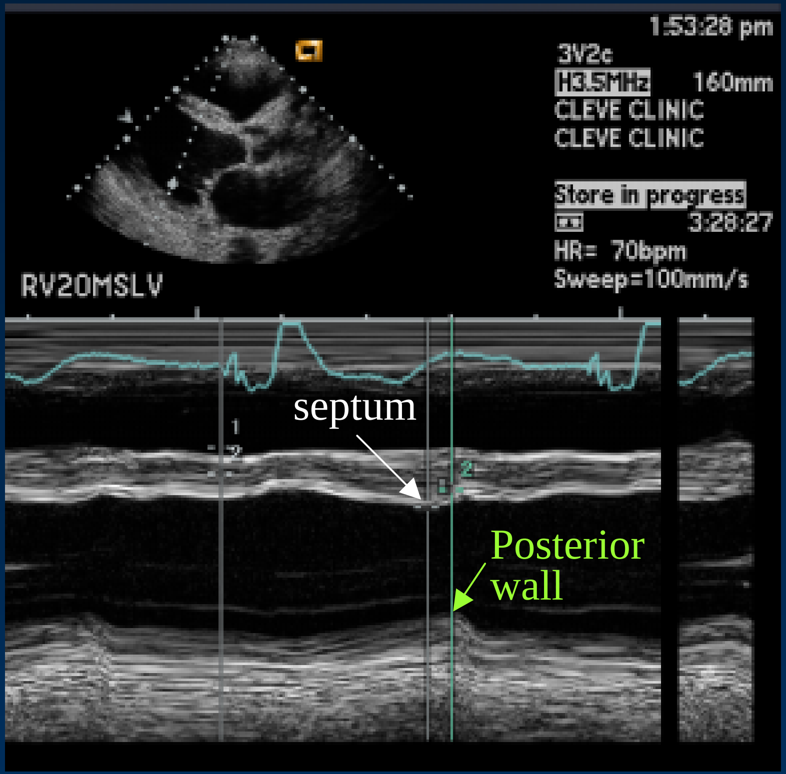




Data Sources:
1. Grines C, et al. *Circulation* 1989; 79: 845-853
2. Cleland JGF, et al. *Eur J Heart Fail* 2001;3:481-489
3. Achilli A, et al. *JACC* 2003;42:2117-24

Intra-ventricular Dyssynchrony Septal-Posterior Wall Motion Delay

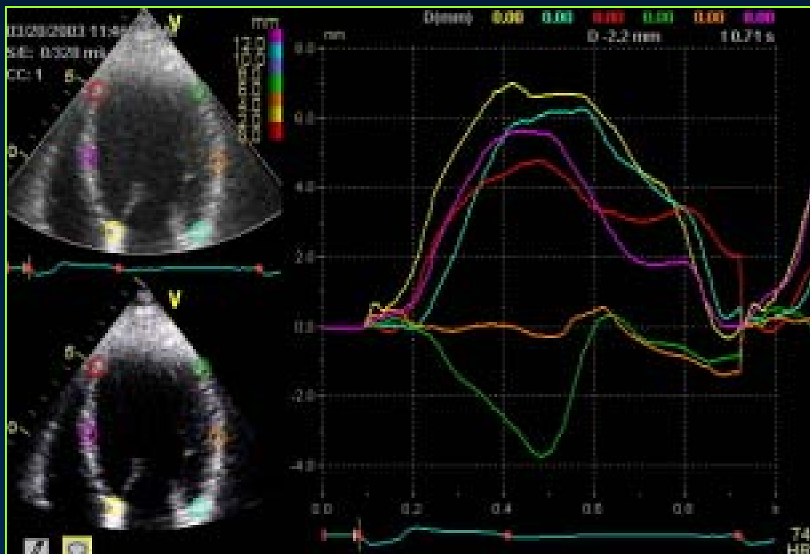
- Difference in times from peak excursions of the septum and of the posterior wall at the papillary muscle level
- **SPWMD ≥ 130 ms** predicted response (LVEDVi) to CRT in study of 25 pts with QRS ≥ 140 ms[1]
  - ✓ From parasternal short-axis view at papillary muscle level



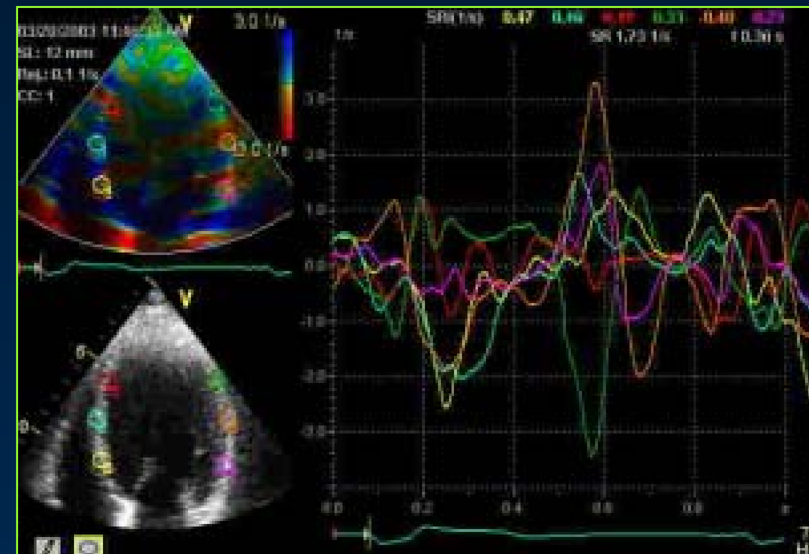
Parasternal Long-axis View Shown

1. Pitzalis M, et al. *JACC* 2002;40:1615-1622

Intra-ventricular Dyssynchrony Tissue Doppler Imaging



Velocity—6 segments



Strain rate—6 segments, same pt.

- **A standard deviation of 32.6 ms in differences in time to peak systolic contraction (velocity) between 12 LV segments predicted response (LVESV) to CRT in 30 pts.** Yu CM et al. *Am J Cardiol* 2002;91:684–688
- **% of 6 basal LV segments with contraction after aortic valve closure measured using strain rate* predicted change in LVEF with CRT in 20 pts.** Søgaard P, et al. *JACC* 2002;40:723–730

* Uses tissue velocity data to calculate regional deformation rates. May be less influenced by translational motion or tethering.

CONTROVERSY

- How can we select responder?
  - Definition of mechanical dyssynchrony?
- LBBB vs. RBBB
- Sinus rhythm vs. Atrial fibrillation
- Non-ischemic vs. Ischemic cardiomyopathy
- Dyssynchrony with “narrow QRS”?
- Epicardial Biventricular pacing

CRT in RBBB?

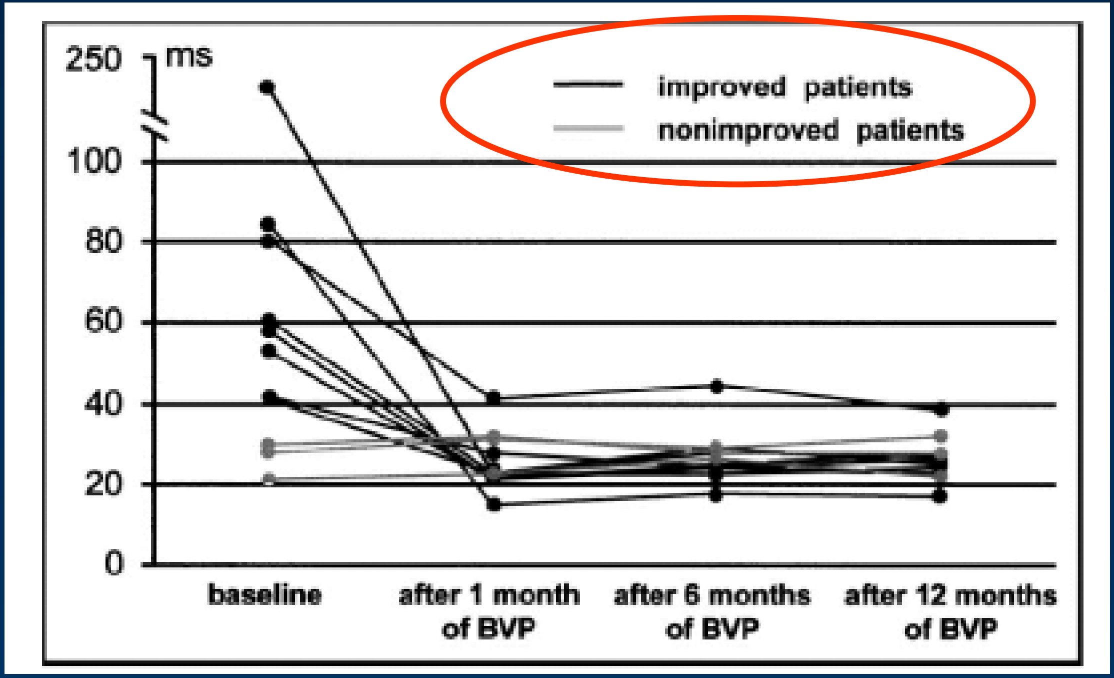
- CONTAK CD subgroup analysis *(ACC 2004)*
  - Among 501 pts.: RBBB 66, LBBB 271, IVCD 164
  - Unlike non-RBBB pts, RBBB pts did not demonstrate improvement in Sx status (FC, VO_2 and 6 min walk), heart size or LVEF

Endpoint	Time	RBBB CRT/No CRT, p	Non RBBB CRT/No CRT, p
V02 (ml/kg/min)	Baseline 6 mo change	13±.5/13±.5 -1±.6/-.1±.6, ns	14±.2/14±.2 1±.3/0±.3, .009
6 min walk (m)	Baseline 6 mo change	302±14/302±13 10±18/21±17, ns	320±6/320±6 39±8/13±8, .02
LVIDs (sys/mm)	Baseline 6 mo change	54±1/54±1 -1±2/-2±2, ns	59±.5/59±.5 59±.5/59±.5 -4±.7/-.6±.7, < .001
LVEF (%)	Baseline 6 mo change	31±1/31±1 2±2/4±1, ns	27±.4/27±.4 6±.8/3±.8, .008

CRT in RBBB?

- Garrigue S et al. *(Am J Cardiol 2001;88:1437)*
  - N=12
  - Only patients with a RBBB associated with left intraventricular asynchrony are likely to respond to CRT

Time difference between
LV free wall and LV septal wall
(intraventricular delay)



CRT in CHF with “narrow” QRS?

- 52 patients with severe heart failure (EF≦35%)
- Echocardiographic evidence of interventricular and intraventricular dyssynchrony
- Group 1(QRS>120 ms) and group 2 (QRS≦120 ms)

Achilli A et al. J Am Coll Cardiol 2003;42:2117-24

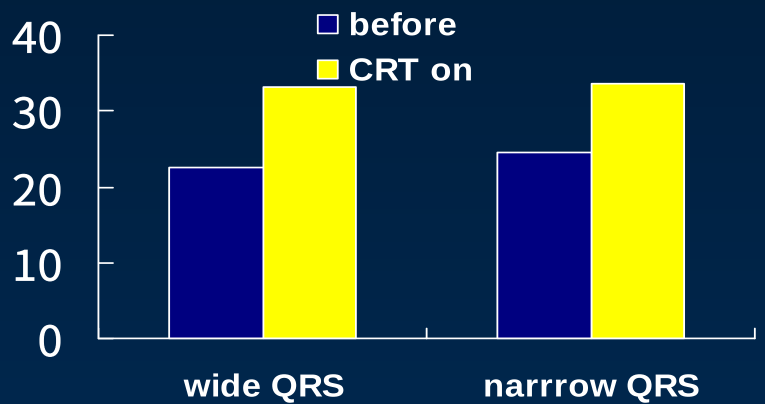
➢ High prevalence of LV systolic and diastolic asynchrony in CHF patients with normal QRS duration

: systolic and diastolic asynchrony – 51%, 46%

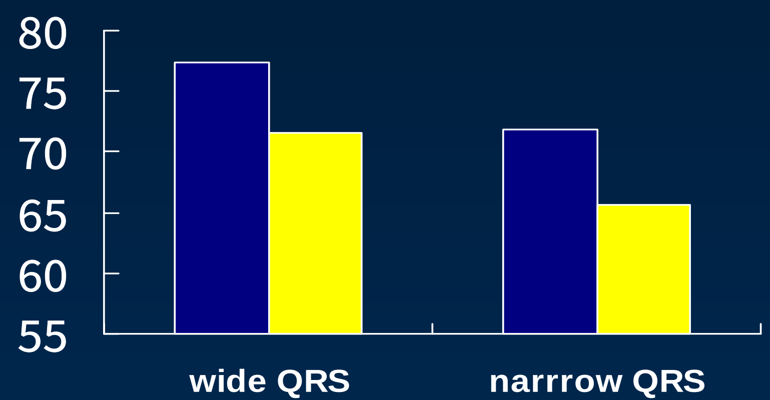
cf. in wide QRS group(>120msec) – 73%, 69%

Yu CM et al. Heart 2003;89:54-60

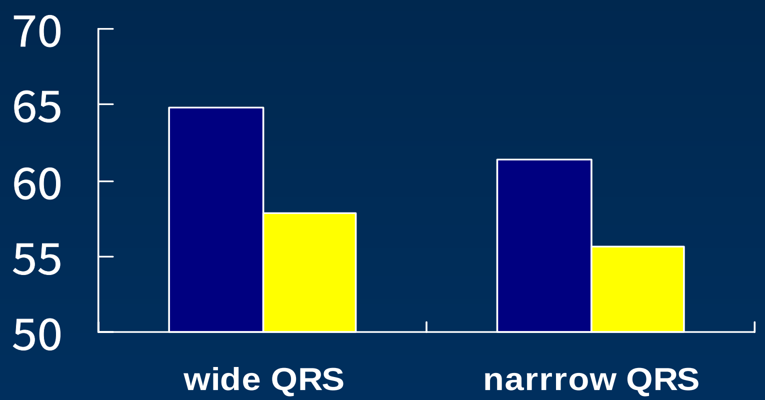
Narrow QRS versus Wide QRS



EF



EDD



ESD

- No significant difference between groups
- CRT may be helpful in CHF with incomplete LBBB and asynchrony evidence on Echo

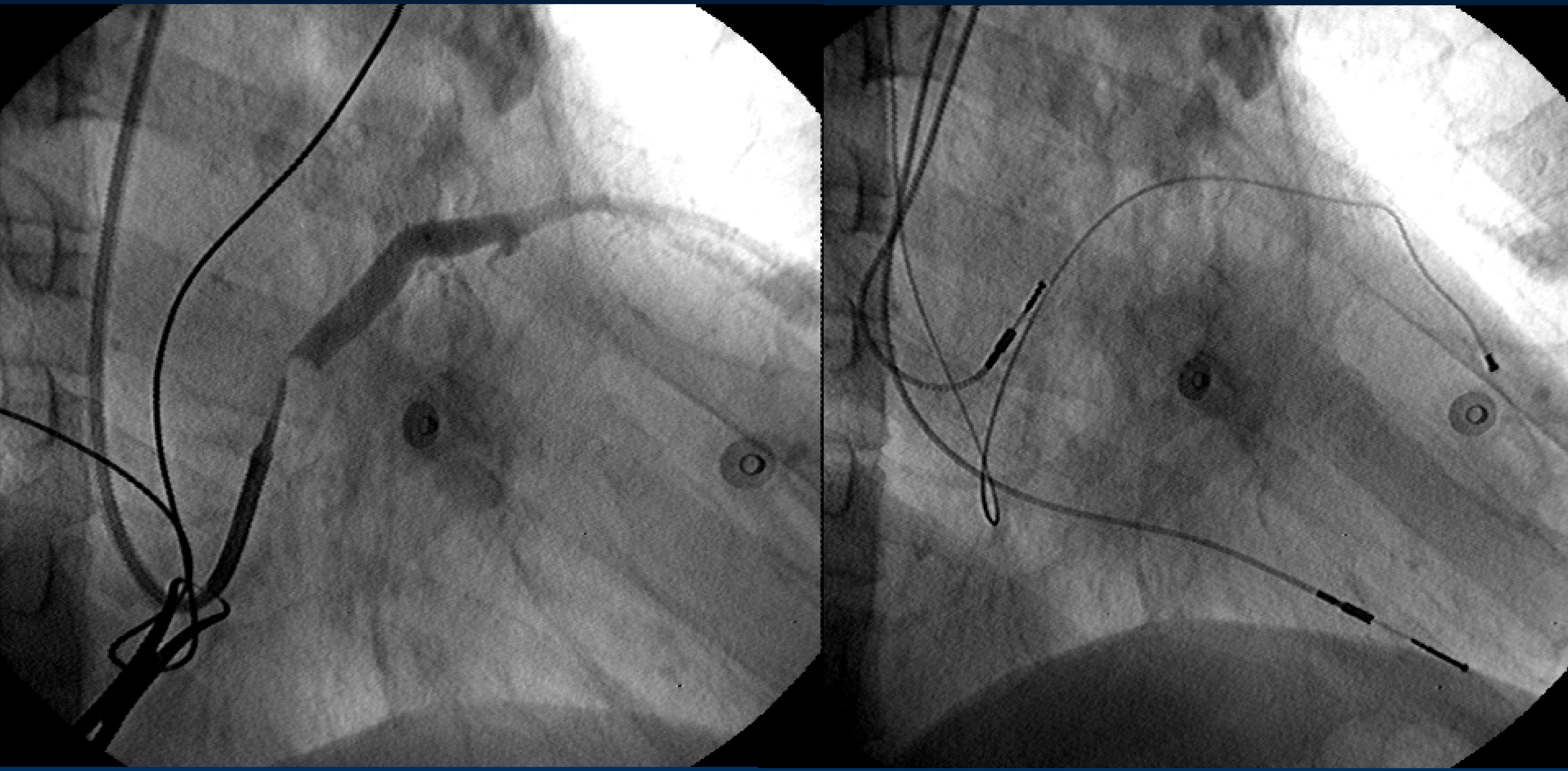
Achilli A et al. J Am Coll Cardiol 2003;42:2117-24

Selection of optimal site

1. Latest activation in relation to QRS onset
2. The site with most extensive reduction of QRS width
3. TEE-guided location
4. Anatomically posterolateral or posterobasal segment : usually in the region of posterior to second or third OM vessels

Ann Thorac Surg 2005;80:751
Eur J Cardio-thorac Surg 2005;27:235
J Am Coll Cardiol 2003;41:1414

67 M Dilated Cardiomyopthy



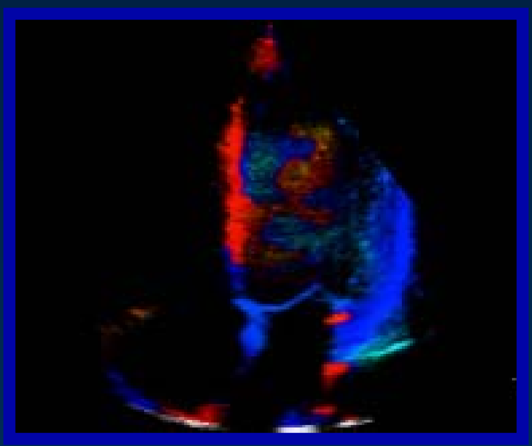
Post Implant Methods to Improve Response to CRT

- Potential Variables
  - Rhythm : maintain NSR
  - Pacing Method i.e. Triggered vs Inhibited
  - RV:LV Timing
  - AV interval

Parametric Imaging

Advance Applications

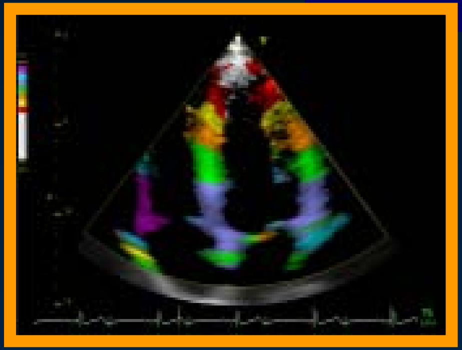
TVI, TTI, TSI, Strain…



TVI

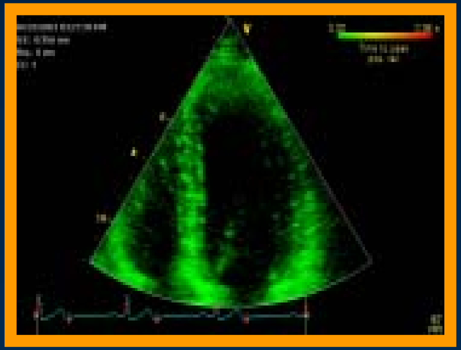
Tissue Velocity Imaging

Measures Myocardial Long. Velocity [m/sec]



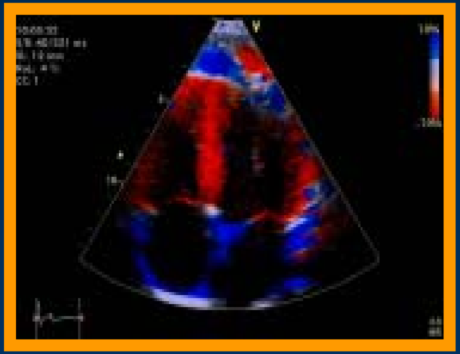
TTI – Tissue Tracking

Measures Myocardial Longitudinal **Displacement [mm]**



TSI – Tissue Synchronisation Imaging

Measures Timing; Time-to-Peak Systolic Velocity [msec]



SI – Strain Imaging

Measures Myocardial Longitudinal **Deformation [%]**

CRT Summary

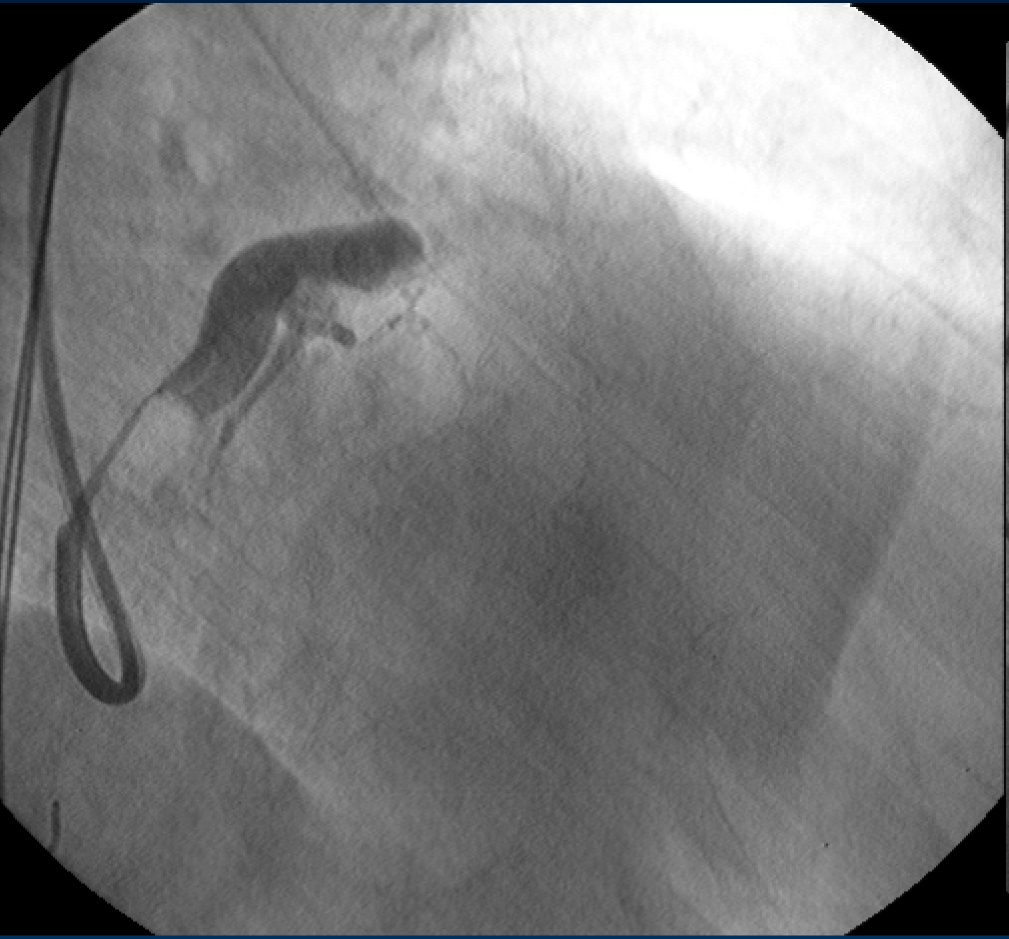
- Promotes E-M resynchronization
- Reverses LV remodeling
- Reduces CHF symptoms
- Reduces overall mortality
- **Does not prevent SCD**

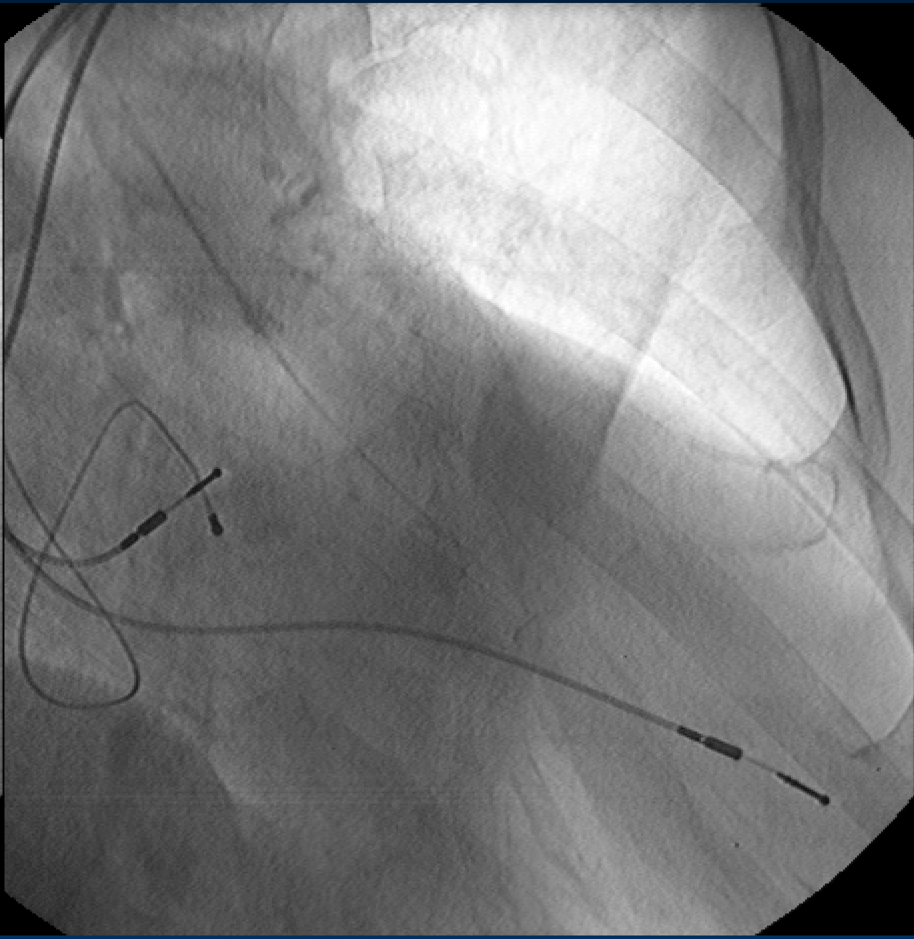
Conclusions:

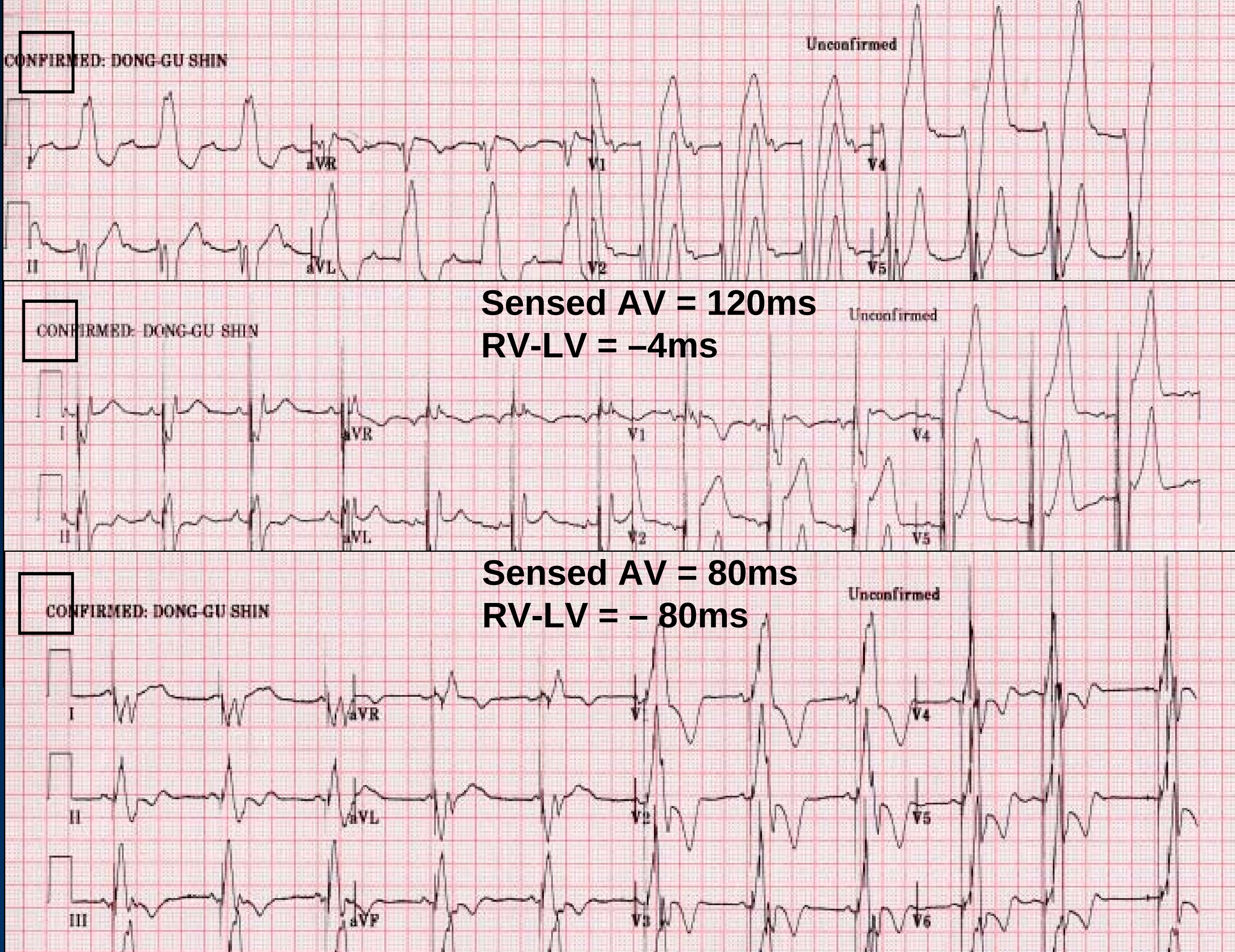
Managing LV Dysfunction

- **Clinicians should utilize therapies to promote LV reverse remodeling to reduce overall Mortality**
  - All Patients: Medical: BB+ACE I
  - IF LV Dyssynchrony: CRT
  - Independent of EKG or CHF Symptoms
- **Prevent SCD in all indicated patients: i.e. ICD**
  - Adhere to current guidelines. LVEF < 35%
  - independent of CHF symptoms or EKG parameters:

78 M Ischemic Cardiomyopathy
LVEDD 76mm LVESD 68mm LVEF 17%



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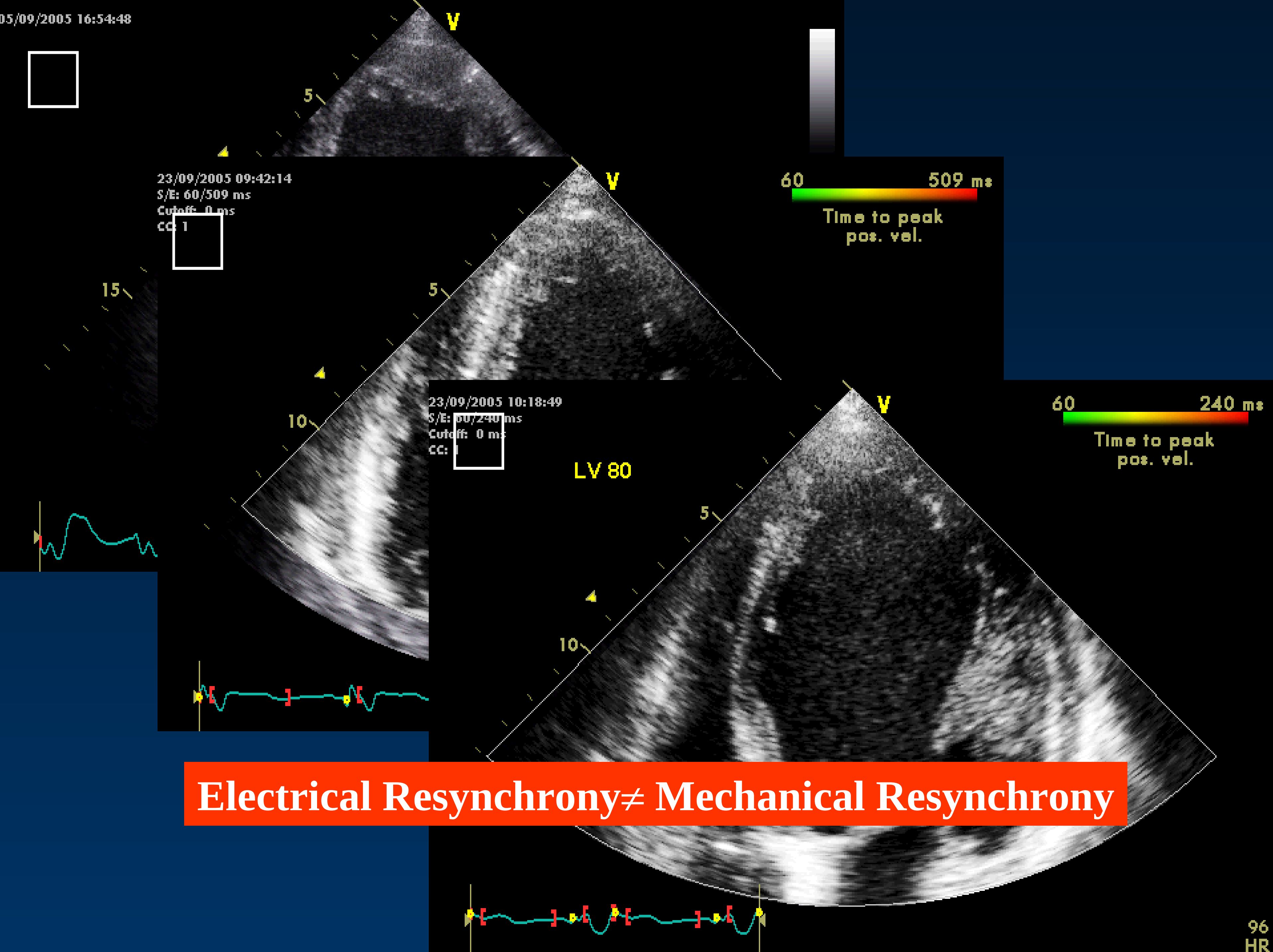
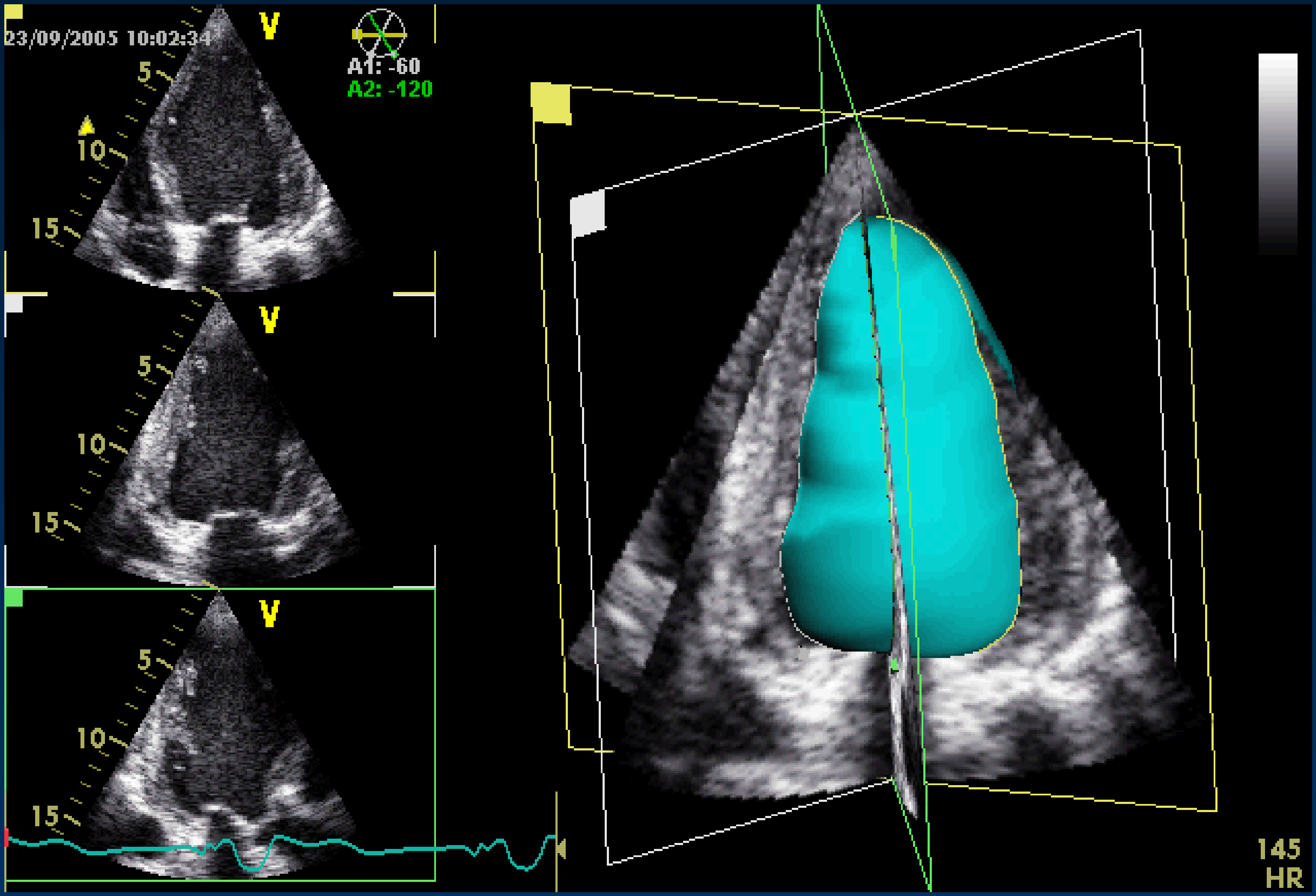


Electrical Resynchrony≠ Mechanical Resynchrony



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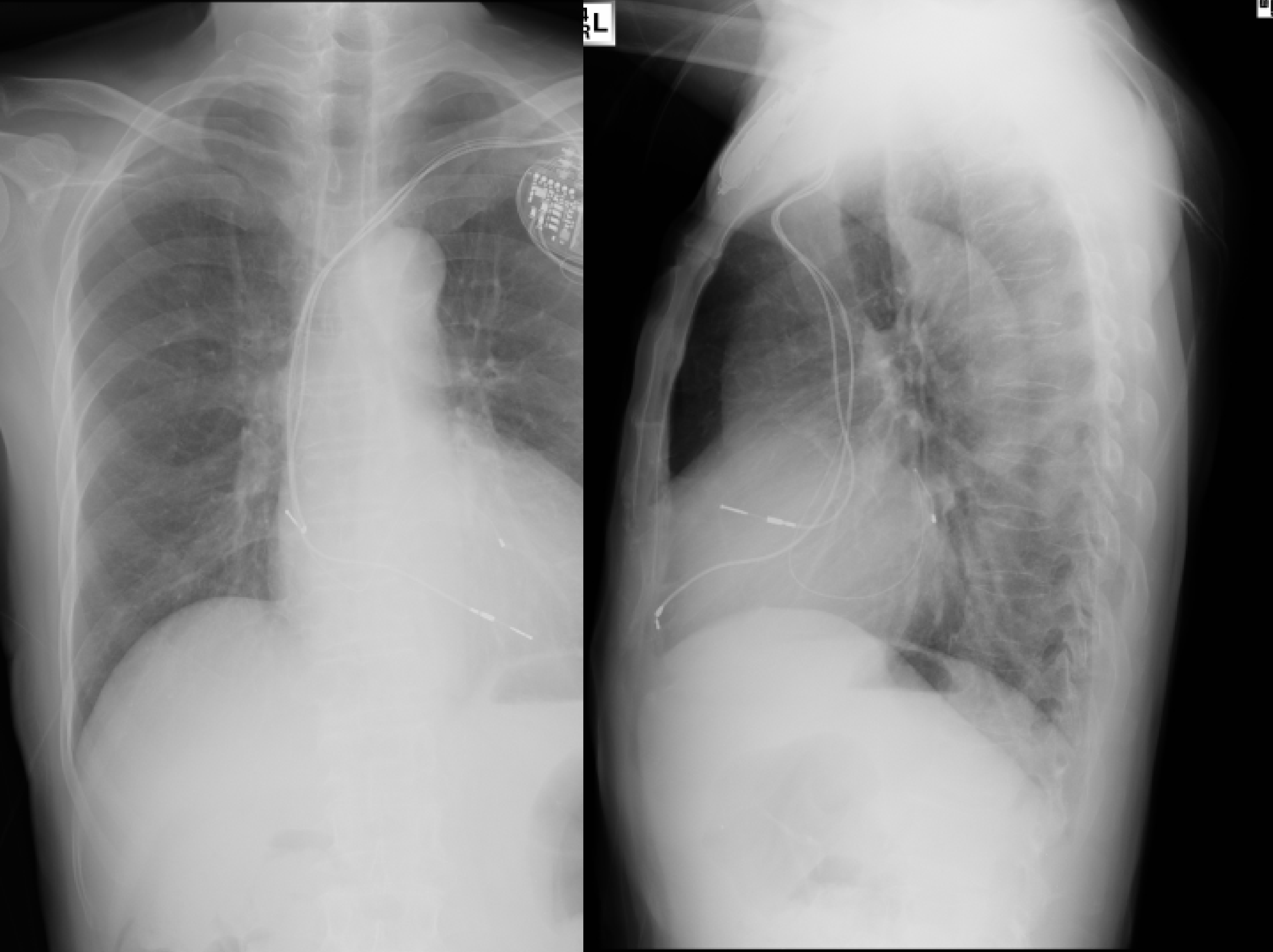
145
HR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CRT in CHF with AF

- Leclercq. C et al. *(Am J cardiol 2000;85:1154)*
  : comparative effects of CRT in CHF with
  SR(n=22) or CAF(n=15)

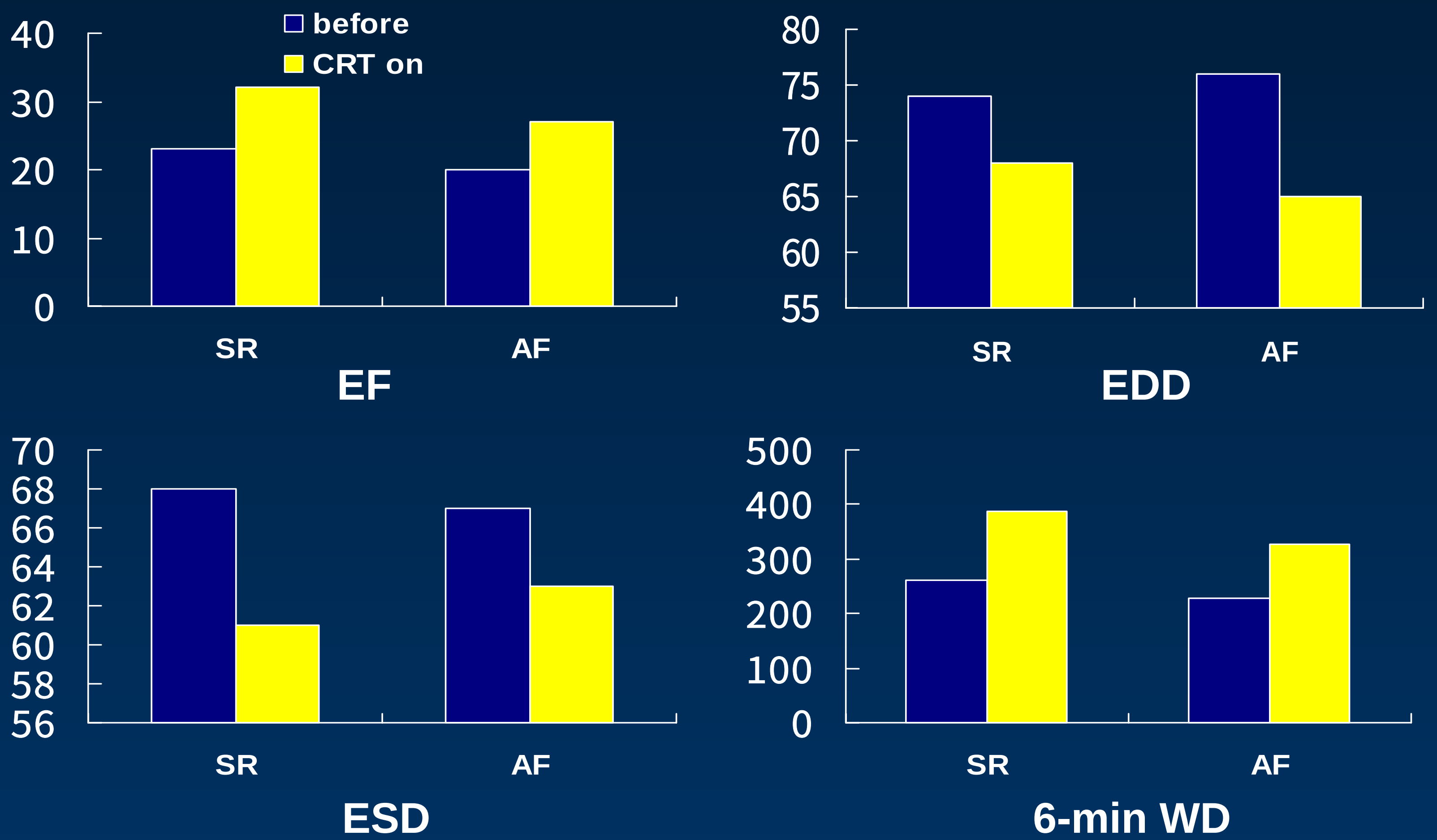
- CRT in CHF and chronic AF, upgrading after chronic RV pacing *(JACC 2002;39:1258)*
  – In 20 patients with CHF, prior AV junction ablation and RV pacing
  – FC class improved 29%, LV EF↑ 44%, LVEDD↓ 6.5%, No. of hospitalization ↓ 81%, QoL score ↑ 33%

CRT in CHF with AF

- MUSTIC-SR/ MUSTIC-AF *(JACC 2002;40:111)*
  - N=131, at 12 months (42/67 SR and 33/64 AF) :
    * AF patients : slow VR, spontaneous or by AVN ablation
  - 6 min. walk distance ↑ : 20%(SR) vs. 17%(AF)
    peak VO_2 ↑ : 11%(SR) vs. 9%(AF)
    QoL improved : 36%(SR) vs. 32%
    NYHA class improved : 25%(SR) vs. 27%(AF)
    LV EF improved : 5%(SR) vs. 4%(AF)
    Mitral regurgitation ↓ : 45%(SR) vs. 50%(AF)
  - In general, results for AF patients were less impressive

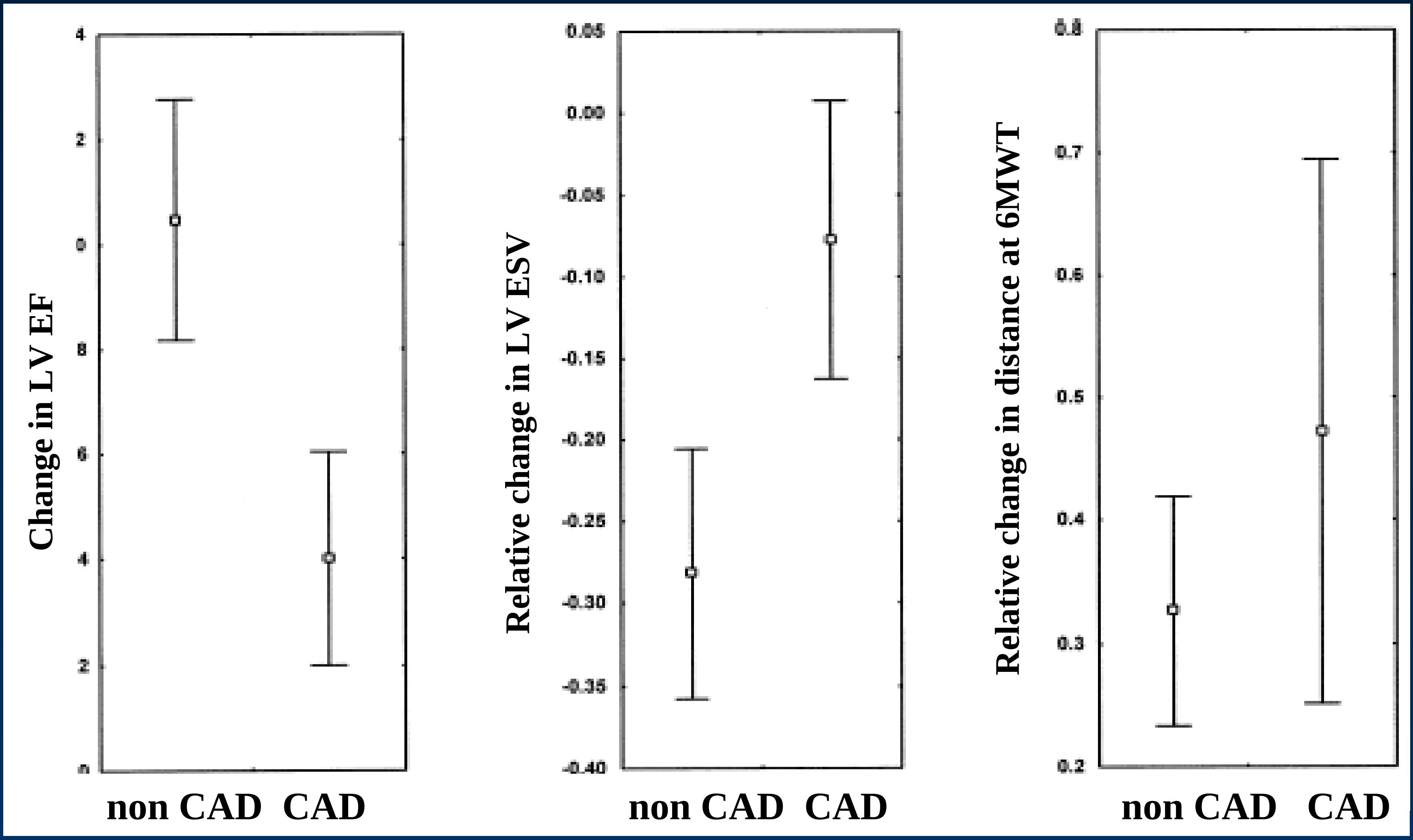
SR(30) versus AF(30)

in NYHA III/IV, LBBB, QRS≥120 ms, LVEF< 35%



Molhoek SG et al. Am J Cardiol 2004;94:1506-1509

CRT outcome and underlying etiology



Gasparini M et al. PACE 2003;26:175

Ischemic vs. non-ischemic

*- **CARE-HF** : NEJM 352(15), 1539-49, 2005 -*