Effect of Ventricular Pacing on Myocardial Function

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Contents

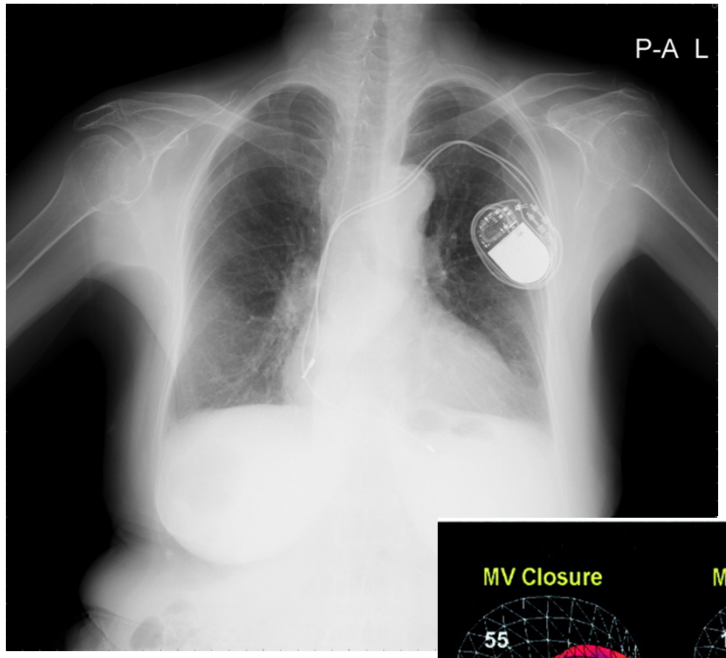
1. The effect of right ventricular apical pacing
2. Strategies for physiologically optimal ventricular pacing
3. Biventricular pacing in heart failure

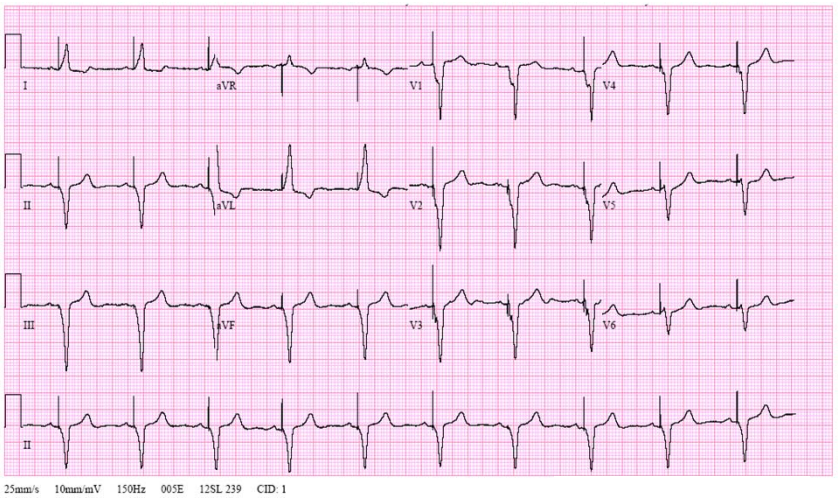
Pacemaker indication

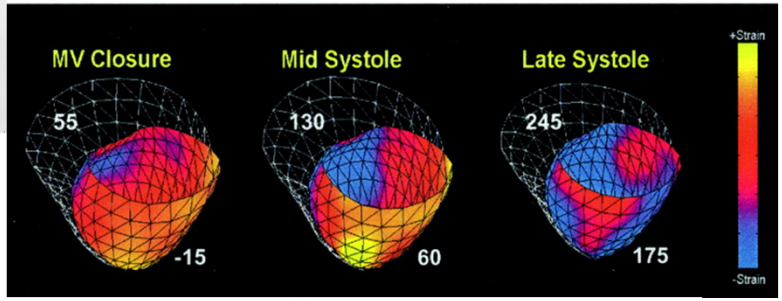
Pacemaker Generator	Sinus Node Dysfunction	Atrioventricular Block	Neurally Mediated Syncope or Carotid Sinus Hypersensitivity
Single-chamber atrial pacemaker	No suspected abnormality of atrioventricular conduction and not at increased risk for future atrioventricular block Maintenance of atrioventricular synchrony during pacing desired	Not appropriate	Not appropriate
Single-chamber ventricular pacemaker	Maintenance of atrioventricular synchrony during pacing not necessary Rate response available if desired	Chronic atrial fibrillation or other atrial tachyarrhythmia or maintenance of atrioventricular synchrony during pacing not necessary Rate response available if desired	Chronic atrial fibrillation or other atrial tachyarrhythmia Rate response available if desired
Dual-chamber pacemaker	Atrioventricular synchrony during pacing desired Suspected abnormality of atrioventricular conduction or increased risk for future atrioventricular block Rate response available if desired	Atrioventricular synchrony during pacing desired Atrial pacing desired Rate response available if desired	Sinus mechanism present Rate response available if desired
Single-lead, atrial-sensing ventricular pacemaker	Not appropriate	Desire to limit the number of pacemaker leads	Not appropriate

Circulation 2008; 117:2820-40

Conventional right ventricular apical (RVA) pacing



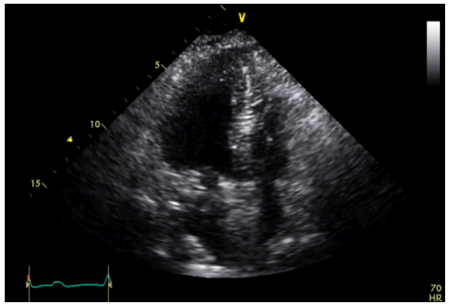


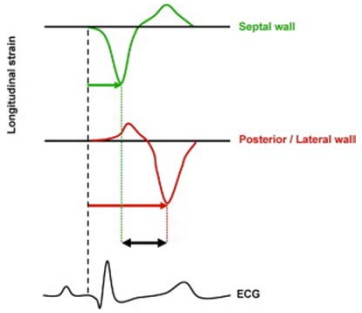


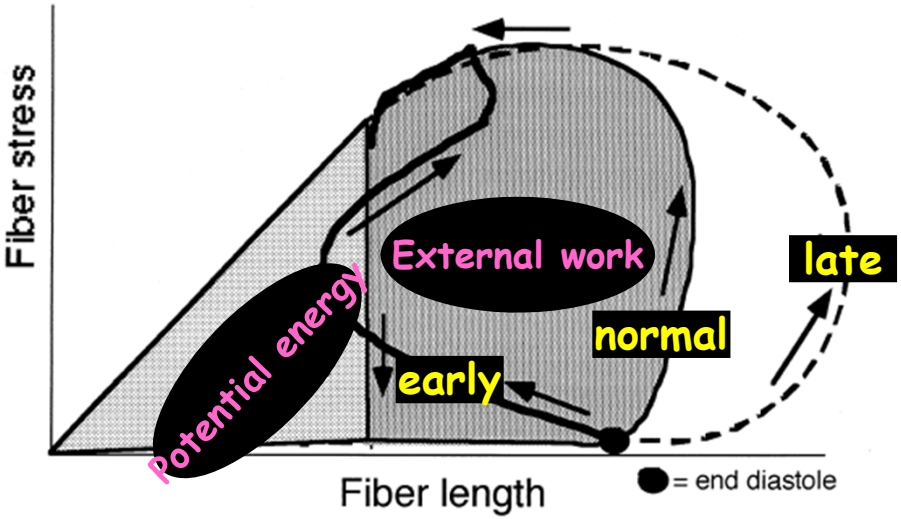
propagation of the electrical wave through the myocardium
→ heterogeneity in activation of the myocardium

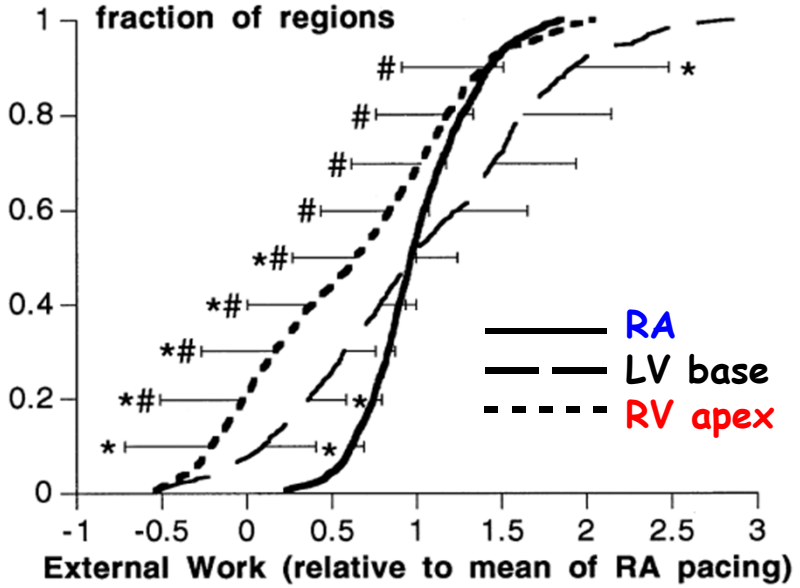
Leclercq C et al. Circ 2002;106:1760-3

Change of mechanical activation by RVA pacing









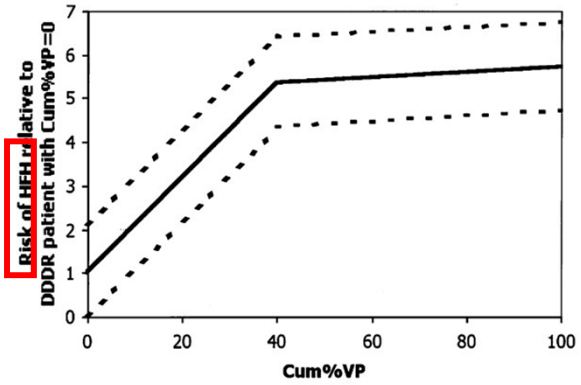
Prinzen FW et al. J Am Coll Cardiol 1999;33:1735-42

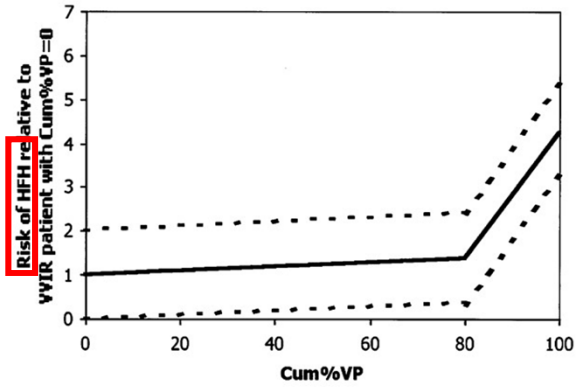
Tops LF et al. J Am Coll Cardiol 2009;54:764-76

Relation of event risk to cumulative % ventricular paced (Cum%VP) as estimated by Cox models: the MOST trial

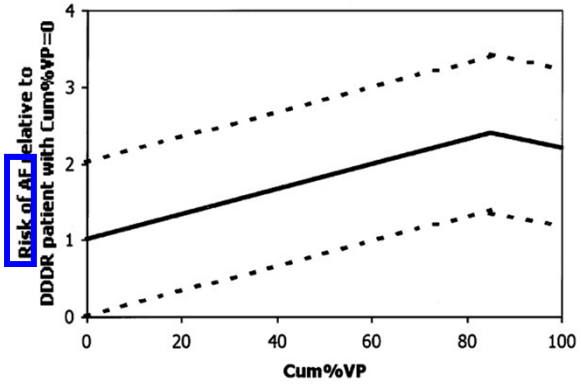
DDDR **VVIR**

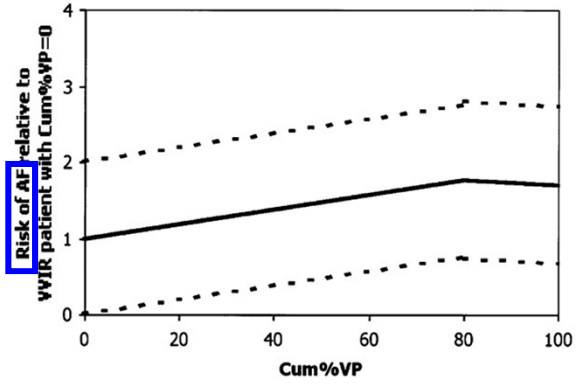
HF hospitalization





Atrial fibrillation

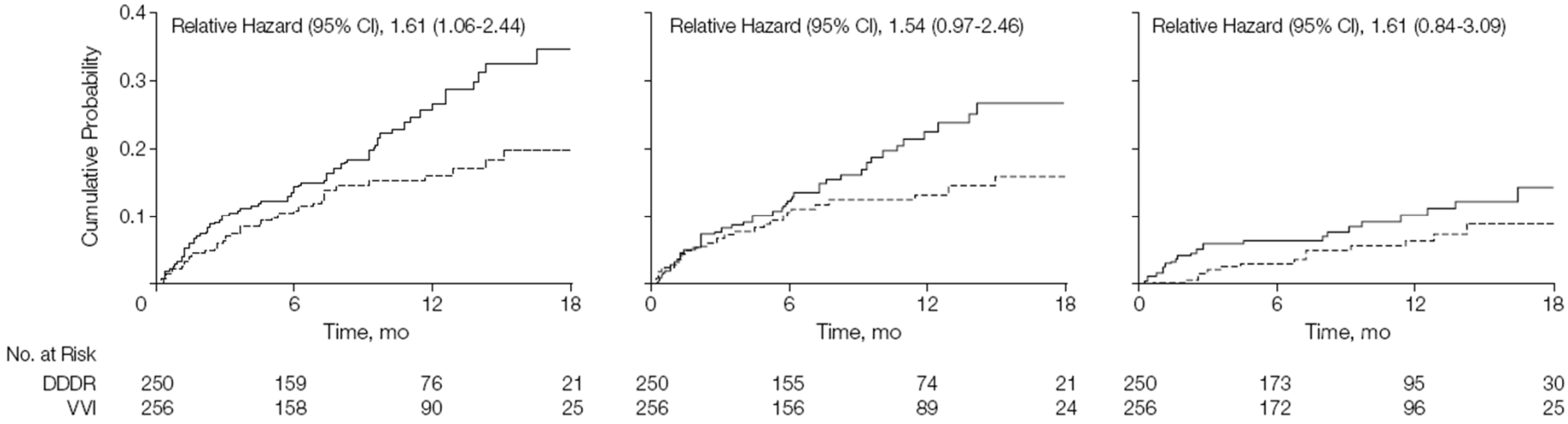




Sweeny et al. Circ 2003;107:2932-7

Increased heart failure and deaths in the DDDR compared with VVI backup pacing in the DAVID trial

Death or hospitalization for HF | **Hospitalization for HF** | **All cause mortality**



——— Dual-Chamber Rate-Responsive Pacing (DDDR-70, lower rate of 70bpm)

– – – – – Ventricular Backup Pacing (VVI-40, lower rate of 40bpm)

- 506 patients with a standard indications for ICD therapy were randomized to either DDDR-70 or VVI-40
- a median follow-up of 8.4 months

Sharma AD et al. JAMA 2002;288:3115-3123

% Beats ventricular paced in the DAVID trial

	VVI	DDDR	P value
3 mo	1.5±8.0 (n=193)	57.9±35.8 (n=188)	<0.001
6 mo	0.6±1.7 (n=150)	59.6±36.2 (n=150)	<0.001
12 mo	3.5±14.9 (n=78)	58.9±36.0 (n=77)	<0.001

The number is a mean±SD.

High % of RVA pacing is associated with adverse clinical outcomes

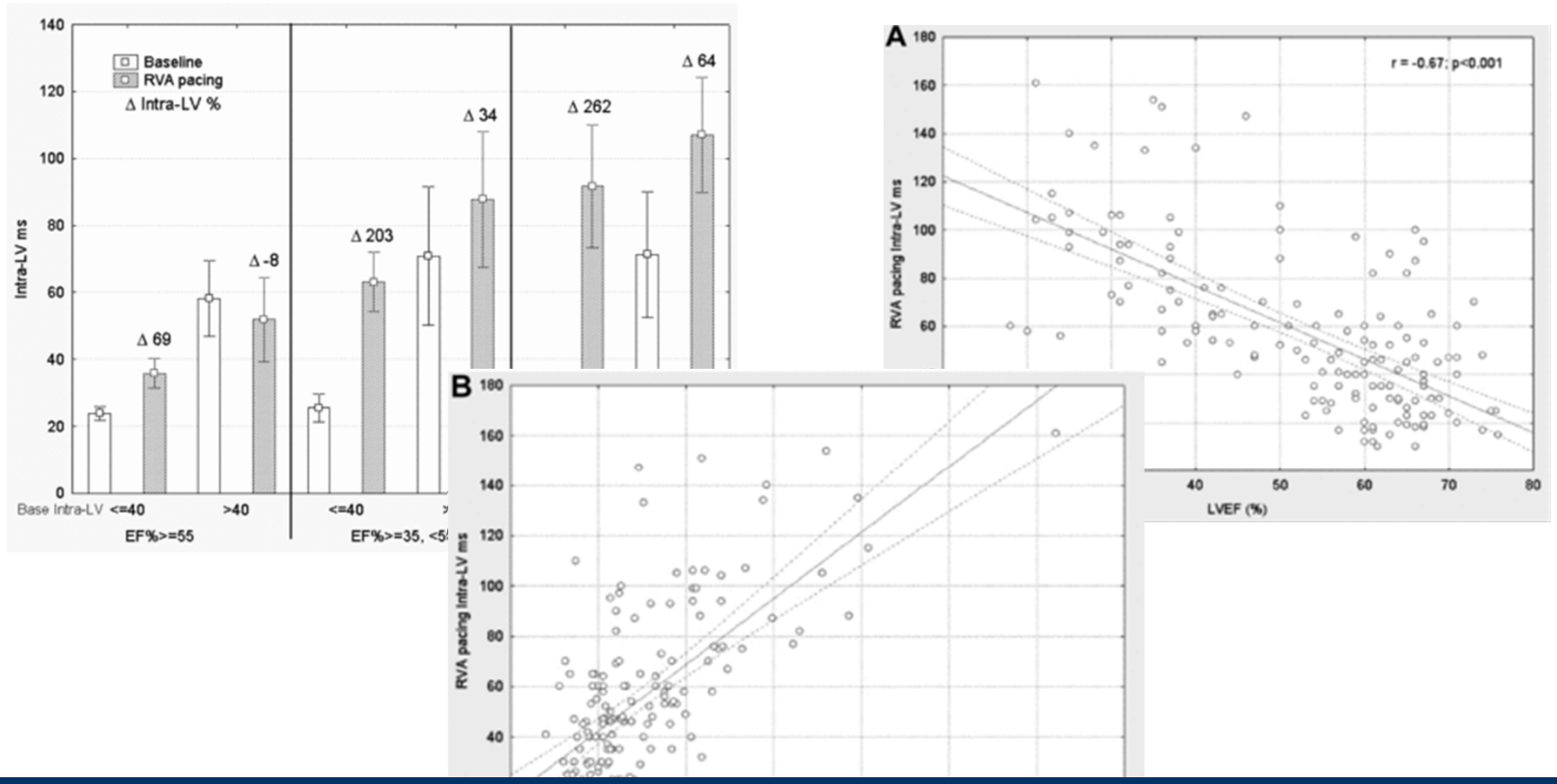
Sharma AD et al. JAMA 2002;288:3115-3123

Risk for predicting heart failure hospitalization during pacemaker therapy for sinus node dysfunction

Baseline variable	Odds ratio	95% CI
Prior heart failure	3.04	2.02~4.58
NYHA class	1.74	1.32~2.29
Low ejection fraction	1.88	1.26~2.81
Prior MI	1.86	1.25~2.76
Antiarrhythmic drugs	1.83	1.22~2.77

Sweeny et al. Heart rhythm 2005:S(2):S75-6

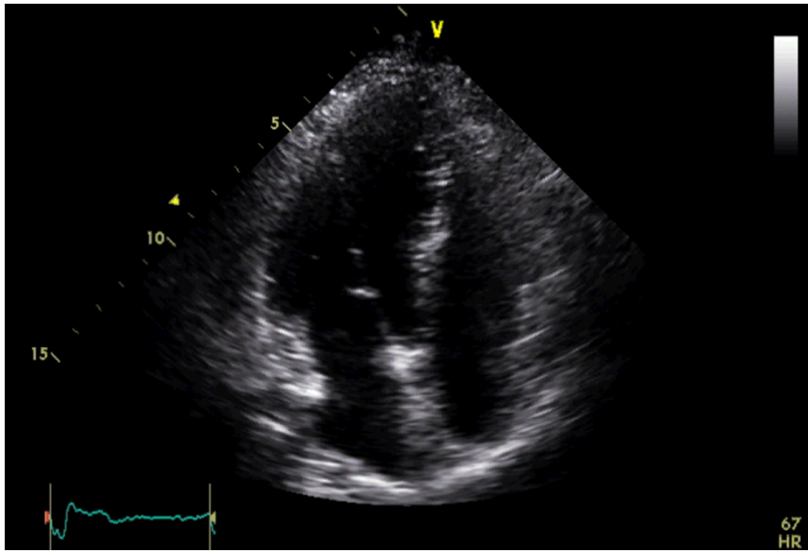
Correlation between LV dyssynchrony after pacing and baseline LV function and volume

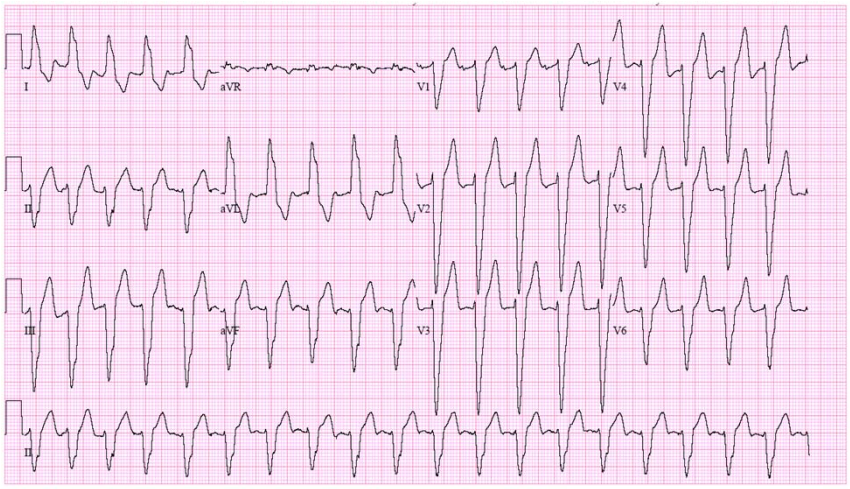


Potentially harmful effects of RVA pacing are more susceptible in the setting of systolic HF

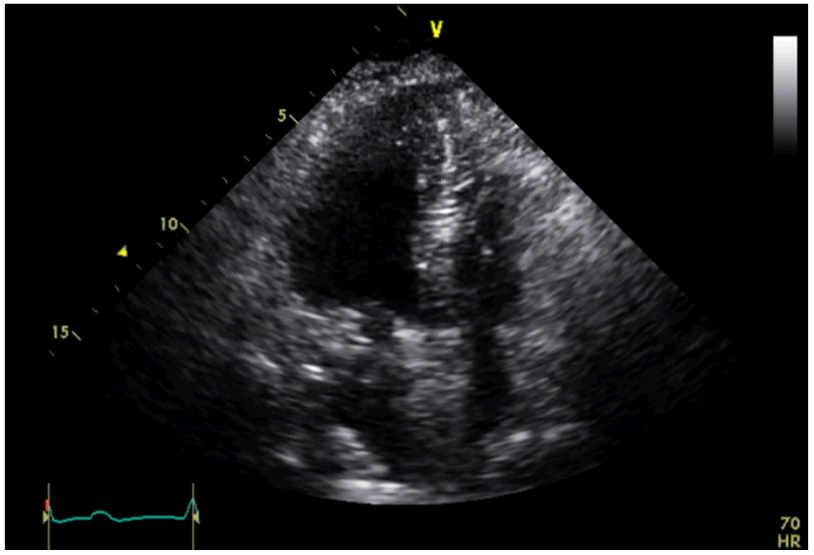
Pastore G et al. Pacing Clin Electrophysiol 2008;31:1456-62

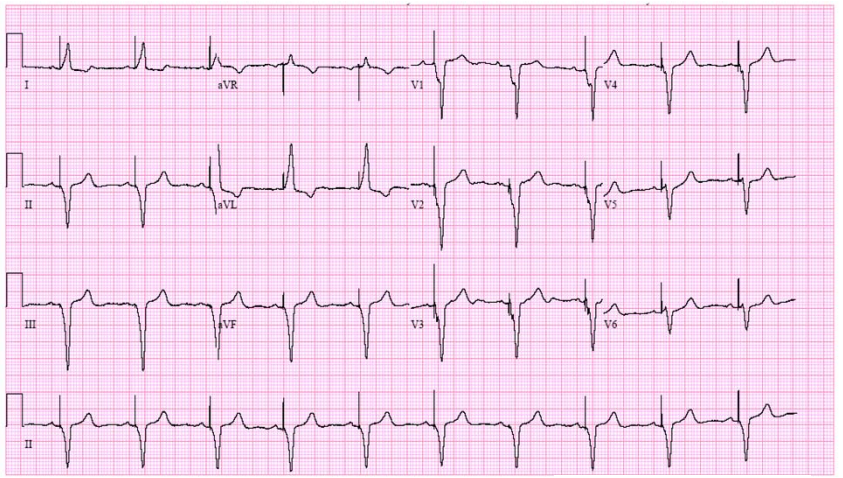
The importance of ventricular asynchrony as in LBBB





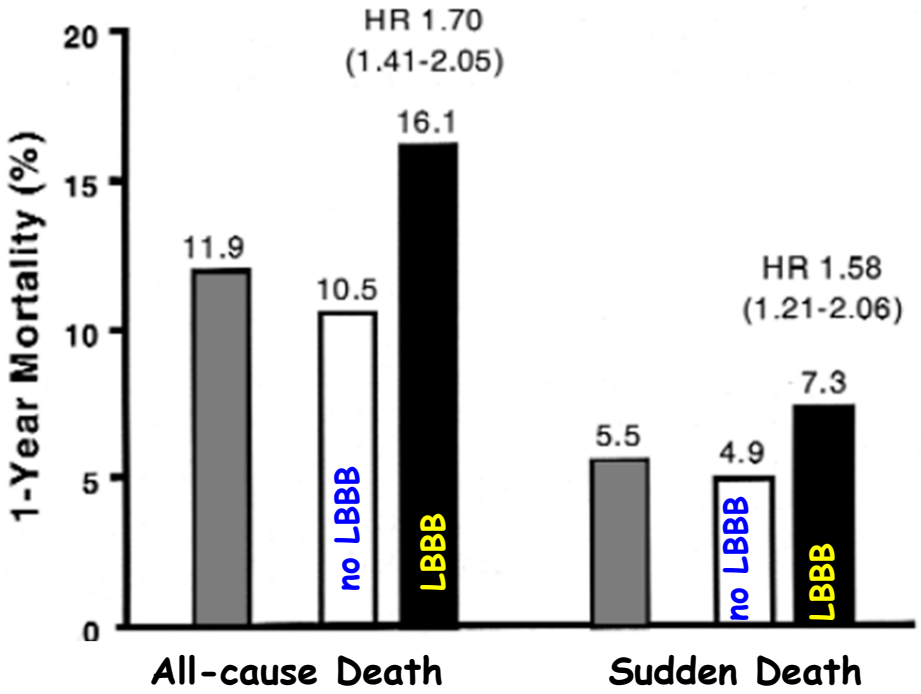
LBBB





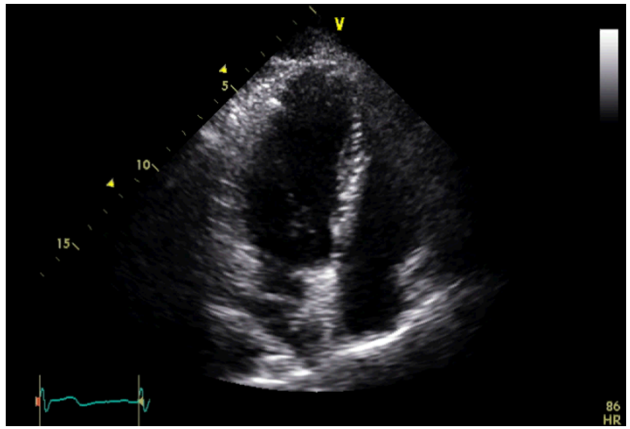
RVA pacing

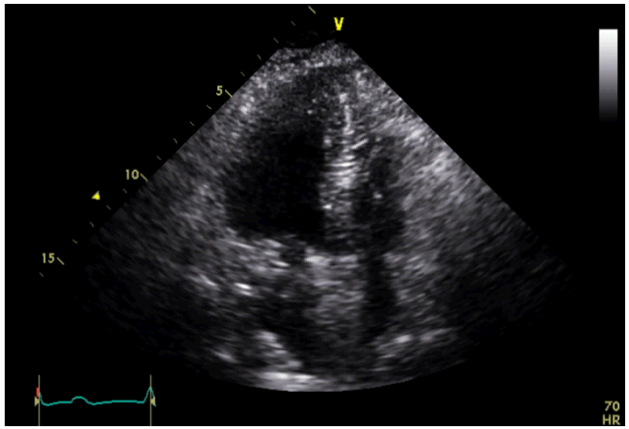
LBBB as an independent predictor for cardiac morbidity and mortality, especially in patients with HF

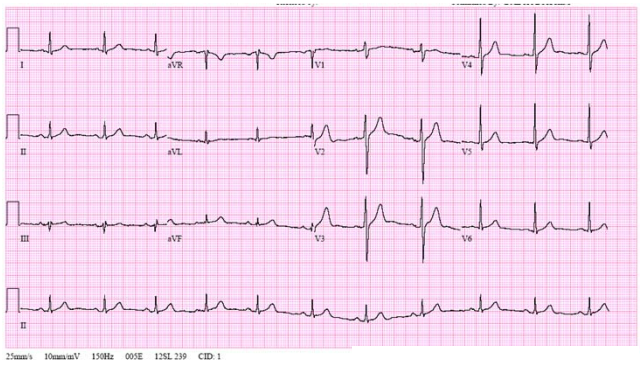


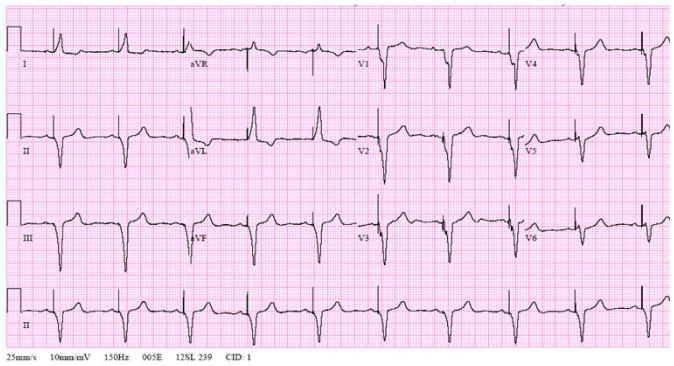
Baldasseroni S et al. Am Heart J 2002;143:398-405

Ventricular asynchrony in pacing mode



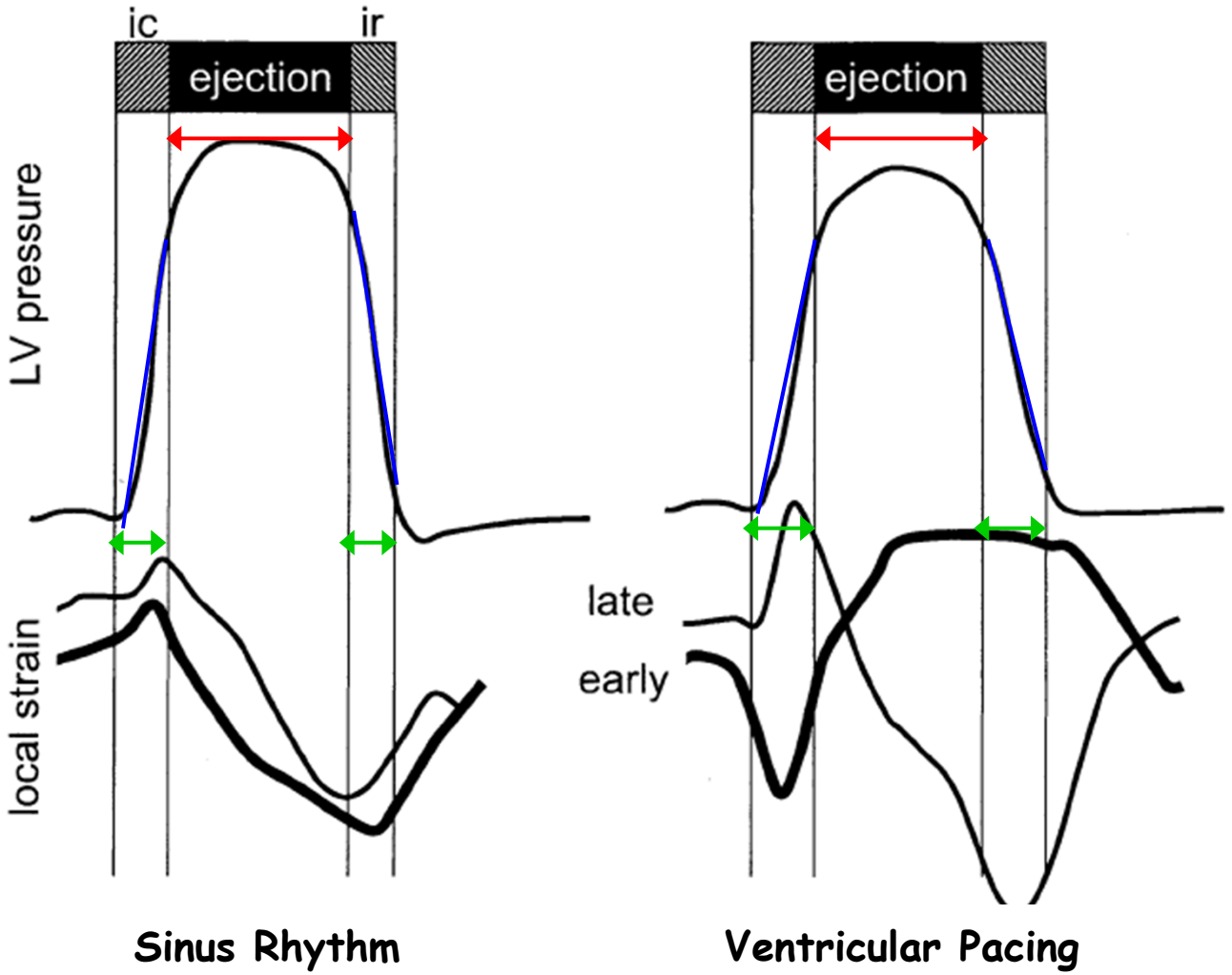






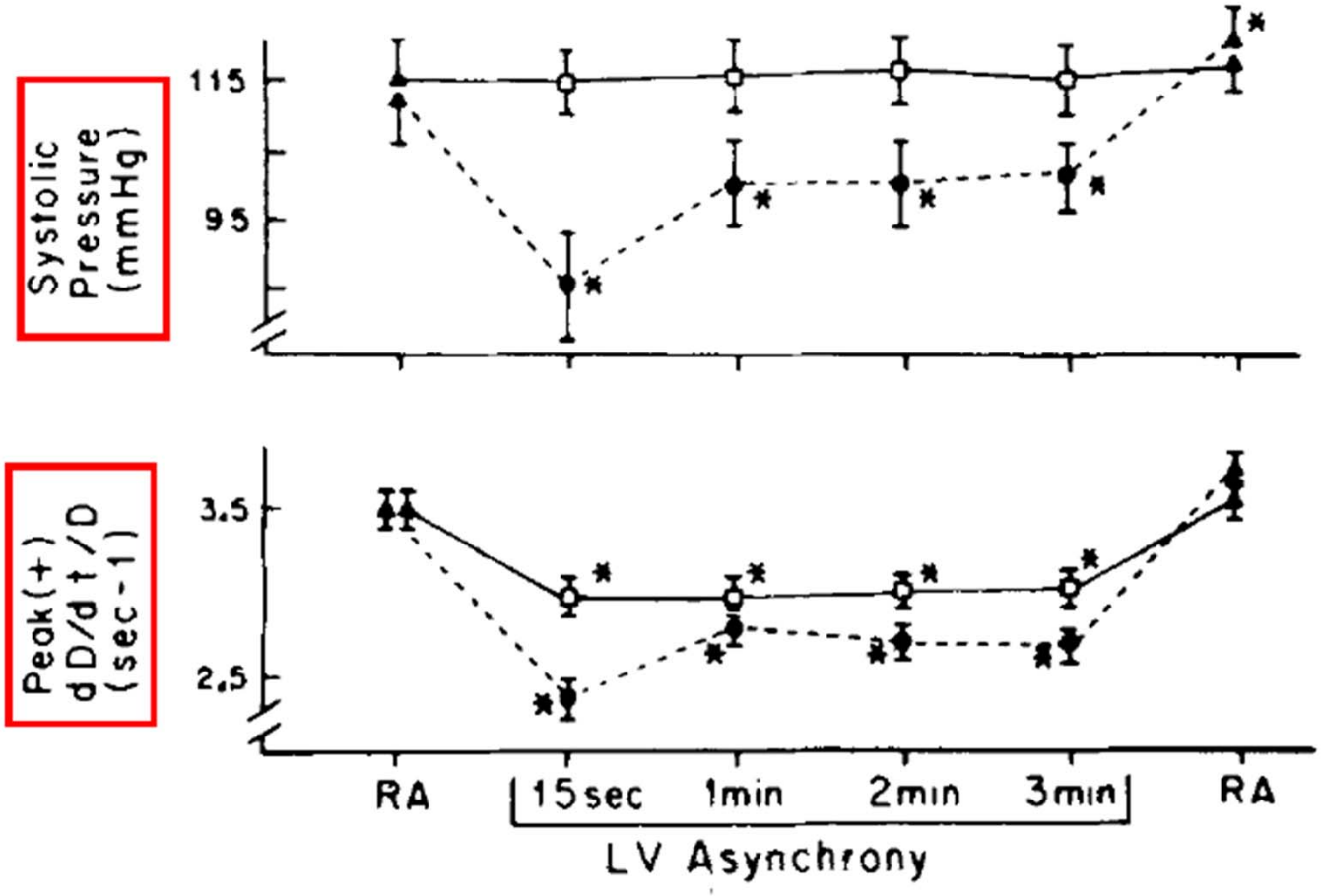
• Pacing at any ventricular site would disturb the natural pattern of ventricular activation and contraction since conduction of the electrical wave propagates slowly through myocardium

Effect of asynchronous ventricular activation



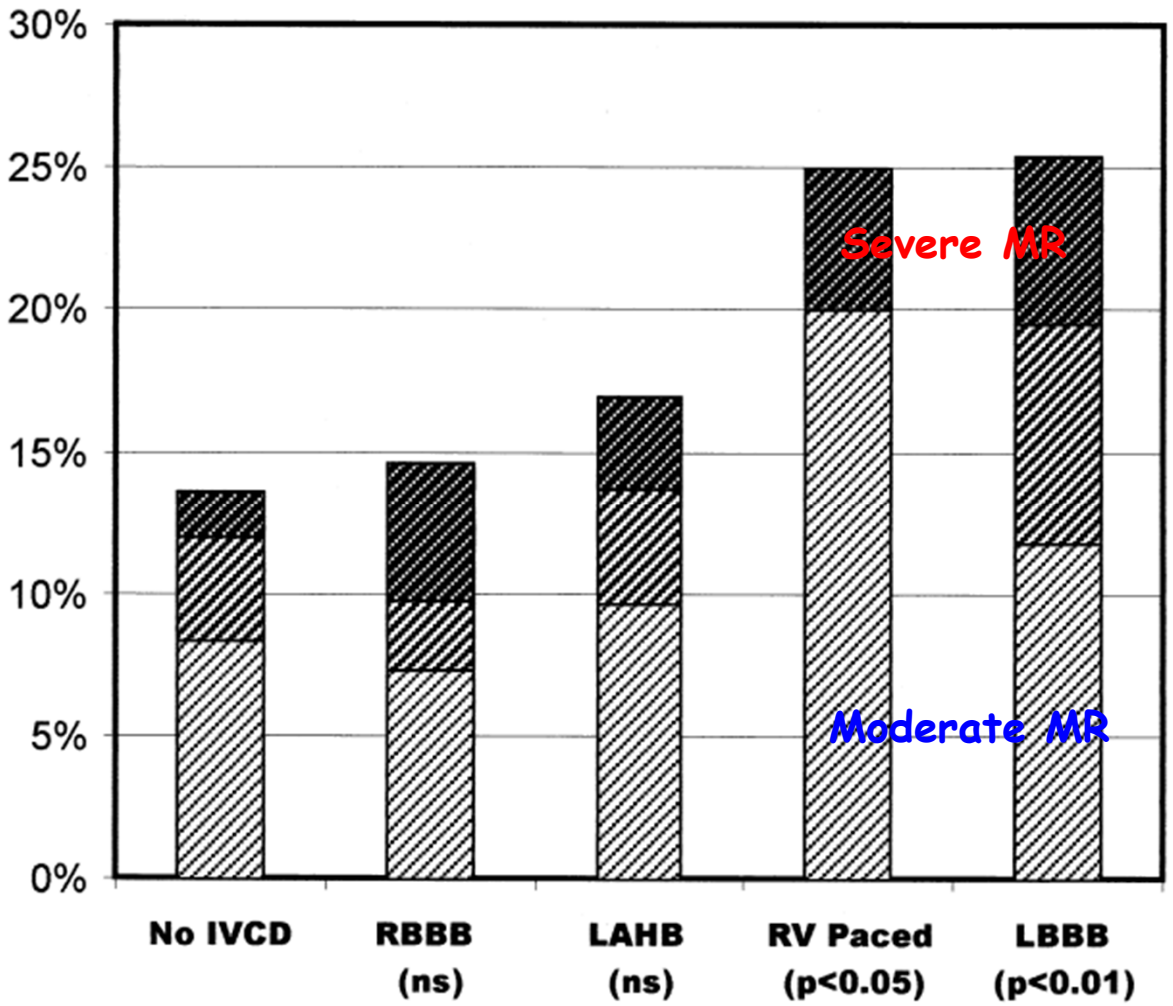
Sweeny MO et al. J Am Coll Cardiol 2006;47:282-8

Effect of RV apical pacing on pressure and dP/dt



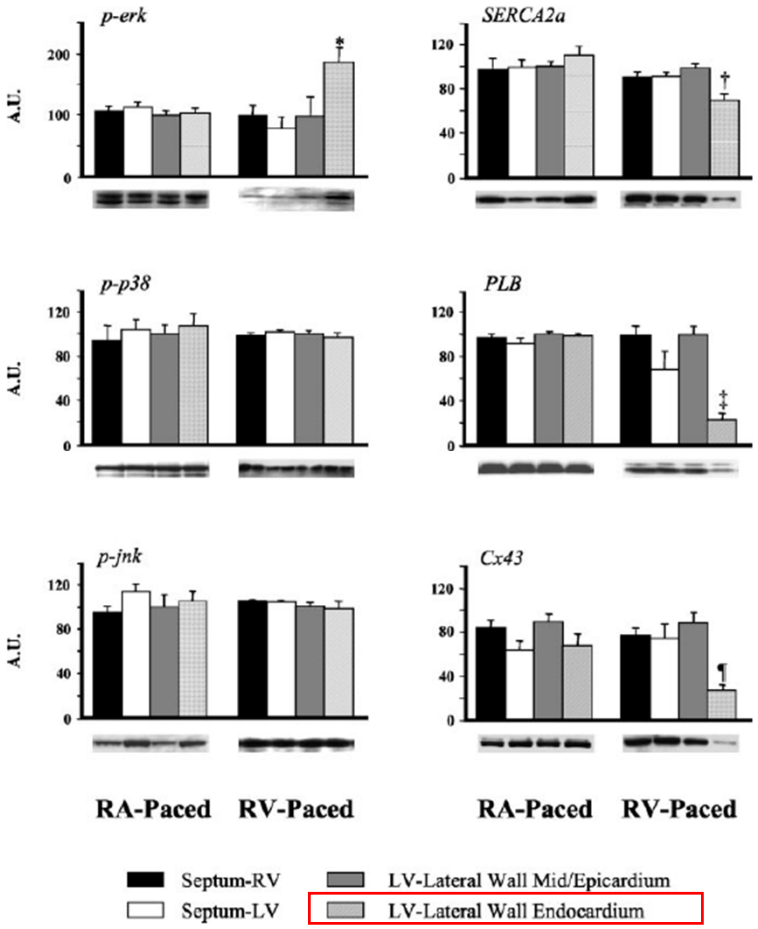
Zile M et al. J Am Coll Cardiol 1987;10:702-9

Increased mitral regurgitation by RV pacing



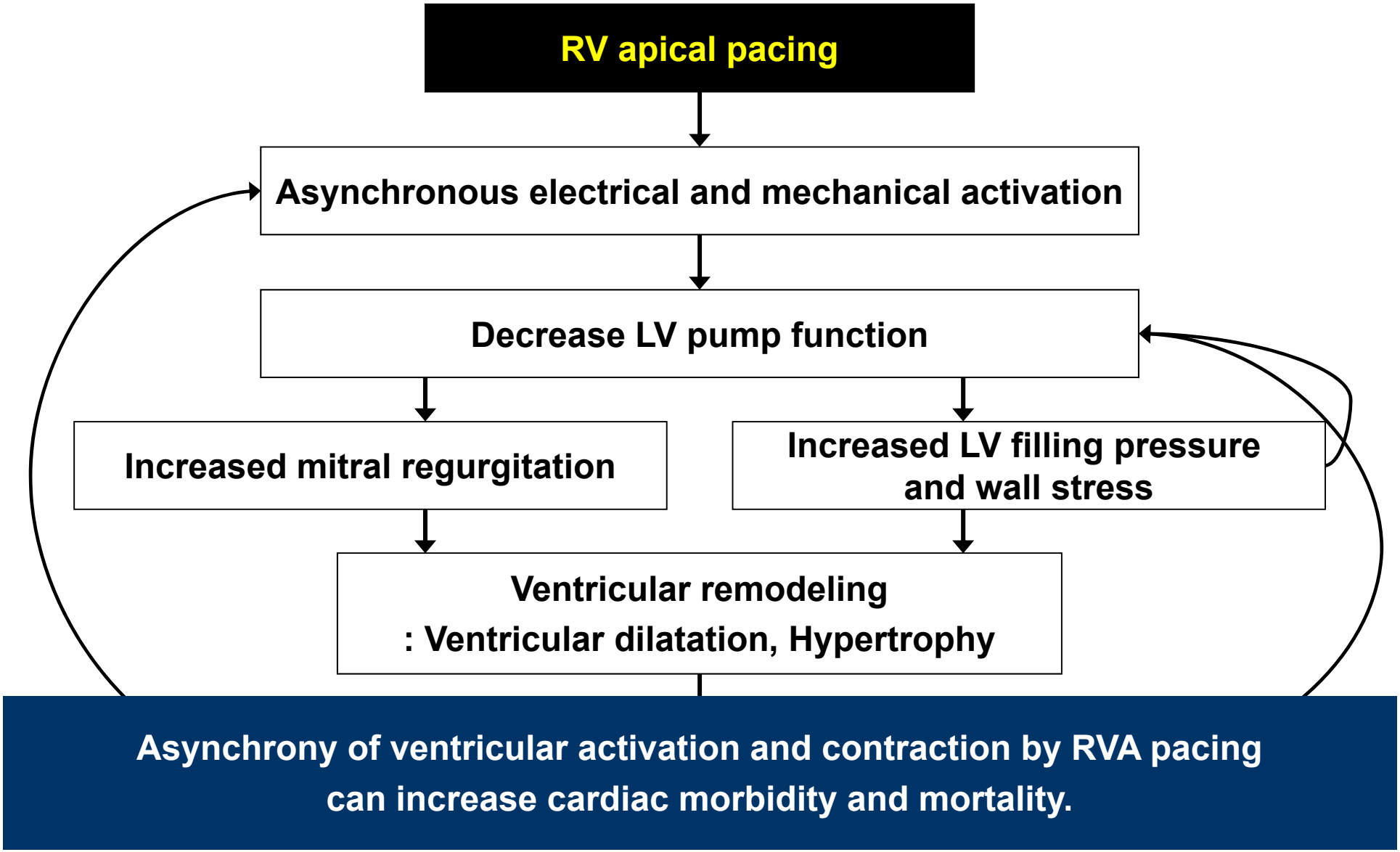
Erlebacher JA et al. Am J Cardiol 2001; 88: 83–6.

Cellular change by RVA pacing



- Mitochondrial variations and degenerative fibrosis
- Regional alteration in protein expression
- The most pronounced cellular derangement, such as down regulation of proteins involved in Ca homeostasis and impulse conduction in the late activated regions

Spragg DD et al. Circ 2003;108:929-32

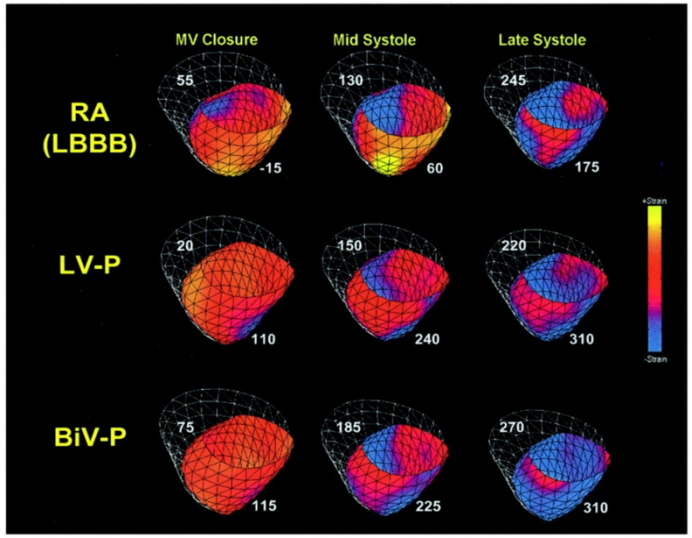


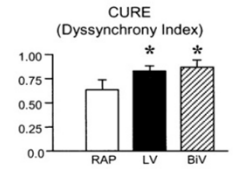
Sweeney MO et al. J Am Coll Cardiol 2006;47:282-8

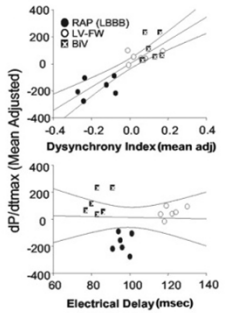
Tops LF et al. J Am Coll Cardiol 2009;54:764-76

Alternative site ventricular pacing

- Alternative RV pacing sites: RVOT, RV septum, His bundle pacing
- Various LV sites
- Biventricular pacing: cardiac resynchronization therapy (CRT)

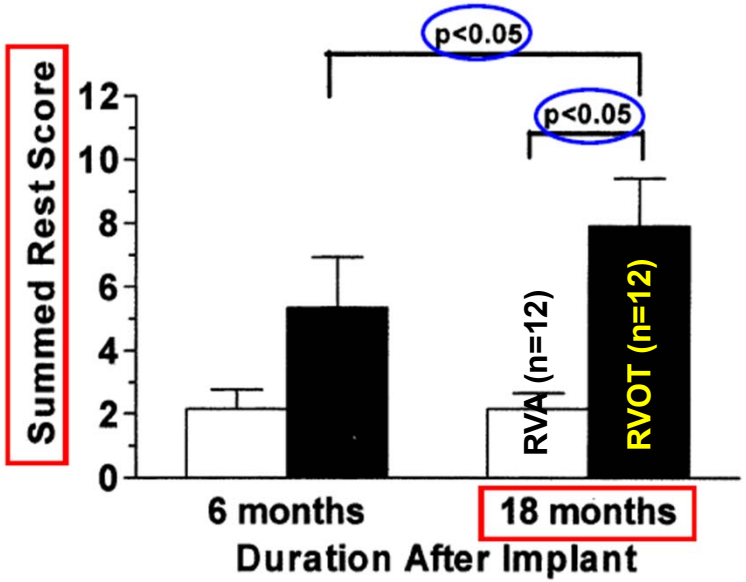


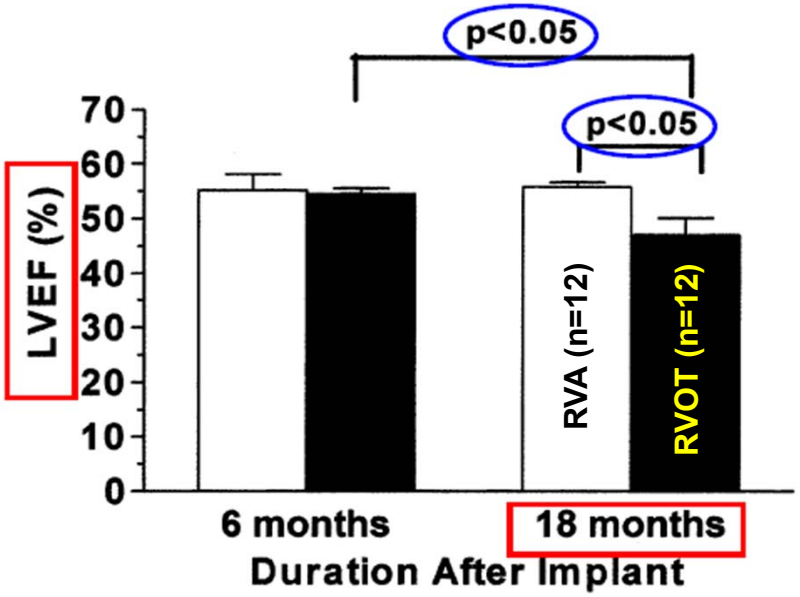


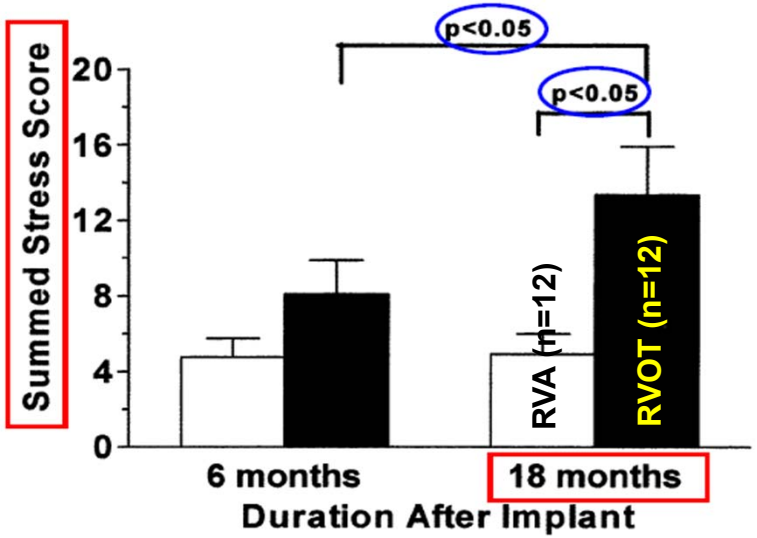


Leclercq C et al. Circ 2002;106:1760-3

RVA vs RVOT pacing







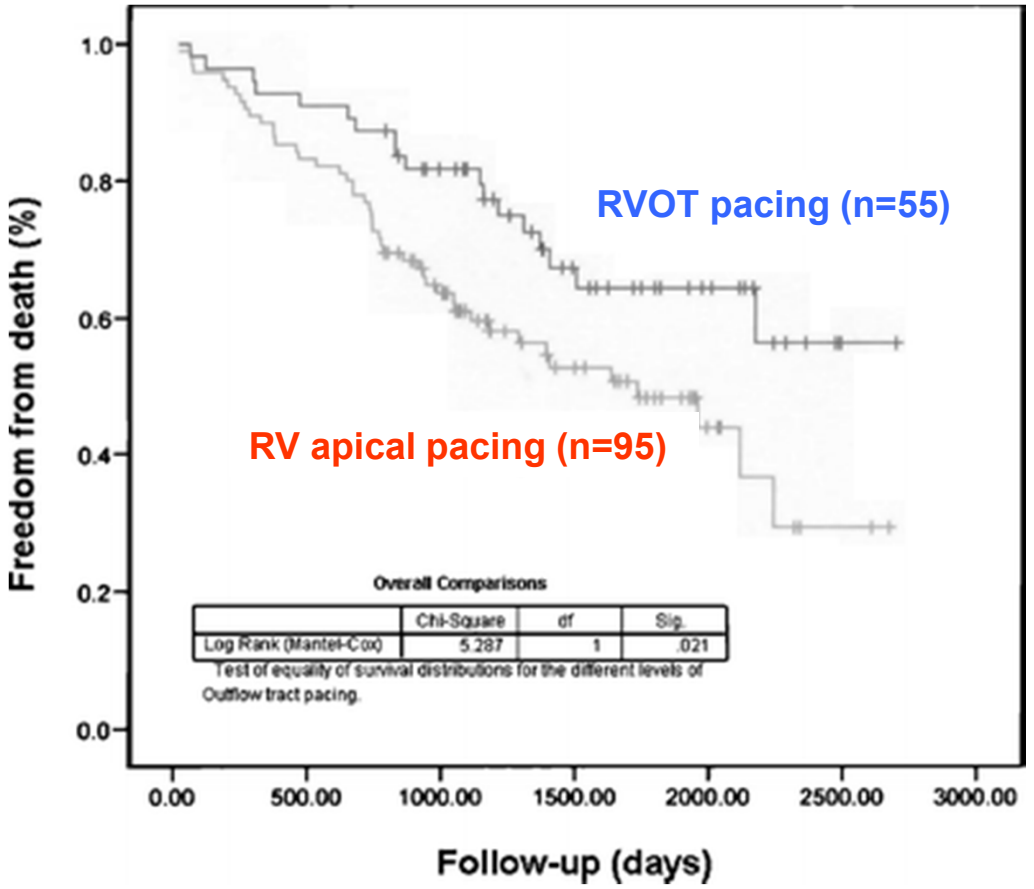
RVOT pacing

: better LV hemodynamic

: reducing perfusion defect

Tse et al. J Am Coll Cardiol 2002;40:1451-8

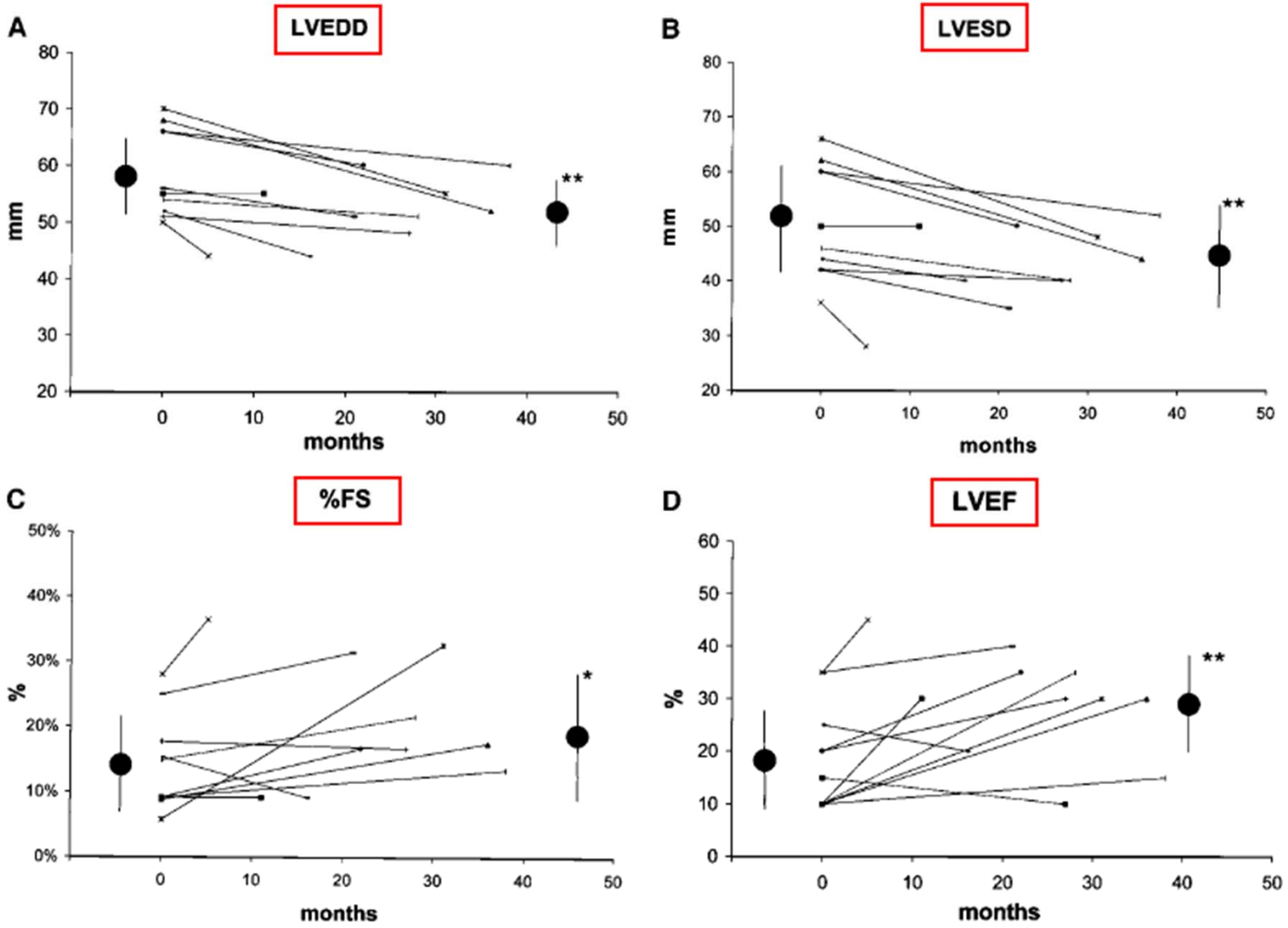
Improved survival with RVOT pacing



- 150 patients
- Retrospective analysis
- 5 years follow-up

Vanerio G et al. J Interv Card Electrophysiol 2008;21:195-201

His and para-hisian pacing



Deshmukh P et al. Circ 2000;101:869-77

Conflicting results in selective site RV pacing

Author	Publication/Year	# of patients	Parameter	Results
Benchimol	Circ/1966	6	CO (T)	±
Barold	Am J Cardiol/1969	52	CO (T)	±
Raichlen	Circ/1984	18	CO (T)	-
Cowell	PACE/1994	15	CO (T)	+
Giudici	Am J Cardiol/1997	89	CO (E)	+
Gold	Am J Cardiol/1997	13	CO (T)	±
Karpawich	PACE/1997	22	LVEDP	+
Blanc	Circ/1997	14	PCWP	±
Buckingham	PACE/1997	11	CO (E)	±
De Cock	PACE/1998	17	CO (E)	+
Saxon	J Card Electr/1998	17	FAC (E)	+
Mera	PACE/1999	12	EF (N)	+
Schwaab	JACC/1999	14	EF (N)	+
Victor	JACC/1999	16	CO (T)	±
Kolettis	Chest/2000	20	CO (E)	+

De Cock CC et al. Europace:2003;5:275-8

Challenges in assessing hemodynamic effect in selective site RV pacing

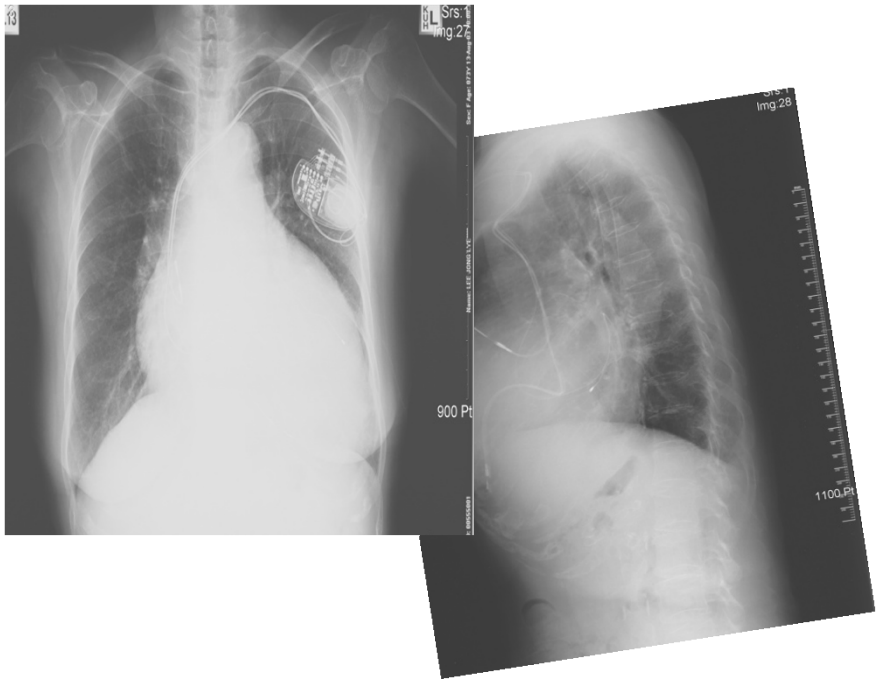
- Conflicting results regarding acute as well as intermediate and long term LV hemodynamics
- Different indication for pacing and various co-morbidities
- Inherent anatomical heterogeneity in the pacing site
- Different methodologies and different end points

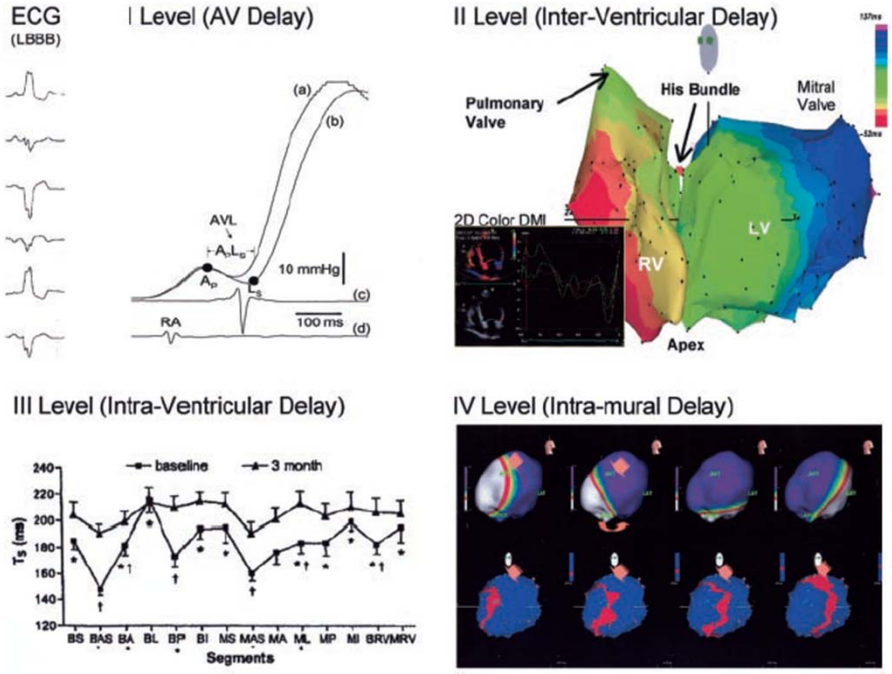
Ongoing randomized multicenter trials for selective site RV pacing

- Ongoing, large, randomized multicenter clinical trial with a minimum of 24 months of follow-up
- Optimize RV Selective Site Pacing Clinical Trial (Optimize RV)
- Right Ventricular Apical and High Septal Pacing to Preserve Left Ventricular Function (Protect Pace)
- Right Ventricular Apical versus Septal Pacing (RASP).
- Expected to help to provide the evidence of the effect of selective site RV pacing on the preservation of LV function

Kaye G et al. Electrophysiol 2009;32:426-33

CRT using biventricular pacing



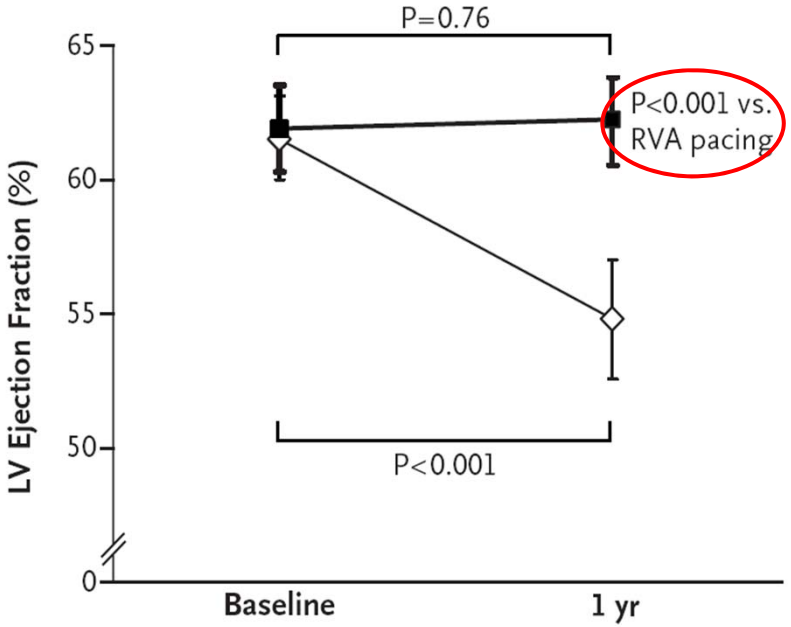


- **greater coordination of overall contraction**
- **improve ventricular contractile function and remodeling**

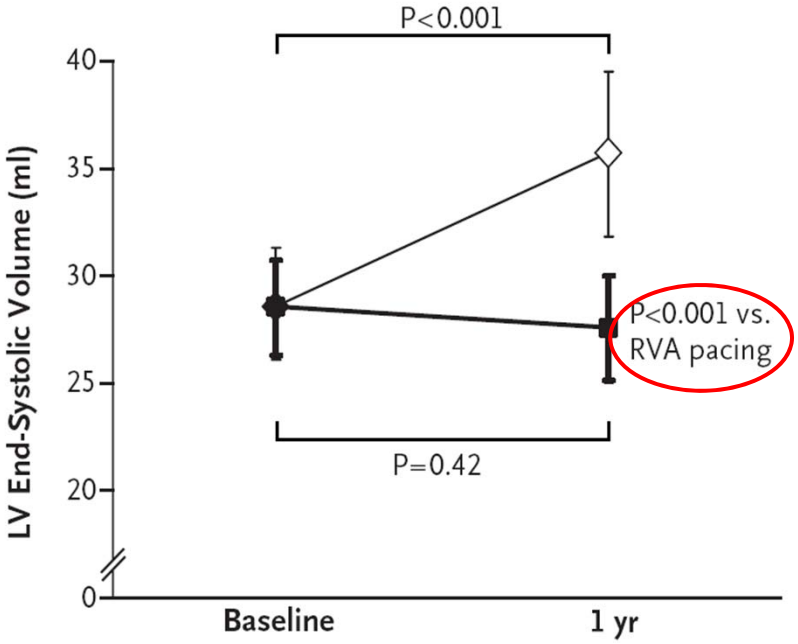
Auricchio et al. Circ 2004;109:300-7

Biventricular pacing in the pacemaker candidates : the PACE trial

LV ejection fraction



LV end-systolic volume

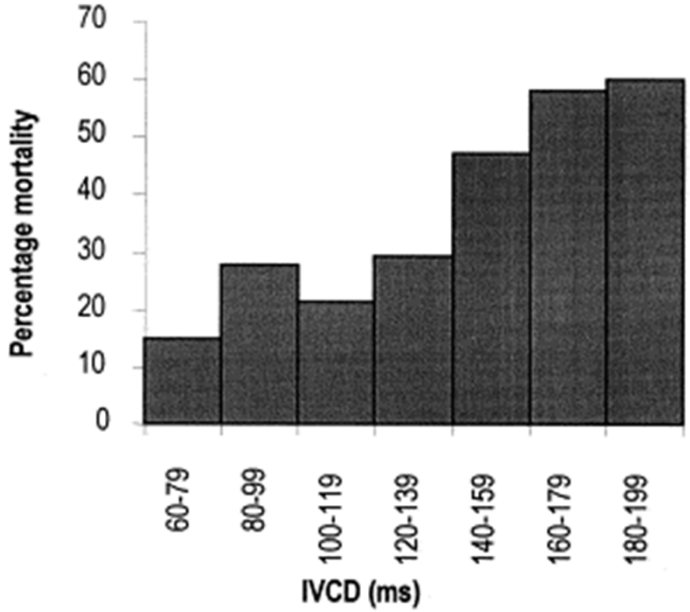


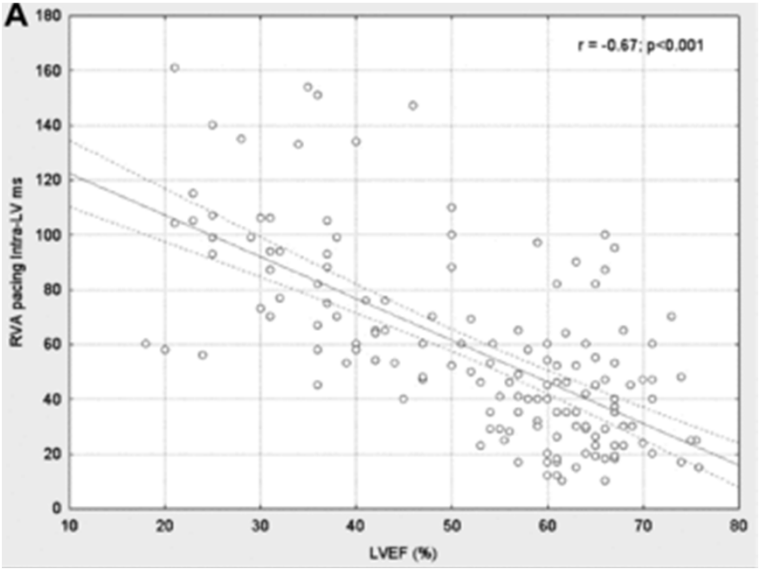
■ BiV pacing (n=87) ◇ RVA pacing (n=86)

- 177 patients with bradycardia and normal ejection fraction
- 12 mo follow-up

Yu CM et al. N Engl J Med 2009;361:1-11

LBBB and IVCD was associated with poor outcome in patients with HF





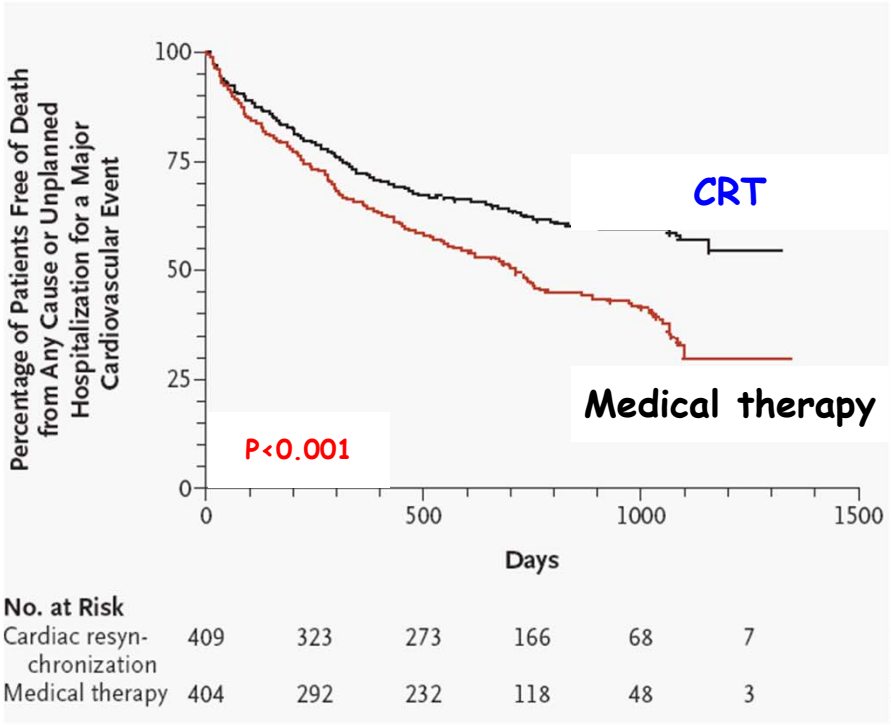
Impact of asynchrony is more significant

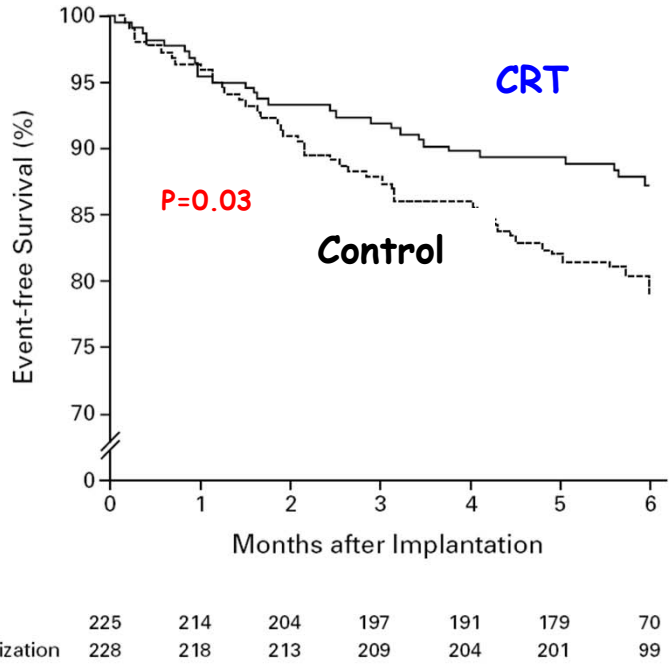
in the patients with underlying heart failure and suppressed LV function

Baldasseroni S et al. Am Heart J 2002;143:398-405

Shamim W et al. Int J Cardiol 1999;70:171-8

Improved clinical outcome with CRT in severe heart failure and wide QRS duration





Abraham WT et al. N Engl J Med 2002;346:1845-53

Cleland JG et al. N Engl J Med 2005;352:1539-49

Hemodynamic and echocardiographic assessment: CARE-HF trial

Variable	Δ means at 3 mo (95% CI)	P value	Δ means at 18 mo (95% CI)	P value
Heart rate, bpm	+1.1 (-1.2 to 3.4)	0.33	+1.0 (-1.5 to 3.6)	0.43
SBP, mmHg	+5.8 (3.5 to 8.2)	<0.001	+6.3 (3.6 to 8.9)	<0.001
DBP, mmHg	+1.5 (0.1 to 2.9)	0.03	+1.3 (-1.8 to 4.4)	0.42
Interventricular mechanical delay	-21 (-25 to -18)	<0.001	-21 (-25 to -17)	<0.001
LVEF, %	+3.7 (3.0 to 4.4)	<0.001	+6.9 (5.6 to 8.1)	<0.001
LVESV, ml/m^2	-18.2 (-21.2 to -15.1)	<0.001	-26.0 (-31.5 to -20.4)	<0.001
MR area	-0.051 (-0.073 to -0.028)	<0.001	-0.042 (-0.070 to -0.014)	0.003
NT pro-BNP	-225 (-705 to 255)	0.36	-1122 (-1815 to -429)	<0.002

- 813 patients with NYHA III/IV HF with EF ≤ 35%, a QRS ≥ 120 msec and LVEDD ≥ 30mm/m^2
- 12 mo follow-up

Cleland JG et al. N Engl J Med 2005;352:1539-49

Effect of CRT: MIRACLE study

	Control group	CRT group	P value
Δ LVEF (%)	-0.2 (-1.0~+1.5)	+4.6 (+3.2~+6.4)	<0.001
Δ LVEDD (mm)	0.0 (-1~+2)	-3.5 (-6~-1)	<0.001
Δ MR area, cm^2	-0.5 (-1.1~0.0)	-2.7 (-4.0~-2.1)	<0.001
Δ QRS duration (ms)	0 (-10~0)	-20 (-20~-12)	<0.001

- 453 patients with moderate to severe HF with EF ≤ 35% and a QRS ≥ 130 msec
- 6 mo follow-up

Abraham WT et al. N Engl J Med 2002;346:1845-53

Sustained reverse LV remodeling for CRT patients: MIRACLE study

	Baseline	6 mo	12 mo
LVEDV, cm^3	306±111	266±109 *	277±114 *¶
LVESV, cm^3	237±102	196±98 *	199±107 *
LVEF, %	24.0±6.8	29.2±9.0 *	31.2±11.4 *¶
MR jet area, cm^2	7.4±6.1	4.2±4.2 *	4.4±4.2 *
LV mass, g	359±95	343±104 *	300±92 *

* $p<0.05$, change from baseline; ¶ $p<0.05$ change from 6 months to 12 months

Sutton MG et al. Cir 2006;113:266-72

Sustained reverse LV remodeling for CRT patients: MIRACLE study

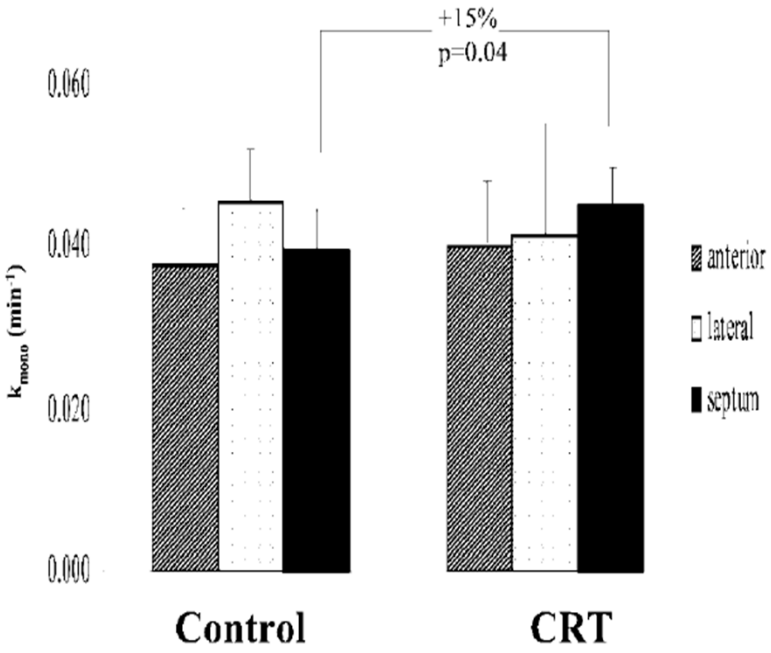
	Baseline	6 mo	12 mo
LV filling time, ms	394±159	446±156 *	441±127 *
E/A ratio	1.5±1.4	1.3±1.1 *	1.2±0.9 *
MPI	1.06±6.8	29.2±9.0 *	31.2±11.4 *

E, early mitral inflow velocity; A, late mitral inflow velocity; MPI, myocardial performance index.

* $p<0.05$, change from baseline to follow-up

Sutton MG et al. Cir 2006;113:266-72

Reduction of myocardial energy demand and oxygen consumption by CRT



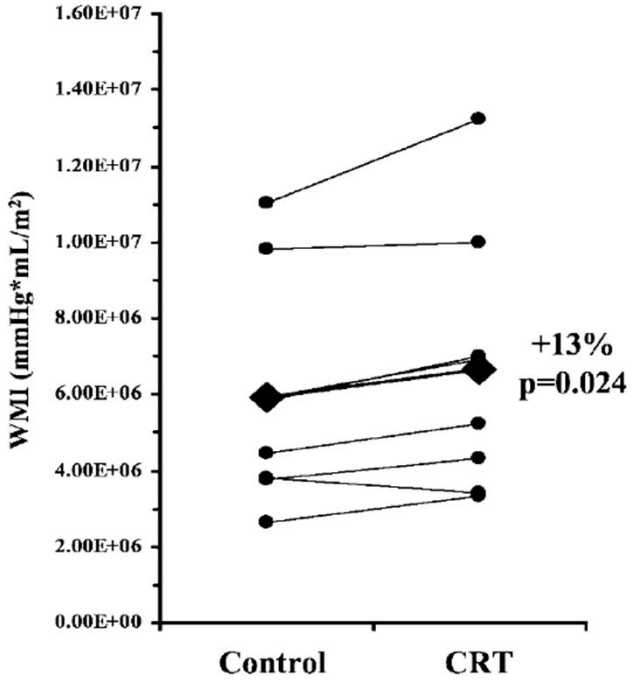


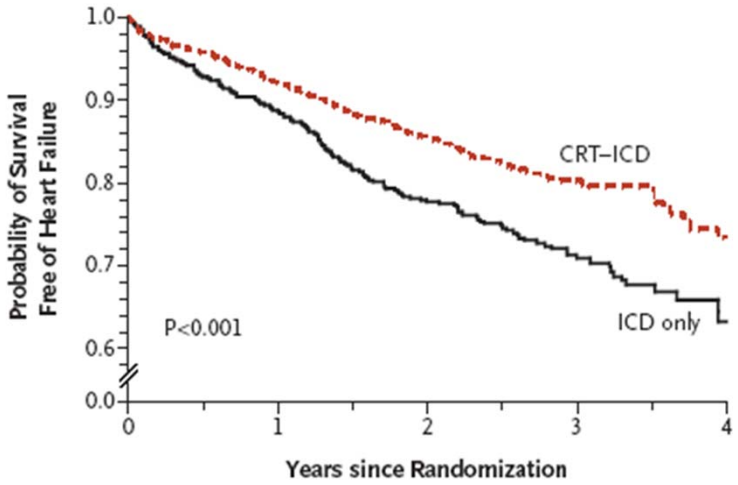
Figure 2. WMI with and without (control) CRT. Group mean=39 (●); individual values=41 (◆).

Ukkonen H et al. Circ 2003;107:28

CRT in patients with milder heart failure : the MADIT-CRT & RAFT trial

the MADIT-CRT trial for NYHA I/II HF

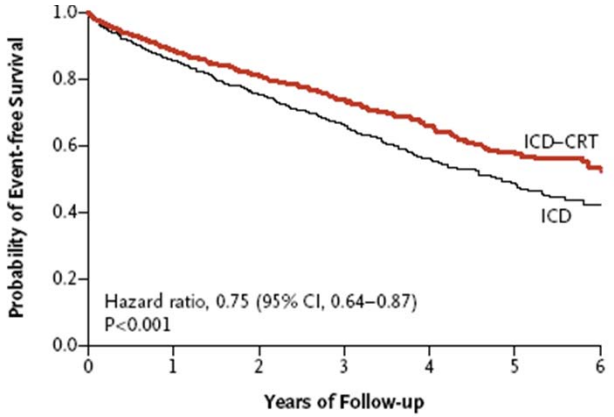
Heart failure



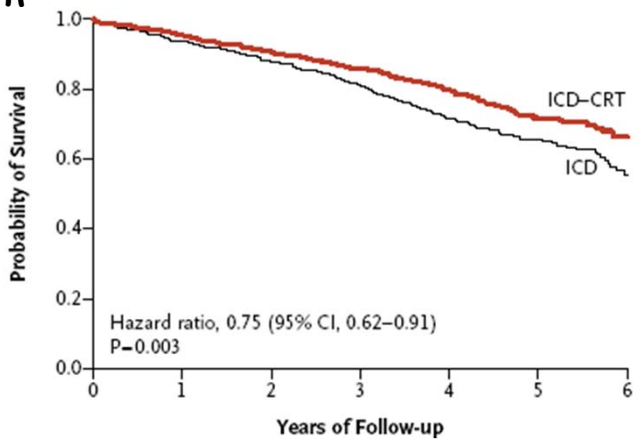
No. at Risk (Probability of Survival)					
ICD only	731	621 (0.89)	379 (0.78)	173 (0.71)	43 (0.63)
CRT–ICD	1089	985 (0.92)	651 (0.86)	279 (0.80)	58 (0.73)

the RAFT trial for NYHA I/II HF

Death or heart failure hospitalization



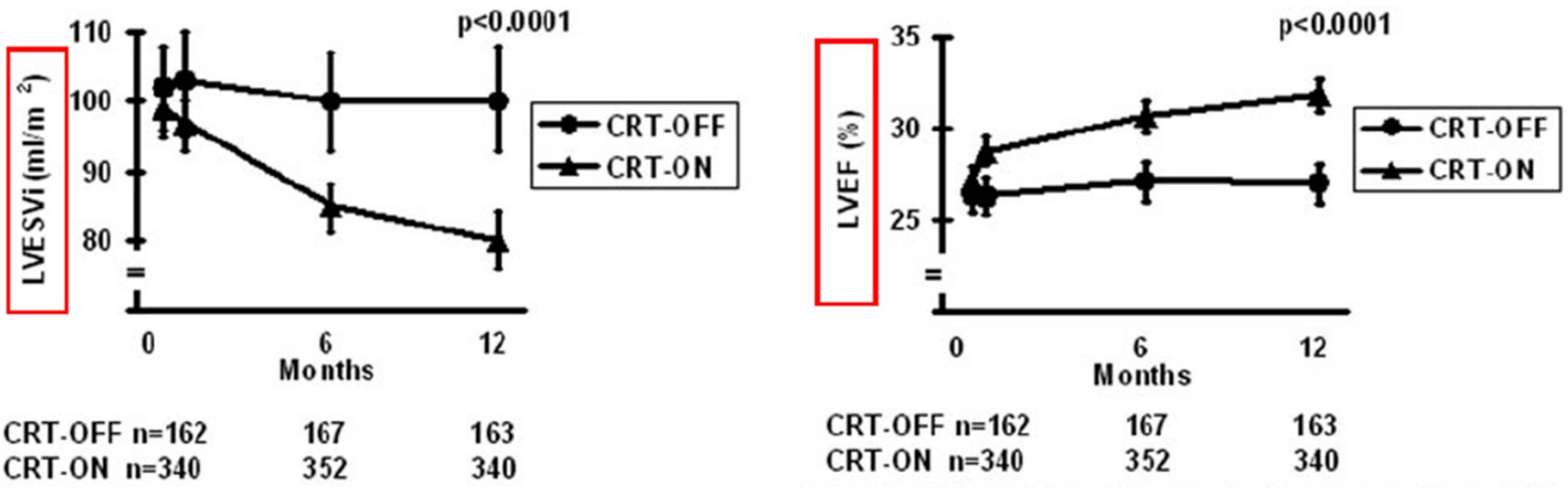
Death



Moss AJ et al. N Engl J Med 2009;361:1329

Tang AS et al. N Engl J Med 2010;363:2385

Improved LV remodeling by CRT in patients with NYHA I/II heart failure: the REVERSE study



- 610 patients with NYHA I/II HF with EF ≤ 40%, a QRS ≥ 120 msec and LVEDD ≥ 55mm
- 12 mo follow-up

Sutton MS et al. Circ 2009;120:1858-65

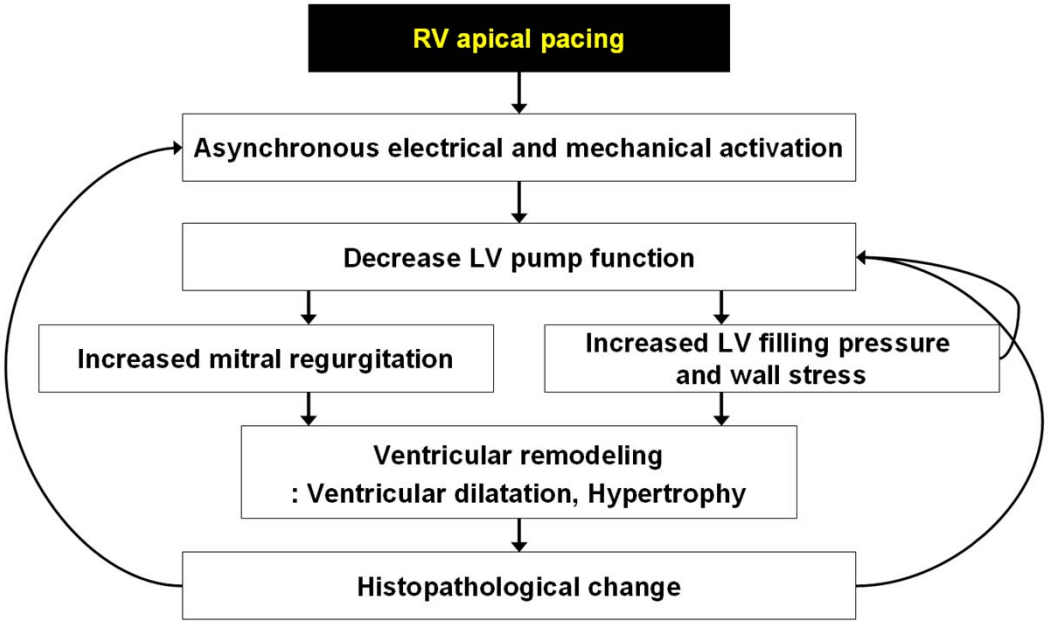
Effects of CRT

Improve	Reduce	Pathophysiologic consequence
Pump function	Myocardial oxygen consumption	Reduction of circulating catecholamine
NYHA class	Mitral and tricuspid regurgitation	Reduction of circulating cytokines
Exercise capacity	Ventricular volumes	Reduction of BNP
Respiration efficiency	Hospitalization rate and hospital duration	Reset of RAAS
Quality of life	Mortality	LV mass
Myocardial metabolism		Reduced incidence of AF

Auricchio et al. Circ 2004;109:300-7

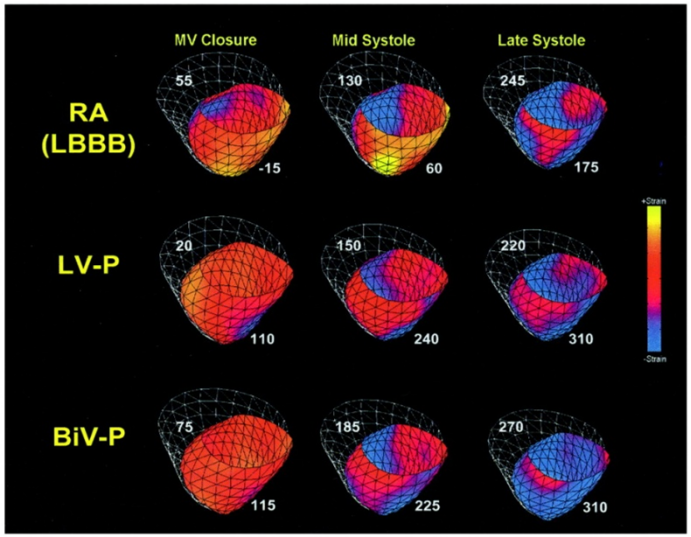
Summary

- Dyssynchrony, induced by conventional RV apical pacing, may have detrimental effects on cardiac structure and function, which are associated with adverse outcomes



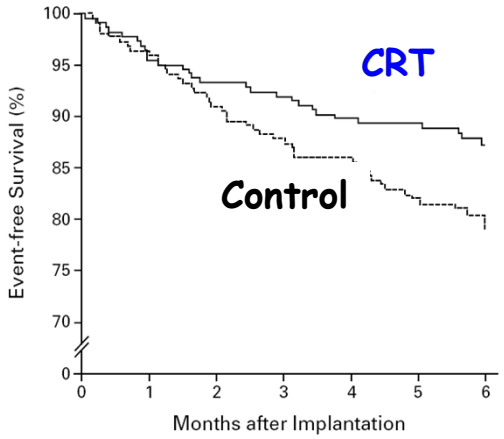
Summary

- To avoid the abnormal activation during ventricular pacing, the strategies to attenuate these effects are attempting such as alternative site ventricular pacing



Summary

- Restoring ventricular synchrony by CRT can provide greater coordination of overall contraction, thus improve ventricular contractile function and ventricular remodeling as well as clinical outcomes



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Myocardial metabolism		Reduced incidence of AF


Thank you for your attention