The road to successful CRT implantation: The role of echo

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Terminology

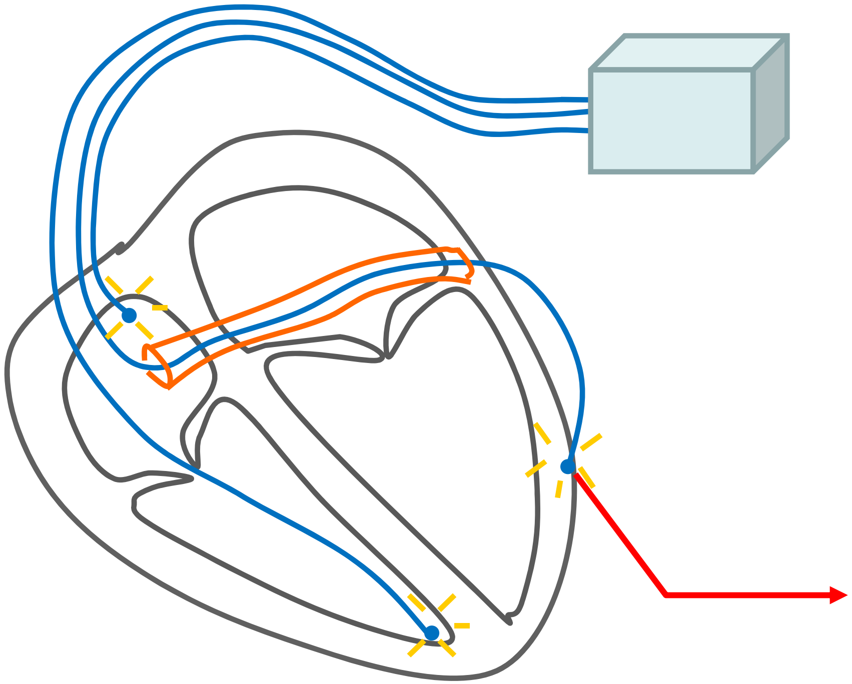
- Cardiac Resynchronization Therapy (CRT)
  = Biventricular pacing (BiV)
  = Left ventricular pacing (LV)
  ≠ Dual chamber pacing

- Dyssynchrony
  = Asynchrony

First developed

- 1960, Pacemaker (Chardack, Wilson, Greatbach)
- 1966, ICD (Mirowski)
- 1983 CRT first report (De Teresa PA, et al) VIIth World Symposium of Cardiac Pacing 1983
- 1996, CRT first systemic report (Cazeau S et al). Multisite pacing for end-stage heart failure: early experience.

What is CRT?



Patient:

- CHF
- LV systolic dysfunction
- Mechanical dyssynchrony

Ventricular pre-activation to improve mechanical synchrony

Indication of CRT

- NYHA class III/IV
- LVEF $\leq$ 35%
- QRS $\geq$ 120-130 ms

Usual study enroll criteria

2005 ACC/AHA guideline

Wide QRS

- Simple marker of mechanical dyssynchrony

- Oversimplification

Clinical benefit of CRT

- Symptoms

- Mortality

Symptoms

- MUSTIC (2002 JACC): NYHA 25% ↓
- CARE-HF (2005 NEJM): NYHA 0.6↓

Mortality

Cardiac Resynchronization and Death From Progressive Heart Failure
A Meta-analysis of Randomized Controlled Trials

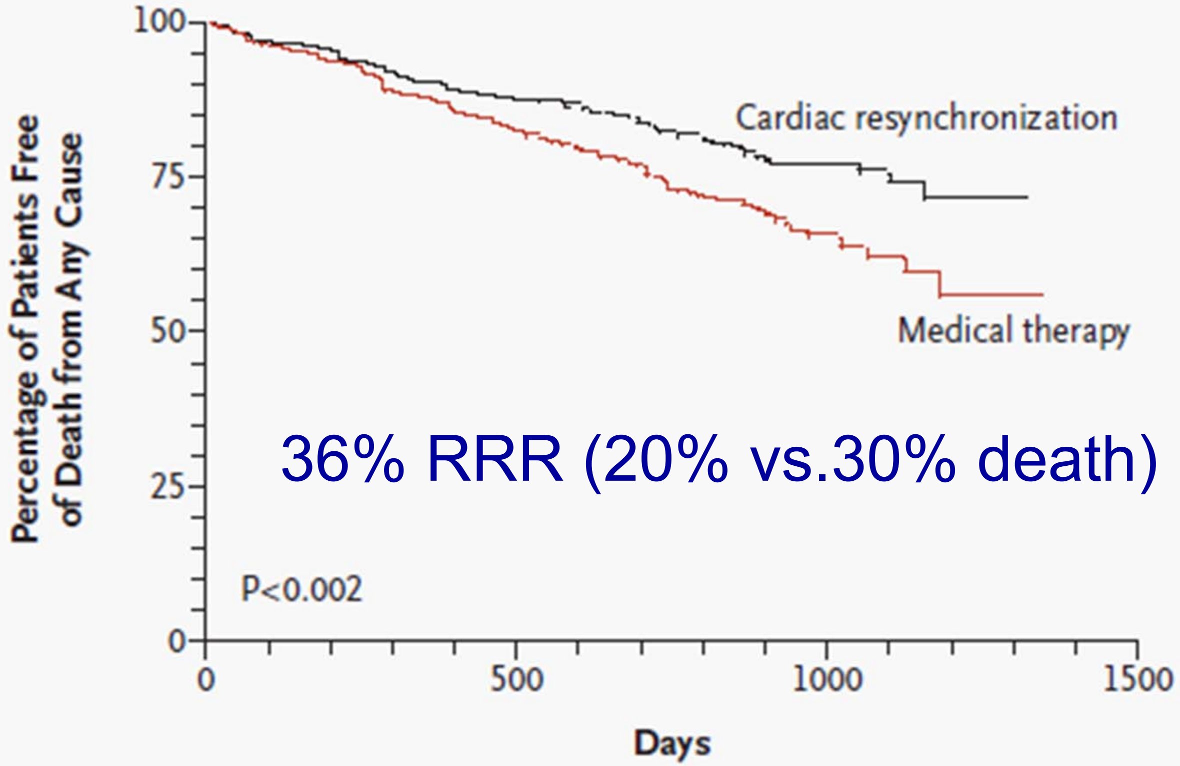
→ 51% reduction (in progressive HF) (2003 JAMA)

Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure

→ 24% reduction (death any cause) (2003 NEJM)

COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in the Heart Failure)

Mortality



No. at Risk

Cardiac resyn-chronization	409	376	351	213	89	8
Medical therapy	404	365	321	192	71	5

CARE-HF, 2005 NEJM

CRT response

Clinical Versus Echocardiographic Parameters to Assess Response to Cardiac Resynchronization Therapy

Gabe B. Bleeker, MD[a,b], Jeroen J. Bax, MD, PhD[a,*], Jeffrey Wing-Hong Fung, MRCP[c], Ernst E. van der Wall, MD, PhD[a], Qing Zhang, BM, MM[c], Martin J. Schalij, MD, PhD[a], Joseph Yat-Sun Chan, MRCP[c], and Cheuk-Man Yu, MD[c]

Definition of responder

NYHA decreased ≥1

EF improvd ≥ 5%

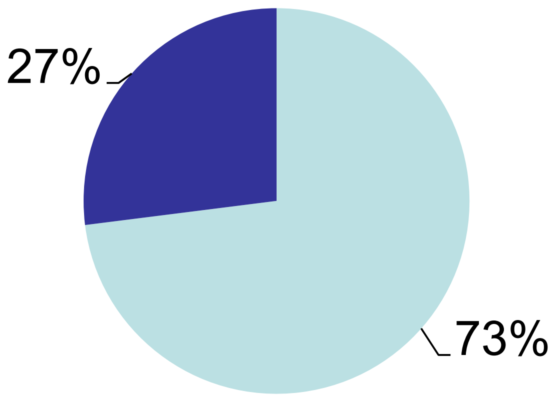
LVEDV dcreased ≥ 15%

	Clinical response	Clinical non-response
LVEF increase >5%	71 (49%)	6 (4%)
LVEF increase ≤5%	30 (21%)	37 (26%)

Am J Cardiol 2006;97:260-3

Echo in CRT

- Patients selection (Symptom, ECG, EF)



Am J Cardiol 2006;97:260-3

- Evaluation of dessynchrony (important of CRT response)

Dyssynchrony

- Definition: incorordination in cardiac contraction and relaxation

- 3 types

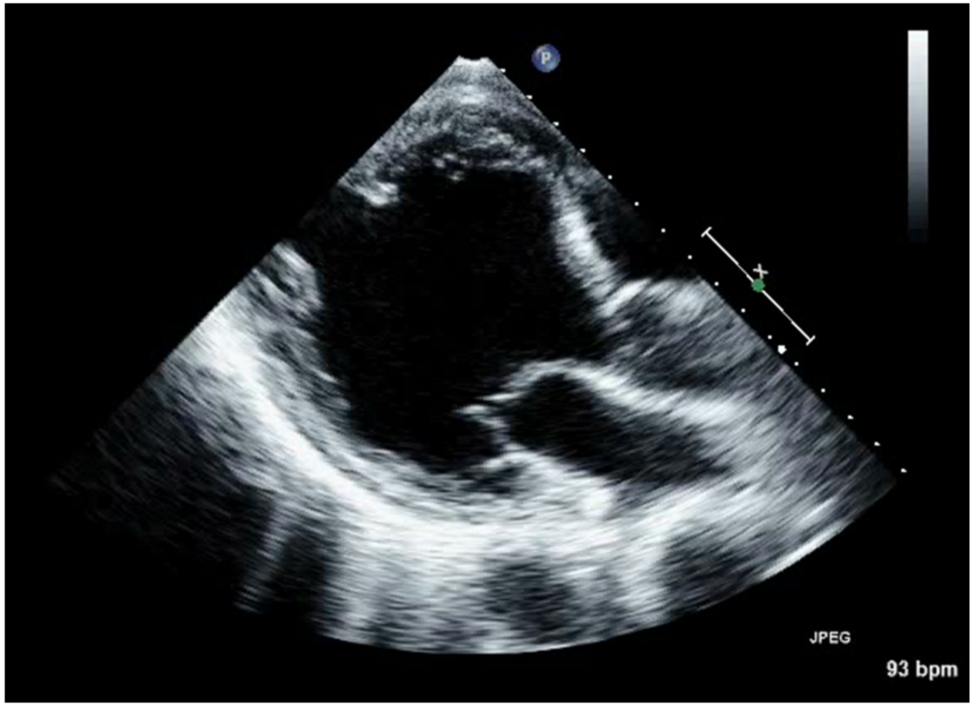
  Atrioventricular dyssynchrony

  Interventricular dyssynchrony

  Intra-(LV) dyssynchrony

Dyssynchrony

- Typically early septal contraction, followed by late posterior-lateral contraction
- Dyssynchrony results in inefficient LV systolic performance, increases in end-systolic volume and wall stress, and delayed relaxation



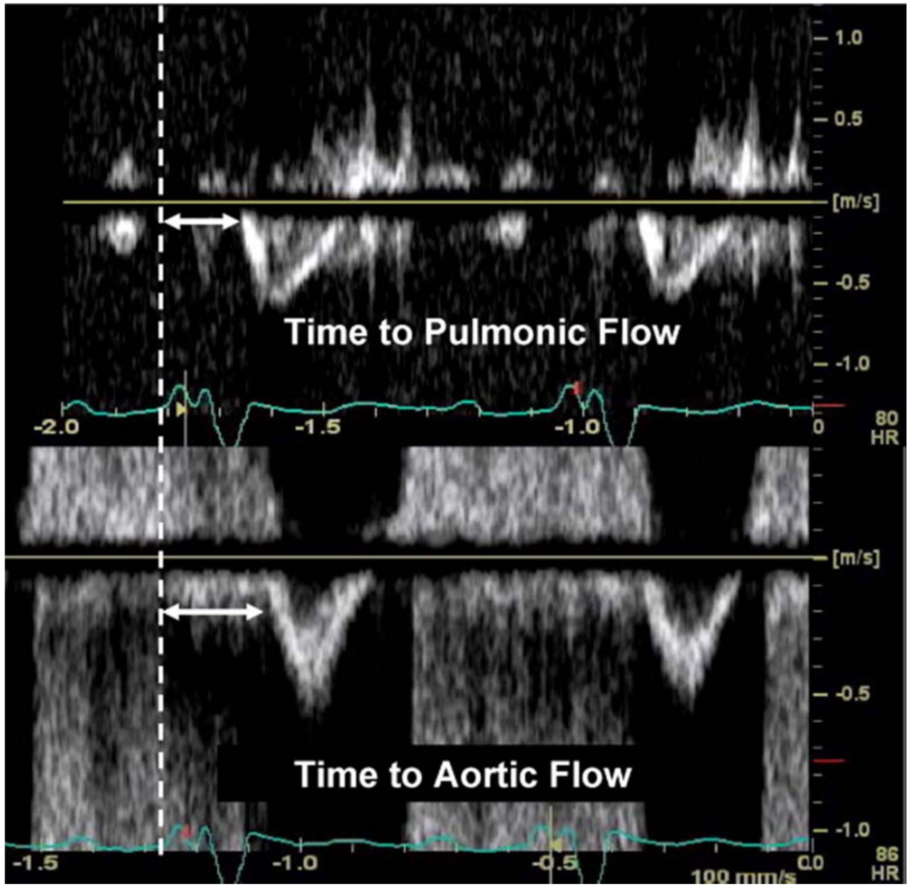
Goal of Echo (imaging)

- Wide QRS without mechanical dyssynchrony

Mechanical dyssynchrony

- Difficult
- No single ideal index exists

(1) Inter-ventricular dyssynchrony

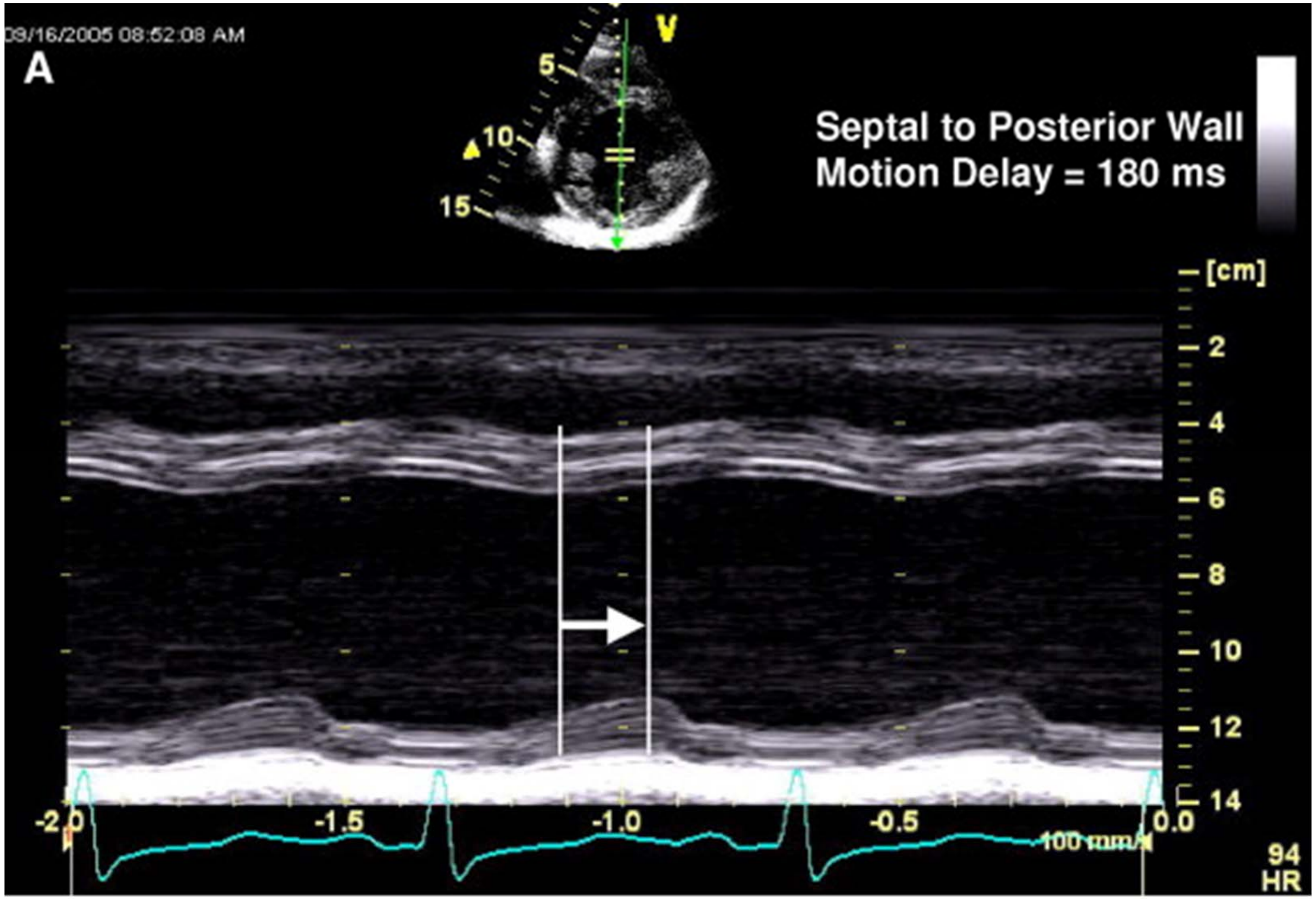


JASE 2008;21:191-213

Most evidence suggests that interventricular dyssynchrony is not useful in the prediction of response of CRT

Bax et al JACC 2005

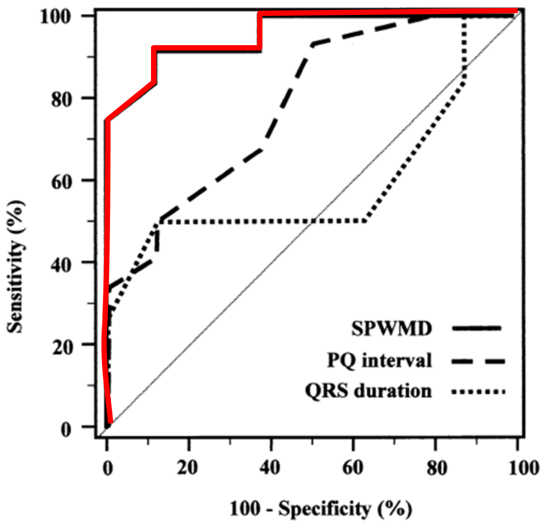
(2) M-mode



JASE 2008;21:191-213

M-mode

- Cut-off value of greater than or equal to 130 milliseconds as a marker of LV dyssynchrony in a pilot series of 20 patients principally with nonischemic cardiomyopathy with a sensitivity of 100% and specificity of 63% to predict a greater than or equal to 15% decrease in LV end- systolic volume index, and improvements in clinical outcome



SPWMD ≥ 130 ms =
Accuracy 85%

Pitzalis et al 2002 JACC

M-mode

Septal to Posterior Wall
Motion Delay Fails to Predict Reverse
Remodeling or Clinical Improvement in
Patients Undergoing Cardiac Resynchronization Therapy

Six-Month Change	Sensitivity	Specificity
LVESVI reduction of at least 15%	24%	66%
Increase of at least one NYHA functional class	24%	66%

Marcus et al. 2005 JACC

M-mode

SPWMD

: Not recommended as single method

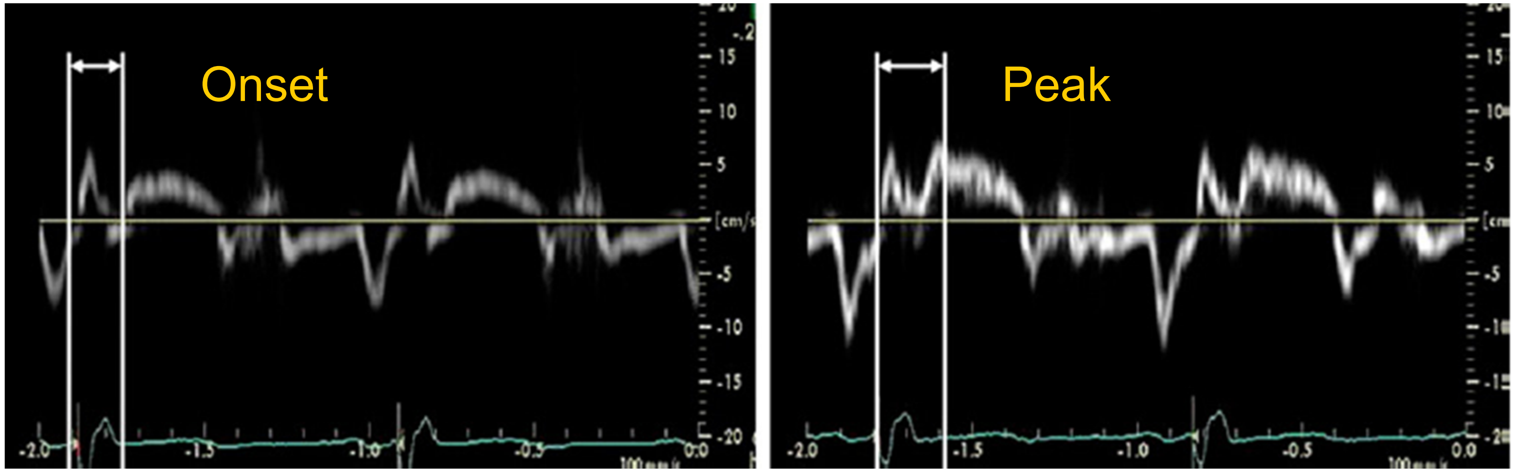
: But consider supplementary with TD method

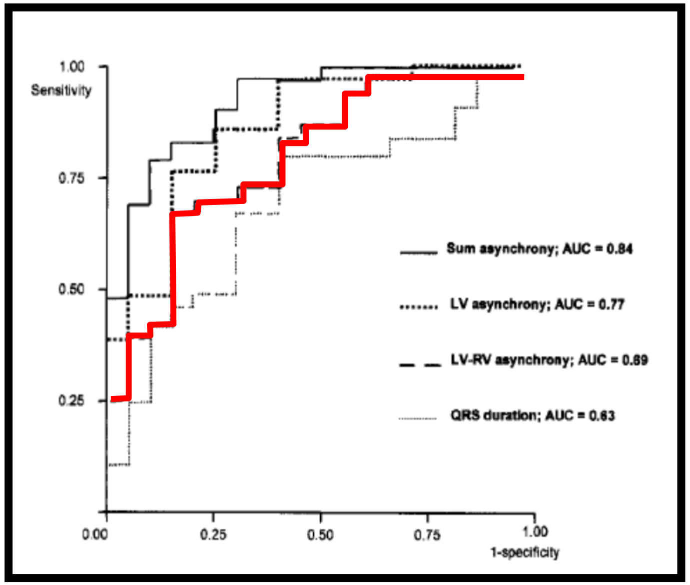
TD

- Pulse TD

- Color TD

(3) Pulsed TD





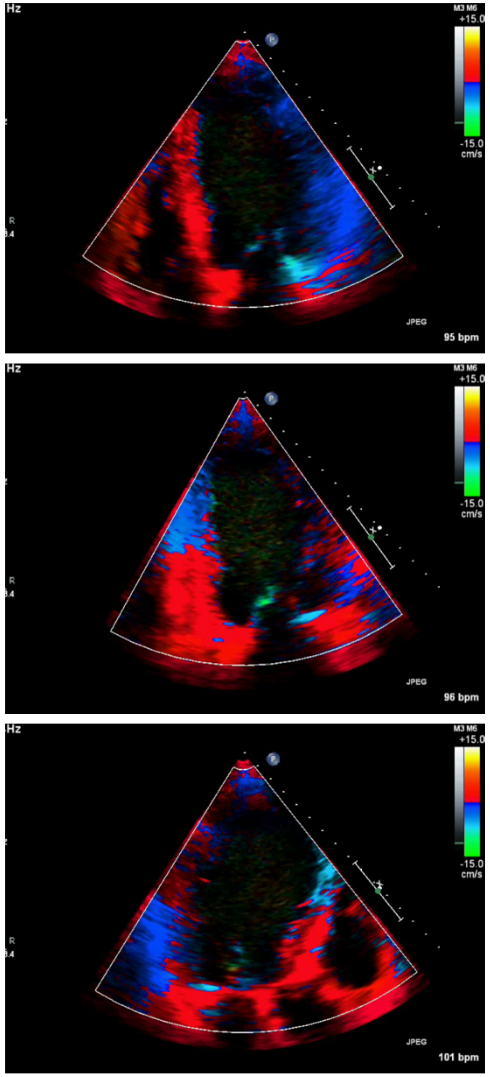
LV asynchrony 102 ms

Accuracy 88%

Penicka M et al 2004 Circulation

Color TD

(1) 3 Standard views with color TD
(2) Ejection time superimposed on time-velocity curve analysis.
(3) ROI (5 × 10 - 7 × 15 mm) in the basal and mid region of opposing LV walls
(4) Identify 4 components of velocity curve
(5) Time from onset of the QRS complex to the peak systolic velocity
(6) Average the time to peak values in captured beats (to improve reproducibility)



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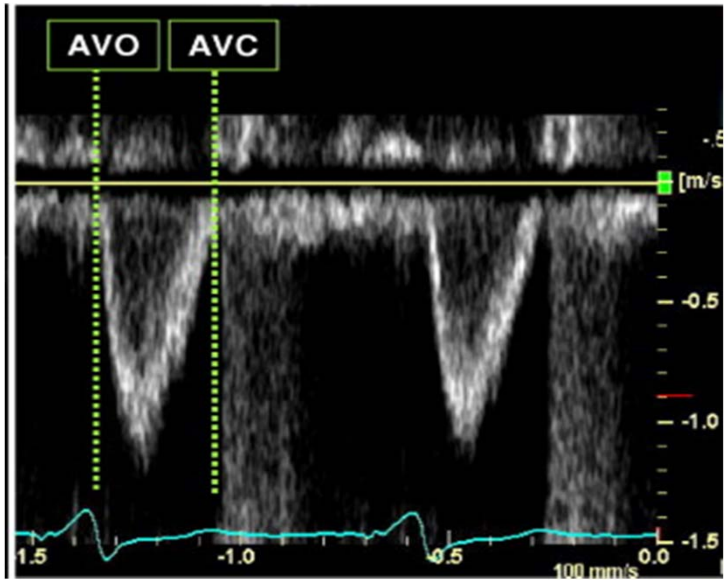

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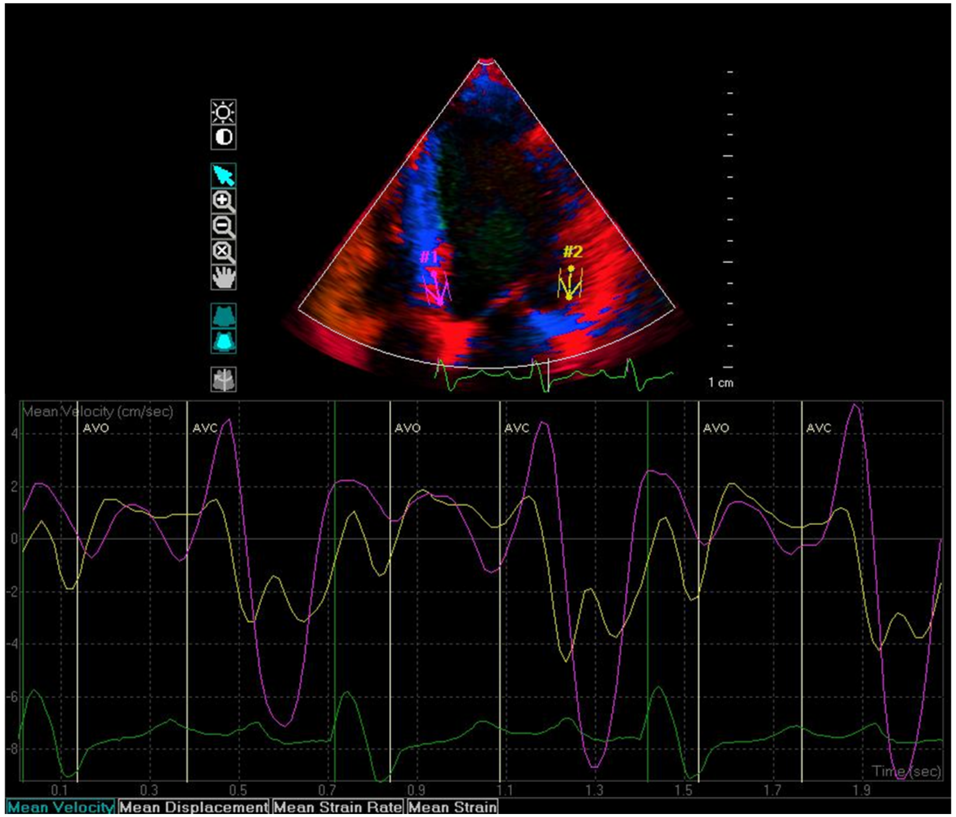

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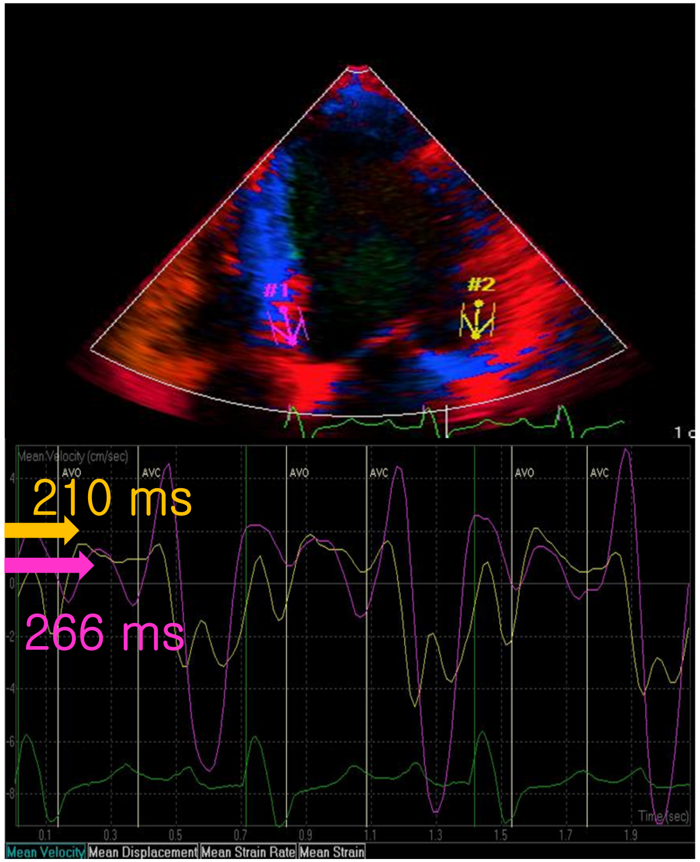

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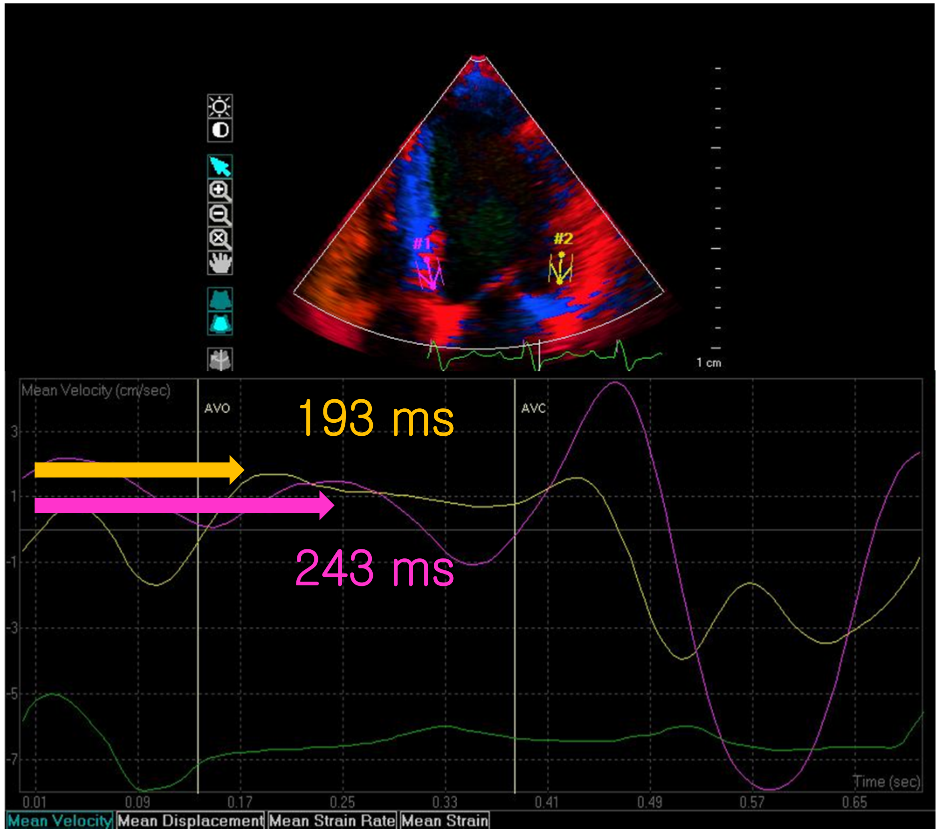
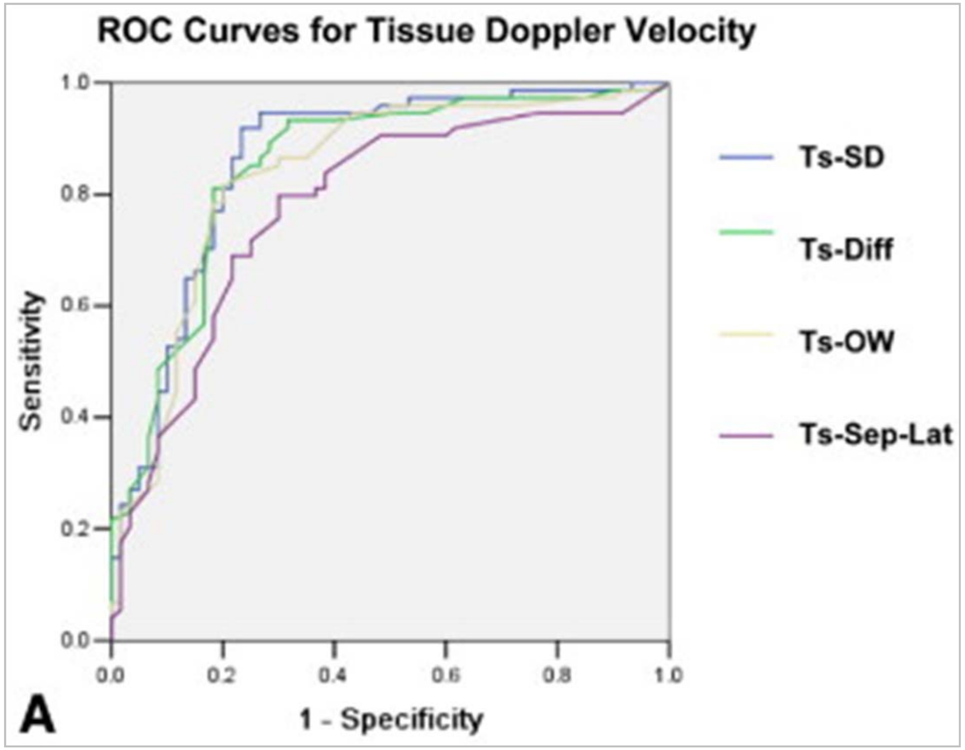


Color TD

- Parameters of systolic dyssynchrony
  - Septal-to-lateral delay (Sep-Lat)
  - Maximal difference among LV segments (12 segments)
  - SD of time to peak systolic time from 12 LV segments

(5) Two site methods

Usefulness of Tissue Doppler Velocity and Strain Dyssynchrony for Predicting Left Ventricular Reverse Remodeling Response After Cardiac Resynchronization Therapy



Ts-Sep-Lat ≥ 65 ms

Sensitivity 70%

Specificity 76%

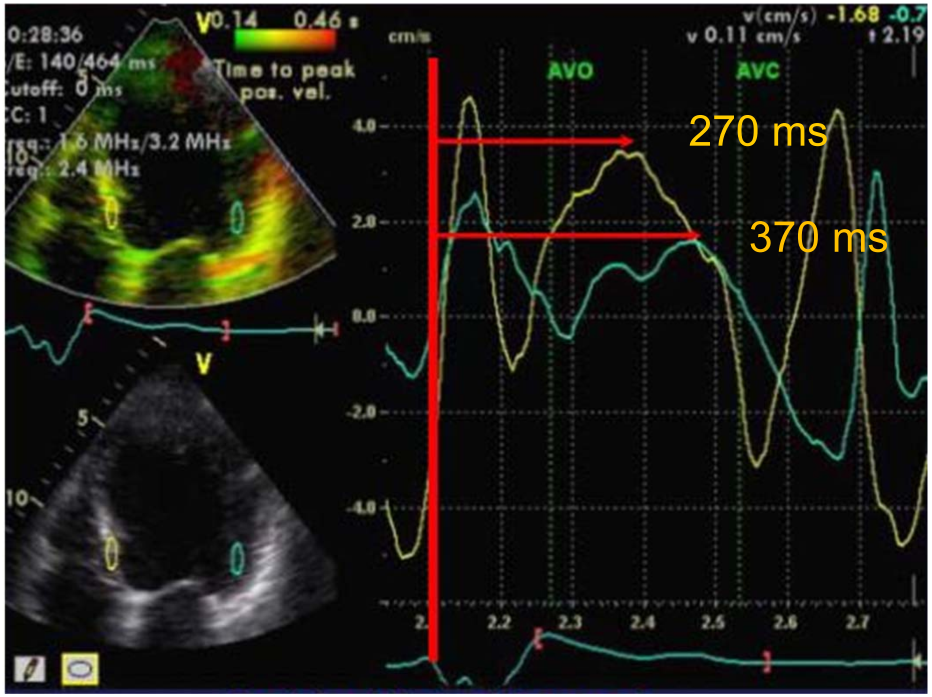
Yu CM et al 2007 AJC

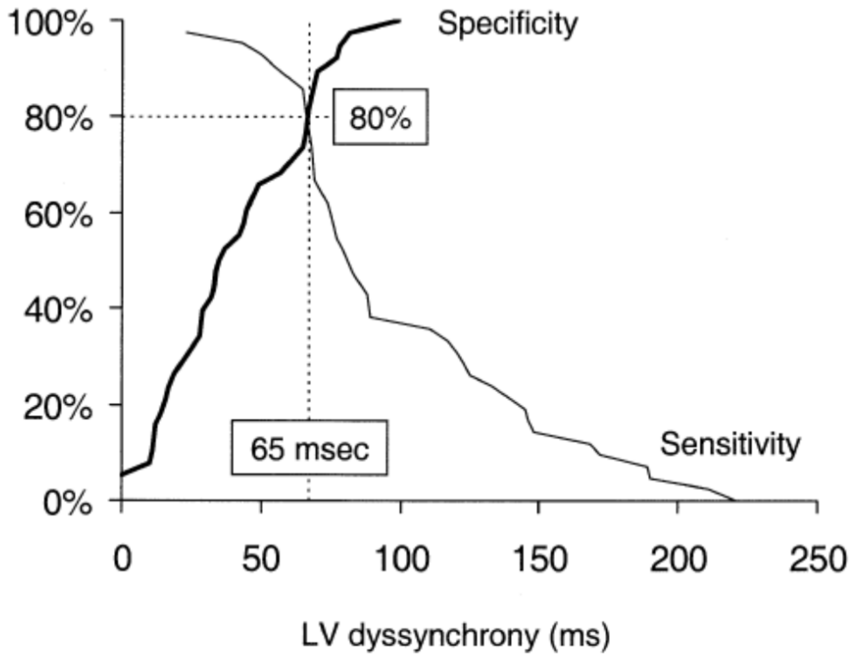
Two site methods

Left Ventricular Dyssynchrony Predicts Response and Prognosis After Cardiac Resynchronization Therapy

Jeroen J. Bax, MD, PhD,* Gabe B. Bleeker, MD,* Thomas H. Marwick, MD,†
Sander G. Molhoek, MD, PhD,* Eric Boersma, PhD,‡ Paul Steendijk, MD, PhD,*
Ernst E. van der Wall, MD, PhD,* Martin J. Schalij, MD, PhD*
Leiden and Rotterdam, The Netherlands; and Brisbane, Australia

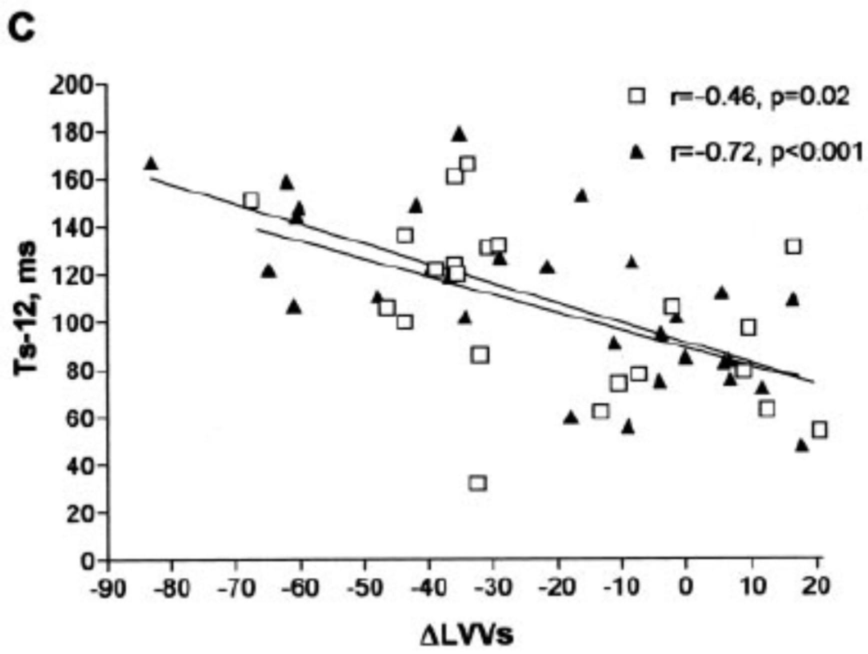
2004 JACC

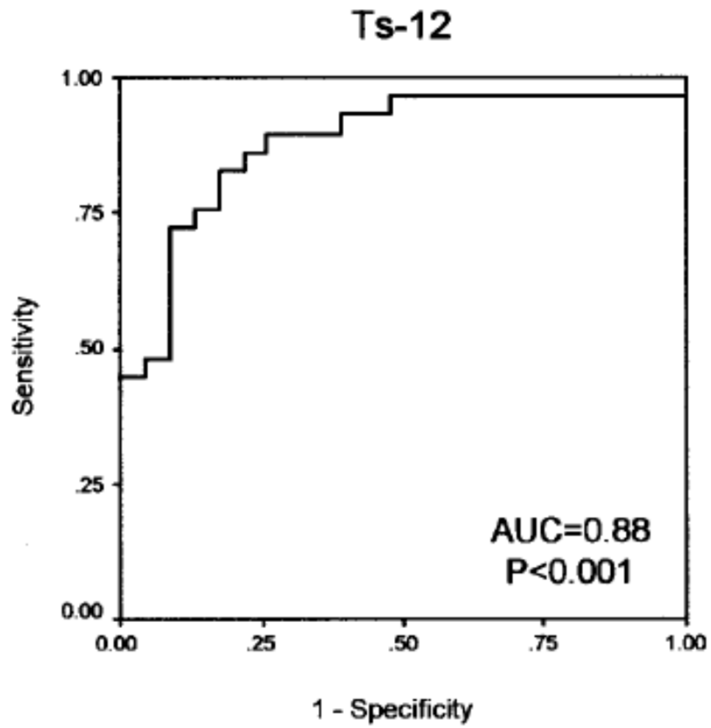




(6) 12 segments methods

- Maximal difference in the time to peak systolic velocity among all segments, where a cut-off value of greater than or equal to 100 milliseconds predicts response to CRT

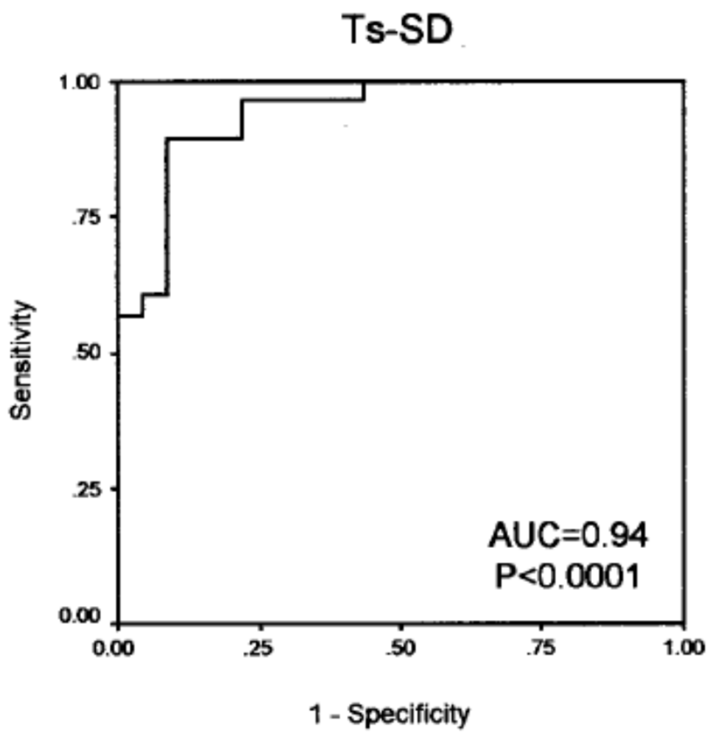




Yu CM et al 2004 Circulation

(7) Yu-index

- Standard deviation of Ts of the 12 LV segments (Ts-SD)



Ts-SD 31.4 ms

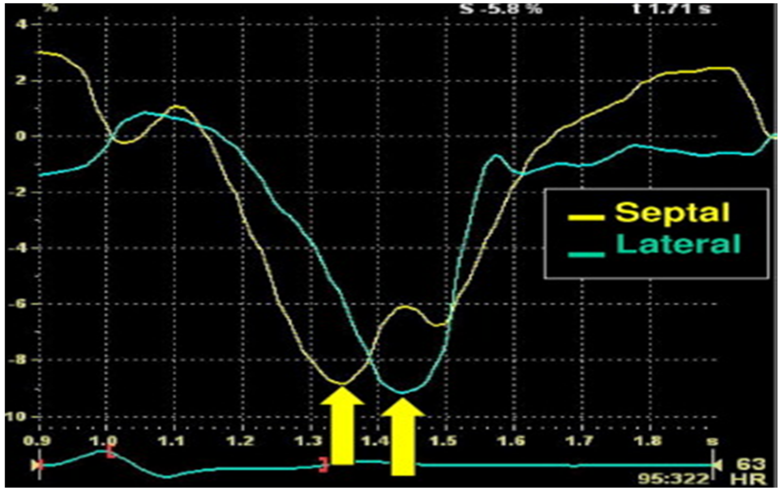
Sensitivity 96%

Specificity 78%

Yu CM et al 2004 Circulation

(8) TDI Strain

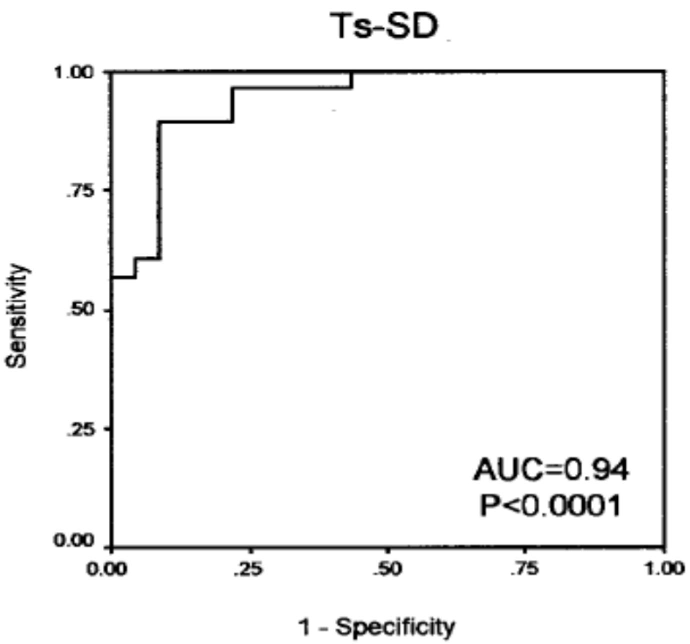
- Longitudinal strain is calculated linearly from TD velocity data as percent shortening
- This enables differentiation between passive wall motion and true contraction and theoretically should more accurately identify dyssynchrony.

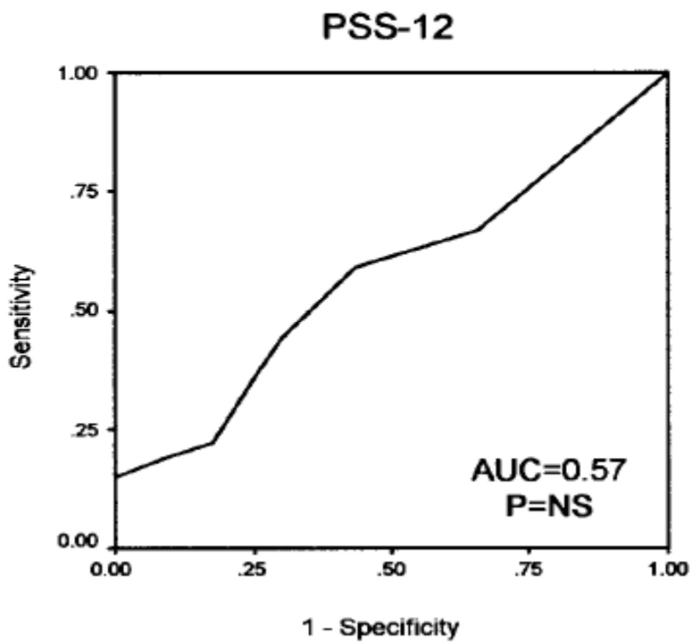


Before CRT

TDI Strain

- Low signal-to-noise ratio is believed to be the explanation for its poor reproducibility independent of the operator's experience.
- PSS, SRI were not able to predict of reverse remodelling

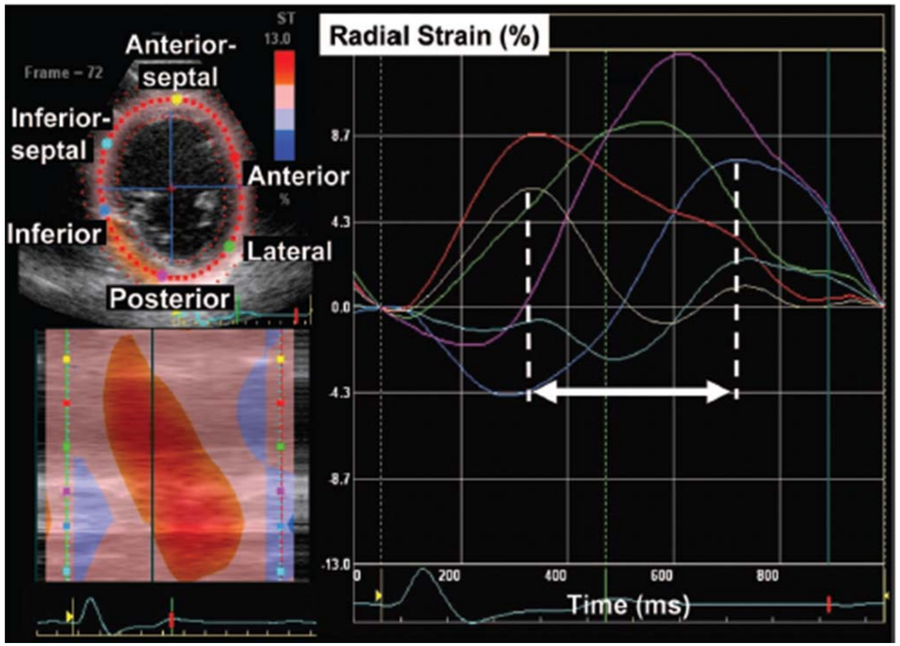


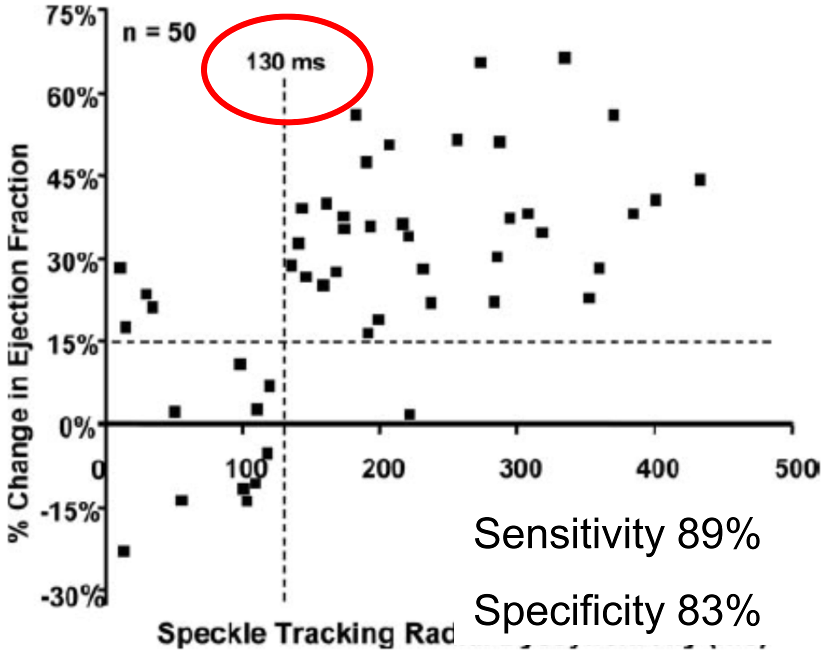


Yu CM et al 2004 Circulation

(9) Speckle tracking strain

- A more recent approach is application of a speckle-tracking program that is applied to routine gray-scale echocardiographic images, which is not limited by Doppler angle.





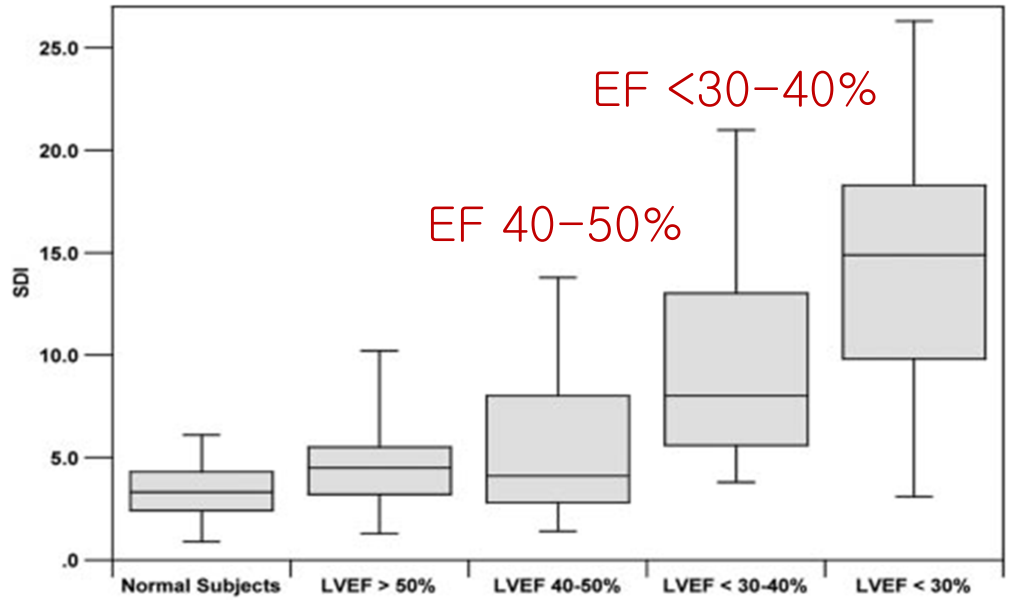
Sensitivity 89%

Specificity 83%

Suffoletto MS et al 2006 Circulation

(10) 3D Echocardiography

- The advantage of real-time 3-dimensional echocardiography is that it allows for a comparison of synchrony between of the segments of the LV together in the same cardiac cycle
- Dyssynchrony index from the dispersion of time to minimum regional volume

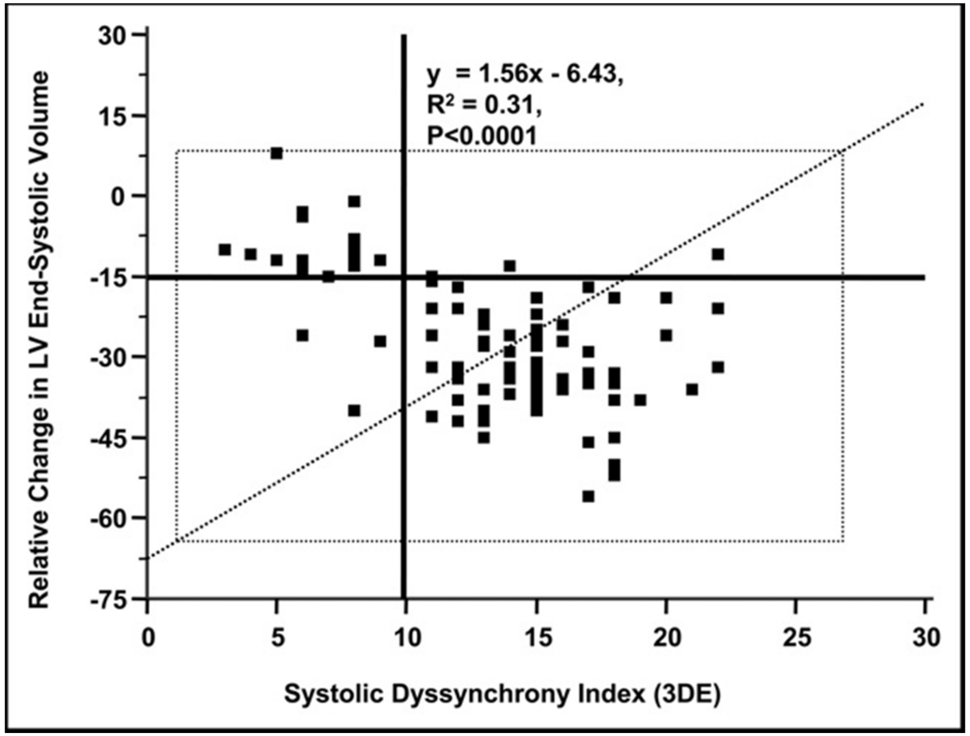


Kapetanakis et al 2005 Circulation

3D Echocardiography

Usefulness of Left Ventricular Systolic Dyssynchrony by Real-Time Three-Dimensional Echocardiography to Predict Long-Term Response to Cardiac Resynchronization Therapy

Osama I.I. Soliman, MD, PhD[a,b,*], Marcel L. Geleijnse, MD, PhD[a], Dominic A.M.J. Theuns, PhD[a], Bas M. van Dalen, MD[a], Wim B. Vletter, MSc[a], Luc J. Jordaens, MD, PhD[a], Ahmed K. Metawei, MD[b], Aly M. Al-Amin, MD[b], and Folkert J. ten Cate, MD, PhD[a]



Soliman et al 2009 AJC

Major dyssynchrony indices

	Normal	Cut-off	Comments
M-mode (SPWMD)	< 50 ms	≥ 130 ms	Widely available
Septal to lateral delay	< 50 ms	≥ 65 ms	Rapidly applied
Maximal delay (12 sites)	< 90 ms	≥ 100 ms	More segments
Yu-index	< 30 ms	≥ 33 ms	More times
TD strain	None	N/A	Technically demand
Radial strain	< 40 ms	≥ 130 ms	Applied to routine image
3DE SDI	< 5 %	≥ 10 %	Same cardiac cycle

JASE (2008;21:191-213) Modified

However,

It is important to point out that most clinical studies were observational series from single-center, which had reported significant inter- and intraobserver variability (up to almost 10%).

Therefore, these results may not be reproducible in other centers, in different patient populations, or with different imaging experiences or capabilities

Results of the Predictors of Response to CRT (PROSPECT) Trial

Eugene S. Chung, MD; Angel R. Leon, MD; Luigi Tavazzi, MD; Jing-Ping Sun, MD; Petros Nihoyannopoulos, MD; John Merlino, MD; William T. Abraham, MD; Stefano Ghio, MD; Christophe Leclercq, MD; Jeroen J. Bax, MD; Cheuk-Man Yu, MD, FRCP; John Gorcsan III, MD; Martin St John Sutton, FRCP; Johan De Sutter, MD, PhD; Jaime Murillo, MD

Background—Data from single-center studies suggest that echocardiographic parameters of mechanical dyssynchrony may improve patient selection for cardiac resynchronization therapy (CRT). In a prospective, multicenter setting, the Predictors of Response to CRT (PROSPECT) study tested the performance of these parameters to predict CRT response.

Methods and Results—Fifty-three centers in Europe, Hong Kong, and the United States enrolled 498 patients with standard CRT indications (New York Heart Association class III or IV heart failure, left ventricular ejection fraction ≤35%, QRS ≥130 ms, stable medical regimen). Twelve echocardiographic parameters of dyssynchrony, based on both conventional and tissue Doppler–based methods, were evaluated after site training in acquisition methods and blinded core laboratory analysis. Indicators of positive CRT response were improved clinical composite score and ≥15% reduction in left ventricular end-systolic volume at 6 months. Clinical composite score was improved in 69% of 426 patients, whereas left ventricular end-systolic volume decreased ≥15% in 56% of 286 patients with paired data. The ability of the 12 echocardiographic parameters to predict clinical composite score response varied widely, with sensitivity ranging from 6% to 74% and specificity ranging from 35% to 91%; for predicting left ventricular end-systolic volume response, sensitivity ranged from 9% to 77% and specificity from 31% to 93%. For all the parameters, the area under the receiver-operating characteristics curve for positive clinical or volume response to CRT was ≤0.62. There was large variability in the analysis of the dyssynchrony parameters.

Conclusion—Given the modest sensitivity and specificity in this multicenter setting despite training and central analysis, no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines. Efforts aimed at reducing variability arising from technical and interpretative factors may improve the predictive power of these echocardiographic parameters in a broad clinical setting. (***Circulation*****. 2008;117: 2608-2616.**)

PROSPECT

Dyssynchrony Measure	Evaluable Echocardiograms, (yield) %	CCS			
		Sensitivity, %	Specificity, %	AUC	P for AUC
SPWMD	71.7	55.4 (48.3-62.3)	50.0 (39.1-60.9)	0.54	0.27
IVMD	92.4	55.2 (48.9-61.4)	56.4 (46.9-65.6)	0.58	0.013
LVFT/RR	85.3	36.3 (30.2-42.7)	76.6 (67.5-84.3)	0.57	0.032
LPEI	94.6	66.3 (60.2-72.0)	47.1 (38.0-56.4)	0.60	0.001
LLWC	60.7	6.3 (3.2-11.0)	91.7 (82.7-96.9)	0.52	0.63
Ts (Lat-Sep)	66.8	42.4 (34.4-50.7)	56.9 (44.7-68.6)	0.50	0.85
Ts-SD	50.0	74.1 (65.2-81.8)	35.3 (22.4-49.9)	0.60	0.034
PVD	81.4	67.6 (60.3-74.3)	37.8 (27.8-48.6)	0.51	0.89
DLC	81.1	41.7 (34.4-49.2)	60.4 (49.6-70.5)	0.51	0.75
TS-peak Displacement	37.4	54.8 (43.5-65.7)	56.1 (39.7-71.5)	0.56	0.32
Ts-peak basal	82.0	51.9 (44.4-59.3)	53.8 (43.1-64.4)	0.55	0.19
Ts-onset basal	82.0	54.1 (46.6-61.5)	60.4 (49.6-70.5)	0.58	0.047

PROSPECT

Table 3. Interobserver and Intraoperator Variability Summary

Echocardiographic Measure	Intraobserver CV, %	Interobserver CV, %	Interobserver κ Coefficient*
LVESV	3.8	14.5	NA
LPEI	3.7	6.5	0.67
SPWMD	24.3	72.1	0.35
Ts-SD	11.4	33.7	0.15
Ts-peak (basal)	15.8	31.9	0.25

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Conclusion—Given the modest sensitivity and specificity in this multicenter setting despite training and central analysis, no single echocardiographic measure of dyssynchrony may be recommended patient selection for CRT interpretative factors may improve the predictive power of these echocardiographic parameters in a broad clinical setting. (*Circulation*. **2008;117:2608-2616.**)

Echocardiography and Noninvasive Imaging in Cardiac Resynchronization Therapy

Results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) Study in Perspective

Jeroen J. Bax, MD, PhD,* John Gorcsan III, MD†
Leiden, the Netherlands; and Pittsburgh, Pennsylvania

- Patient selection: EF>35% in 20.5% of patients
- Technical issue: high interobserver variability
- Pathophysiologic issue: scar tissue, lead position

Dyssynchrony Indices To Predict Response to Cardiac Resynchronization Therapy

A Comprehensive Prospective Single-Center Study

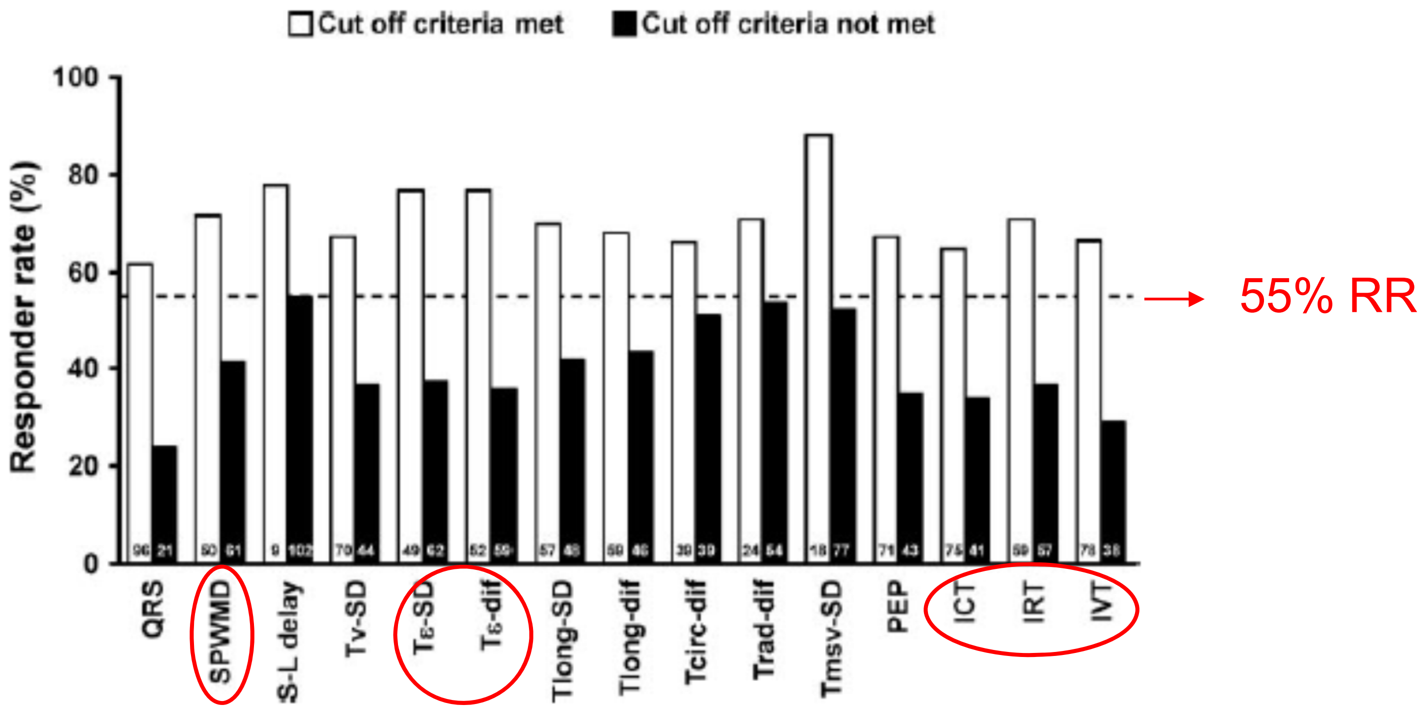
Chinami Miyazaki, MD*; Margaret M. Redfield, MD*; Brian D. Powell, MD; Grace M. Lin, MD; Regina M. Herges, BSs; David O. Hodge, MS; Lyle J. Olson, MD; David L. Hayes, MD; Raul E. Espinosa, MD; Robert F. Rea, MD; Charles J. Bruce, MD; Susan M. Nelson, LPN; Fletcher A. Miller, MD; Jae K. Oh, MD

Background—Whether mechanical dyssynchrony indices predict reverse remodeling (RR) or clinical response to cardiac resynchronization therapy (CRT) remains controversial. This prospective study evaluated whether echocardiographic dyssynchrony indices predict RR or clinical response after CRT.

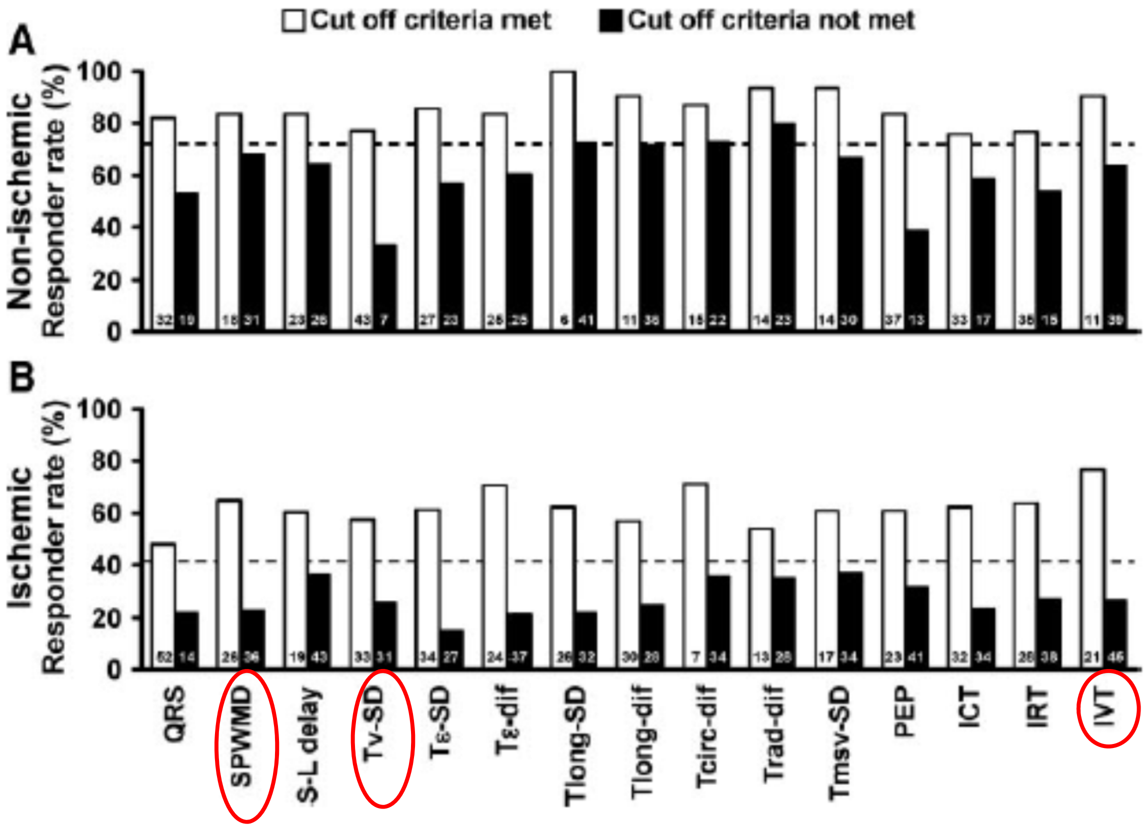
Methods and Results—Of 184 patients with heart failure with anticipated CRT who were prospectively enrolled, 131 with wide QRS and left ventricular ejection fraction <35% had 6-month follow-up after CRT implantation. Fourteen dyssynchrony indices (feasibility) by M-mode (94%), tissue velocity (96%), tissue Doppler strain (92%), 2D speckle strain (65% to 86%), 3D echocardiography (79%), and timing intervals (98%) were evaluated. RR (end-systolic volume reduction ≥15%) occurred in 55% and more frequently in patients without (71%) than in patients with (42%) ischemic cardiomyopathy (P=0.002). Overall, only M-mode, tissue Doppler strain, and total isovolumic time had a receiver operating characteristic area under the curve (AUC) greater than the line of no information, but none of these were strongly predictive of RR (AUC, 0.63 to 0.71). In nonischemic cardiomyopathy, no dyssynchrony index predicted RR. In ischemic cardiomyopathy, M-mode (AUC, 0.67), tissue Doppler strain (AUC, 0.79), and isovolumic time (AUC, 0.76) -derived indices predicted RR (P<0.05 for all), although the incremental value was modest. No indices predicted clinical response assessed by Minnesota Living with Heart Failure Questionnaire, 6-minute walk distance, and peak oxygen consumption.

Conclusions—These findings are consistent with the Predictors of Response to CRT study and do not support use of these dyssynchrony indices to guide use of CRT. (*Circ Heart Fail*. **2010;3:565-573.**)

RR after CRT 6 months (all patients)



Role of Echo



No index for prediction of RR

AUC

TD strain 0.79

IVT 0.76

M-mode 0.67

Dyssynchrony Indices To Predict Response to Cardiac Resynchronization Therapy

A Comprehensive Prospective Single-Center Study

Chinami Miyazaki, MD*; Margaret M. Redfield, MD*; Brian D. Powell, MD; Grace M. Lin, MD; Regina M. Herges, BSs; David O. Hodge, MS; Lyle J. Olson, MD; David L. Hayes, MD; Raul E. Espinosa, MD; Robert F. Rea, MD; Charles J. Bruce, MD; Susan M. Nelson, LPN; Fletcher A. Miller, MD; Jae K. Oh, MD

This prospective single-center study confirmed the PROSPECT trial's conclusion and does not support a routine use of any echocardiographic dyssynchrony index to select patients for CRT.

Future investigations should focus on further characterizing the clinical and laboratory features of the patients who do not respond to CRT

Summary

CHF (NYHA III-IV)

EF<35%

Screening? — QRS widening

Likelihood? — Dyssynchrony Echo

CT (normal anatomy)

MRI (no scar)

High CRT response