Cardiac Resynchronization Therapy for Heart Failure

Mechanisms, Clinical Outcomes and Patient Selection

Robert Styperek, M.D., F.A.C.C.
Cardiac Electrophysiology
SCI / Harbin Clinic
Rome, Georgia

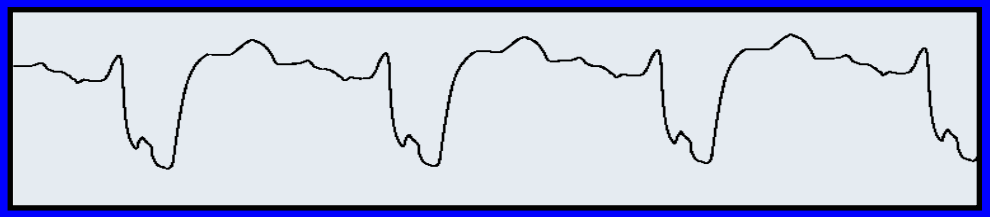
This presentation provides an overview of the proposed mechanisms and proven clinical benefits of cardiac resynchronization therapy. Patient selection guidelines their approved indications are included at the end of this presentation. It is intended for audiences who manage heart failure patients in their practices and may refer patients for cardiac resynchronization therapy.

Topics to be Discussed

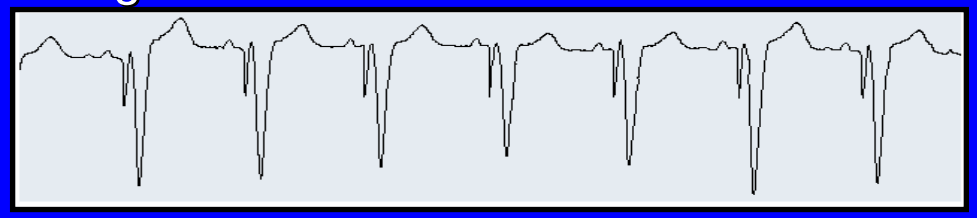
- Ventricular Dysynchrony
- Overview of Cardiac Resynchronization
- Summary of Results from Clinical Trials
- Patient Selection – Device Indications
- Implant and Follow-up Considerations
- Patient Case Studies

Each of the topics listed will be addressed in subsequent slides.

Ventricular Dysynchrony and Cardiac Resynchronization



- 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

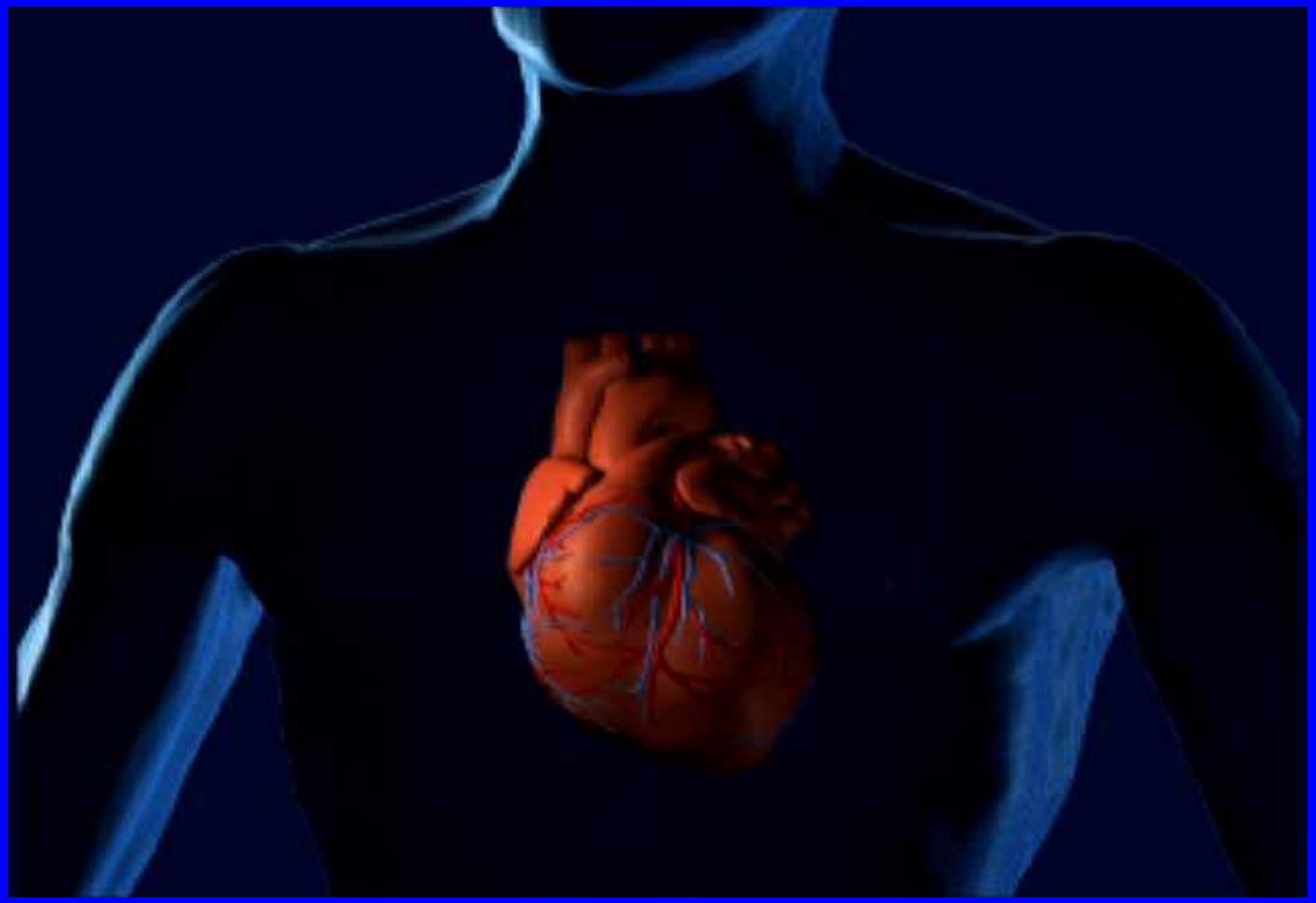


- Cardiac Resynchronization
  - Therapeutic intent of atrial synchronized biventricular pacing
    - Modification of interventricular, intraventricular, and atrial-ventricular activation sequences in patients with ventricular dysynchrony
    - Complement to optimal medical therapy

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

- Introduces “new” terms used in this slide series.
- **Ventricular dysynchrony** is defined as the effect caused by intra- and inter-ventricular conduction defects or bundle branch block. Read Dr. Tavazzi’s editorial referenced here for a summary of the three potential causes of ventricular dysynchrony.
- **Cardiac resynchronization** is defined as the therapeutic intent of atrial synchronized biventricular pacing for patients with heart failure and ventricular dysynchrony. The intent of the therapy is to resynchronize the ventricular activation sequence, and to better coordinate atrial-ventricular timing to improve pumping efficiency.
- Cardiac resynchronization therapy is currently indicated for the reduction of symptoms of moderate to severe heart failure (NYHA Function Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction $\leq$ 35% and a QRS duration $\geq$130 ms. An ICD is also available for patients with a standard ICD indication who also meet the above listed criteria.
- Using atrial-synchronized biventricular pacing in combination with optimal drug therapy has been shown to significantly improve a patient’s symptoms.

Animation – Ventricular Dysynchrony



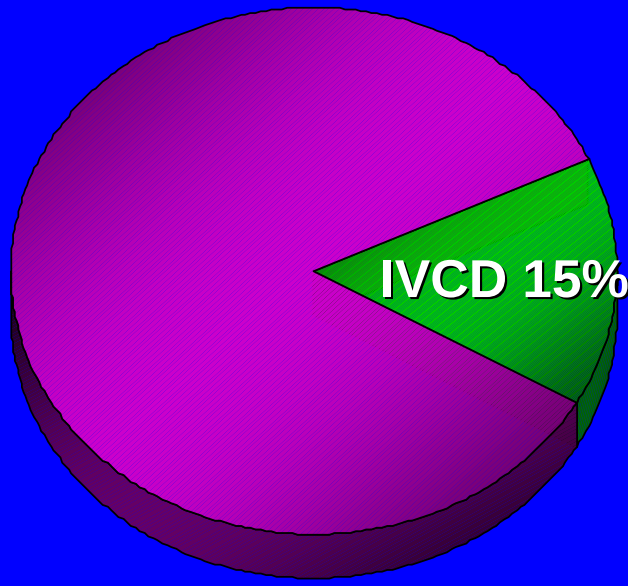
Click to Start/Stop

- This animation shows the normal heart changing into a dilated, remodeled heart, followed by a depiction of a mechanical perspective of ventricular dysynchrony. An ECG showing intra- or interventricular conduction delays is displayed along the bottom.

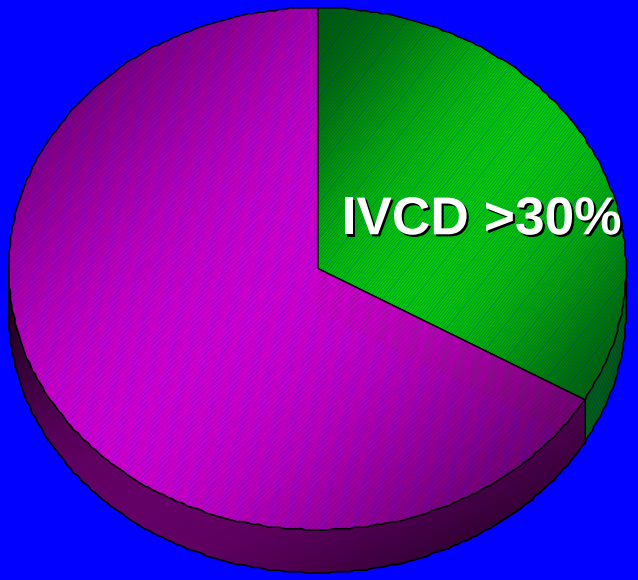
- Animation Filename: “Clip1-Vdysynchrony.mpg.” The animation can be started by positioning the mouse-cursor over the image and clicking once. To stop or restart the animation video at anytime, click once on the image.

Prevalence of Inter- or Intraventricular Conduction Delay

General HF Population[1,2]



Moderate to Severe HF Population[3,4,5]



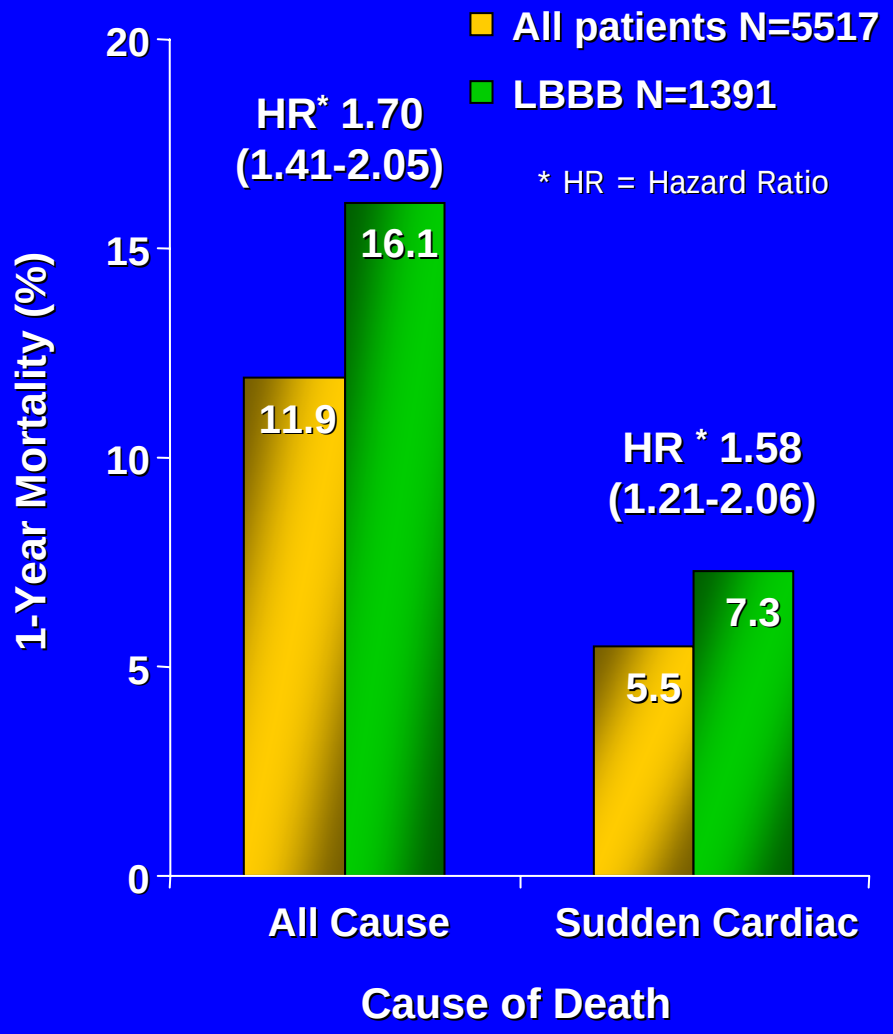
[1] Havranek E, Masoudi F, Westfall K, et al. *Am Heart J* 2002;143:412-417
[2] Shenkman H, McKinnon J, Khandelwal A, et al. *Circulation* 2000;102(18 Suppl II): abstract 2293
[3] Schoeller R, Andersen D, Buttner P, et al. *Am J Cardiol.* 1993;71:720-726
[4] Aaronson K, Schwartz J, Chen T, et al. *Circulation* 1997;95:2660-2667
[5] Farwell D, Patel N, Hall A, et al. *Eur Heart J* 2000;21:1246-1250

- Approximately 15% of all heart failure patients have an inter- or intraventricular conduction delay (QRS > 120 msec)[1-2].
- Over 30% of moderate to severe heart failure patients have a prolonged QRS. The prevalence of conduction defects increases with severity of heart failure.[3-5]
- Shenkman and colleagues found the factors associated with prolonged QRS included: Older age, Male gender, Caucasian race, Lower EF, Higher LVESD

- [1] **Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM. Spectrum of heart failure in older patients: Results from the National Heart Failure Project. *Am Heart J* 2002;143:412-417**
- [2] **Shenkman HJ, McKinnon JE, Khandelwal AK, et al. Determinants of QRS Prolongation in a Generalized Heart Failure Population: Findings from the Conquest Study [Abstract 2993]. *Circulation* 2000;102(18 Suppl II)**
- [3] **Schoeller R, Andersen D, Buttner P, Oezcelik K, Vey G, Schroder R. First-or second-degree atrioventricular block as a risk factor in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993;71:720-726**
- [4] **Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development & prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997; 95: 2660-2667.**
- [5] **Farwell D, Patel NR, Hall A, Ralph S, Sulke AN. How many people with heart failure are appropriate for biventricular resynchronization? *Eur Heart J* 2000;21:1246-1250**

Increased Mortality Rate with LBBB

- Increased 1-year mortality with presence of complete LBBB (QRS > 140 ms)
- Risk remains significant even after adjusting for age, underlying cardiac disease, indicators of HF severity, and HF medications



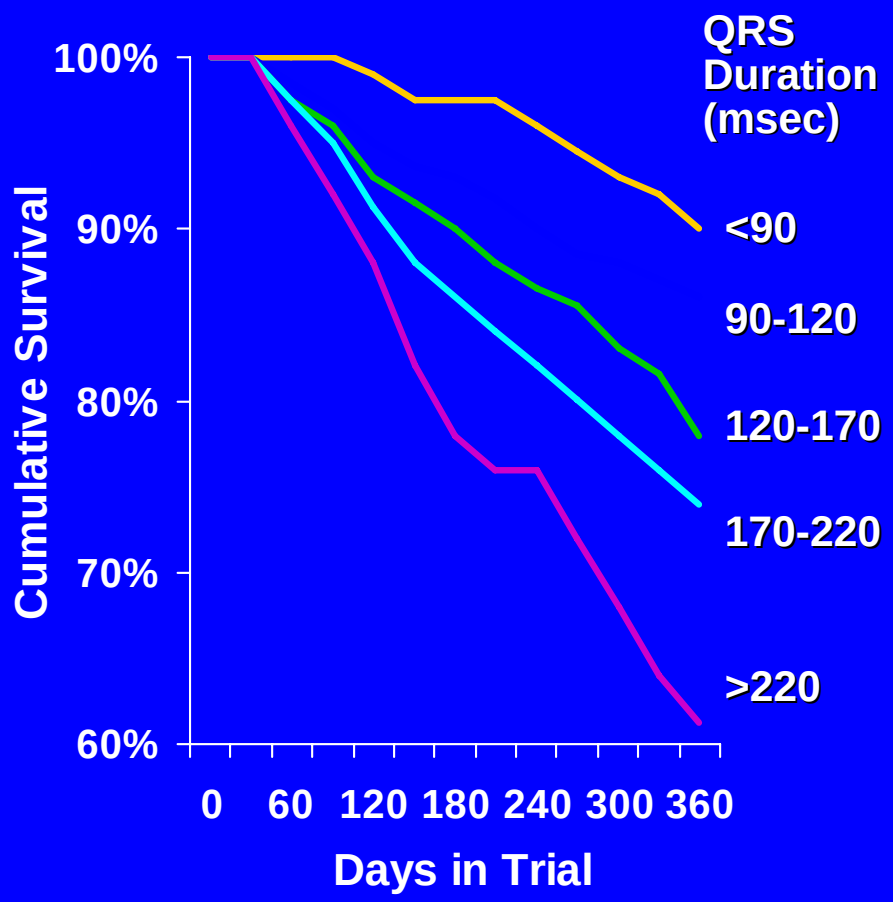
Baldasseroni S, Opasich C, Gorini M, et al. *Am Heart J* 2002;143:398-405

- This slide was developed using data from Italian Network on CHF Registry, established in 1995 in 150 cardiology centers distributed throughout Italy. The group defined complete LBBB as a QRS duration greater than 140 ms.
- The graph displays 1-year unadjusted mortality for all patients, and for those with complete LBBB. Hazard Ratios (HR) with 95% Confidence Interval are labeled. A Hazard Ratio of 1.70 for all-cause mortality means a 70% greater risk of death with LBBB. With respect to sudden cardiac death, patients with LBBB have a 58% greater risk than the general patient group.
- Of interest is 25% of the patients had a QRS duration greater than 140 msec. This may reflect the fact that these patients were seen in cardiology centers, were likely sicker than the HF population at large and therefore were more likely to have LBBB.
- **Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, Campana C, Perini G, Deorsola A, Masotti G, Tavazzi L, Maggioni AP. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: A report from the Italian Network on Congestive Heart Failure. *Am Heart J* 2002;143:398-405**

Wide QRS – Proportional Mortality Increase

Vesnarinone Study[1] (VEST study analysis)

- NYHA Class II-IV patients
- 3,654 ECGs digitally scanned
- Age, creatinine, LVEF, heart rate, and QRS duration found to be independent predictors of mortality
- Relative risk of widest QRS group 5x greater than narrowest

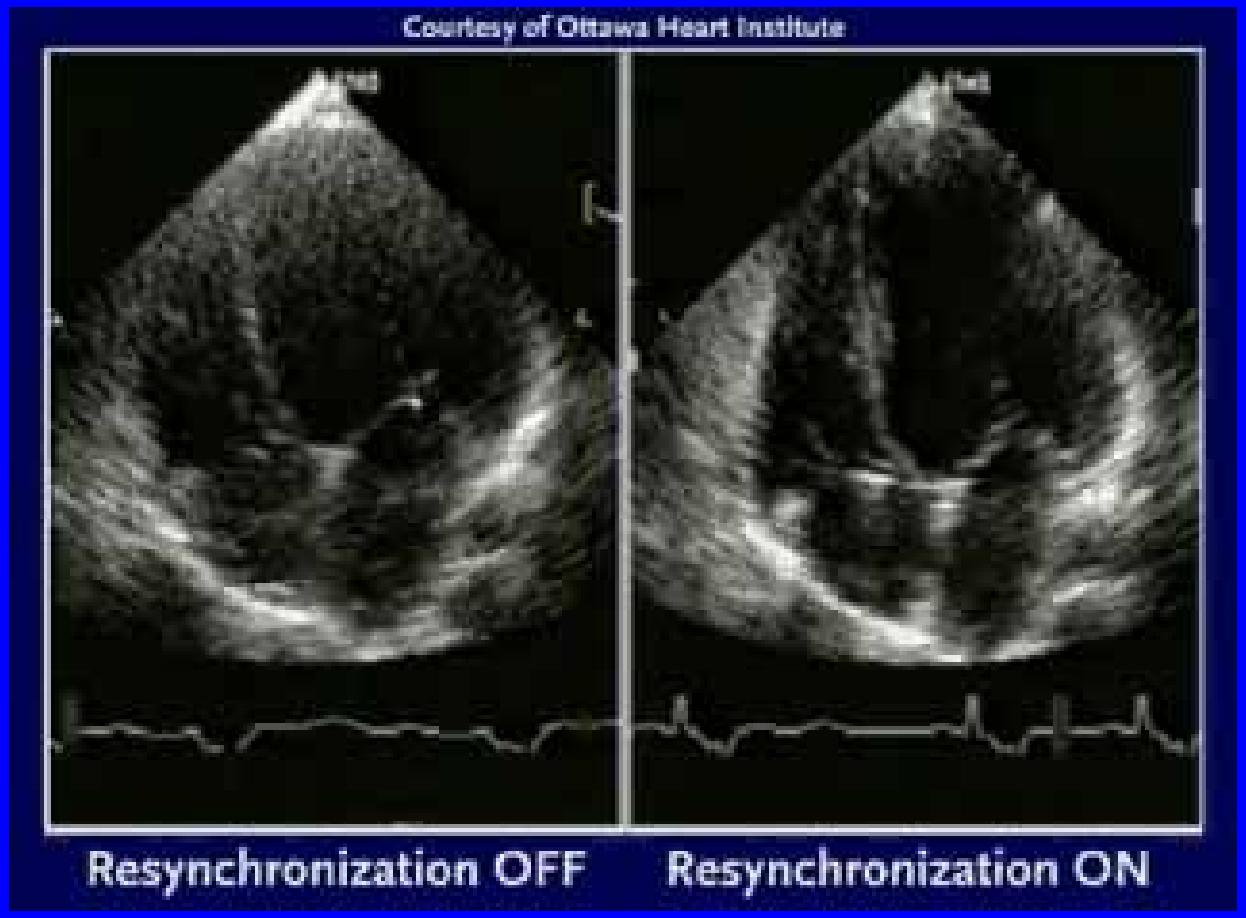


[1] Gottipaty V, Krelis S, Lu F, et al. *JACC* 1999;33(2) :145 [Abstr847-4].

- The VEST Study demonstrated QRS duration was found to be an independent predictor of mortality.
- Patients with wider QRS (> 200 ms) had five times greater mortality risk than those with the narrowest (< 90 ms).
- Resting ECG is a powerful yet accessible and inexpensive marker of prognosis in patients with DCM and CHF.

- **ACC 1999; Abstract: 847-4**
- The Resting Electrocardiogram Provides a Sensitive and Inexpensive Marker of Prognosis in Patients with Chronic Congestive Heart Failure
- **Venkateshwar K. Gottipaty**, Steven P. Krelis, Fei Lu, Elizabeth P. Spencer, Vladimir Shusterman, Raul Weiss, Susan Brode, Amie White, Kelley P. Anderson, B.G. White, Arthur M. Feldman *For the VEST investigators; University of Pittsburgh, Pittsburgh PA, USA*

Clinical Consequences of Ventricular Dysynchrony



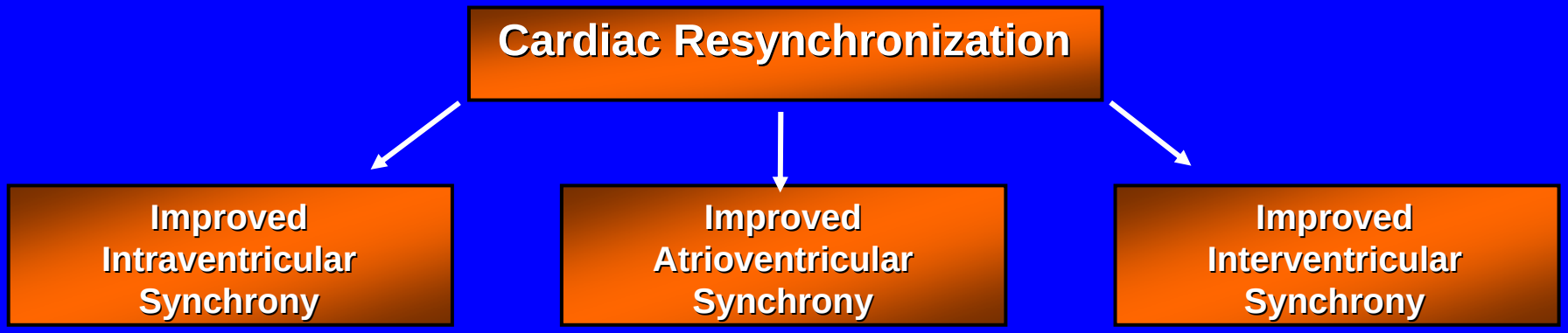
Click to Start/Stop

- Abnormal interventricular septal wall motion[1]
- Reduced dP/dt[3,4]
- Reduced pulse pressure[4]
- Reduced EF and CO[4]
- Reduced diastolic filling time[1,2,4]
- Prolonged MR duration[1,2,4]

[1] Grines CL, Bashore TM, Boudoulas H, et al. *Circulation* 1989;79:845-853.
[2] Xiao, HB, Lee CH, Gibson DG. *Br Heart J* 1991;66:443-447.
[3] Xiao HB, Brecker SJD, Gibson DG. *Br Heart J* 1992;68:403-407.
[4] Yu C-M, Chau E, Sanderson JE, et al. *Circulation*. 2002;105:438-445.

- **Key Messages: Ventricular dysynchrony has been associated with paradoxical septal wall motion, reduced dP/dt_{max}, prolonged mitral regurgitation duration, and reduced diastolic filling times in studies comparing patients with left bundle branch block with normals or with comparable patients without LBBB.**
- **Grines C, Bashore T, Boudoulas H, et al. Functional abnormalities in isolated left bundle branch block: the effect of interventricular asynchrony. *Circulation* 1989;79:845-853**
- Using simultaneous ECG, phonocardiogram, radionuclide ventriculograms, and 2D and M-mode echoes, **Grines** et al studied 18 patients with LBBB (and no other underlying cardiac disease) compared with 10 normals. In LBBB patients she found significant delays in LV systolic and diastolic events, reduced diastolic filling times, abnormal interventricular septal wall motion, and a loss of septal contribution to global ejection fraction.
- This study concluded that a LBBB causes a delay in the left ventricular depolarization resulting in delayed left ventricular contraction and relaxation compared with the right ventricle. Delay in left ventricular systole results in a delay in left ventricular diastole, which may contribute to displacement of the interventricular septum. In addition, asynchronous right-left ventricular contraction and relaxation may produce dynamic alterations in transseptal pressure and volume that may be responsible for the abnormal septal deflections. This abnormal septal motion results in an altered regional ejection fraction with decreased septal contribution to global left ventricular performance.
- **Xiao Lee C, Gibson D. effect of left bundle branch block on diastolic function in dilated cardiomyopathy. *Br Heart J* 1991;66:443-447.**
- **Xiao H, Brecker S, Gibson D. Effects of abnormal activation on the time course of left ventricular pressure pulse in dilated cardiomyopathy. *Br Heart J* 1992;68:403-407.**
- **Yu C-M, Chau E, Sanderson J, et al. Tissue Doppler Echocardiographic Evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-445.**
- Animation Filename: “4-chamber.avi.” The animation can be started by positioning the mouse-cursor over the image and clicking once. To stop or restart the animation video at anytime, click once on the image. In this video clip, when cardiac resynchronization is off in a patient with a LBBB, the interventricular septum is not able to contribute to the global ejection fraction and is displaced. When cardiac resynchronization is ON, the interventricular septum appears more stable and is able to contribute to the global ejection fraction.

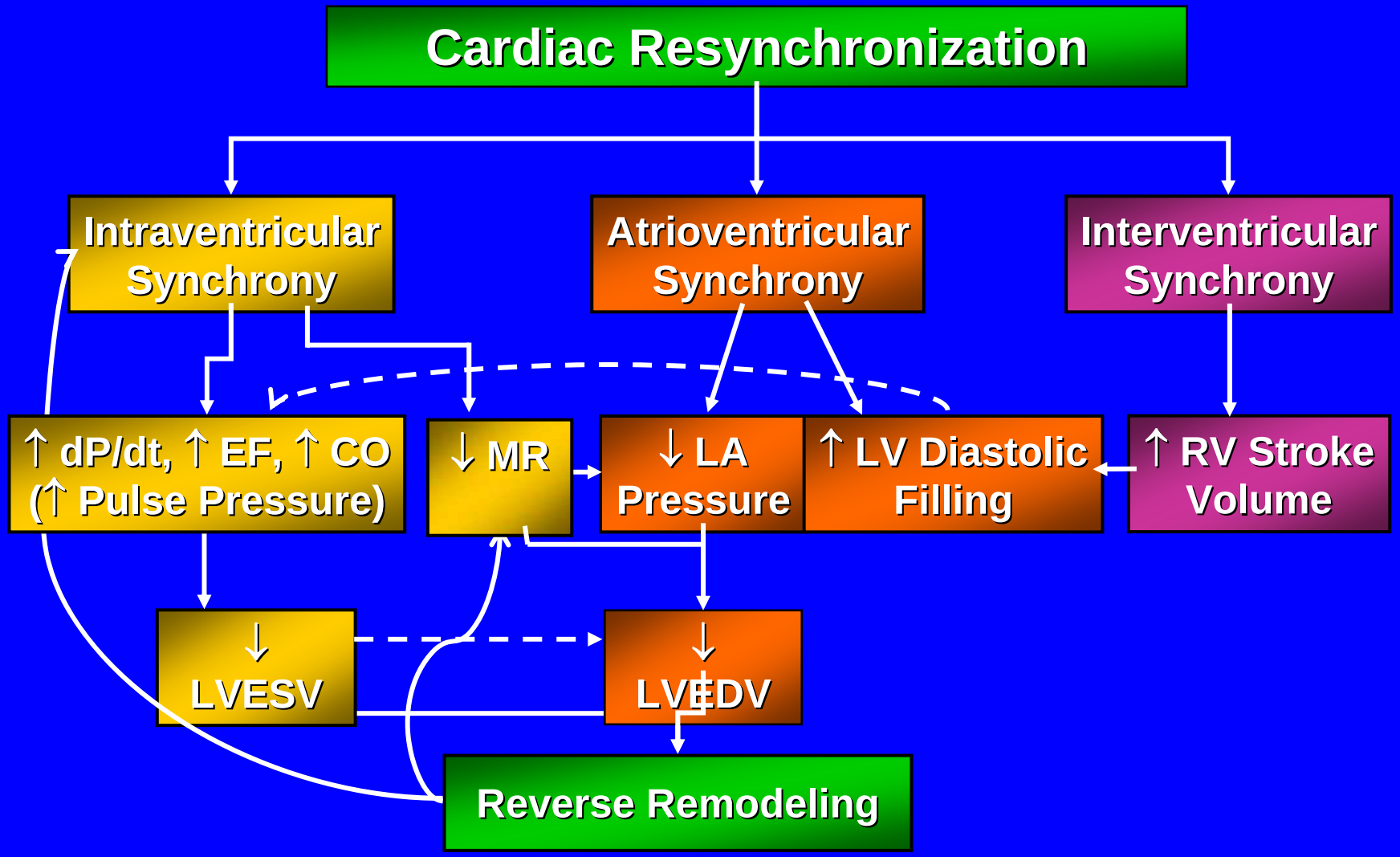
Proposed Mechanisms of Cardiac Resynchronization



Yu C-M, Chau E, Sanderson J, et al. *Circulation* 2002;105:438-445

- Heart failure patients have problems with ventricular remodeling (progressive LV dilitation and loss of contractile function). The goal in treating these patients is to prevent remodeling or reverse it, if possible. This slide reflects the three proposed mechanisms of benefit attributed to cardiac resynchronization therapy. Below is an article that describes the mechanisms in detail. The next few slides will give a brief overview of the 3 proposed mechanisms.
-
- **Yu C-M, Chau E, Sanderson J, Fan K, Tang M, Fung W, Lin H, Kong S, Lam Y, Hill M, Lau C.P. Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-445.**
- Study of 25 HF pts (65±12 yrs, NYHA III-IV, LVEF <40%, QRS>140 ms) both ischemic and non-ischemic, receiving biventricular pacing therapy for 3 months, then biventricular pacing stopped. Pts assessed serially up to 3 mo after pacing and when pacing was withheld for 4 wks.
- Results after 3 mo of biventricular pacing: improvement of ejection fraction, dP/dt, and myocardial performance index; decrease in mitral regurgitation, LV end-diastolic (205±68 to 168±67 ml) and end-systolic volume (162±54 to 122±42 ml); and improved 6-min hall-walk distance and quality of life score. Mechanisms of benefits: (1) improved (intraventricular) LV synchrony; (2) improved interventricular synchrony; and (3) shortened isovolumic contraction time but increased diastolic filling time. Benefits are pacing dependent, because withholding pacing resulted in loss of cardiac improvements. Improvement of LV mechanical synchrony found to be the predominant mechanism. Conclusion: Biventricular pacing reverses LV remodeling and improves cardiac function.

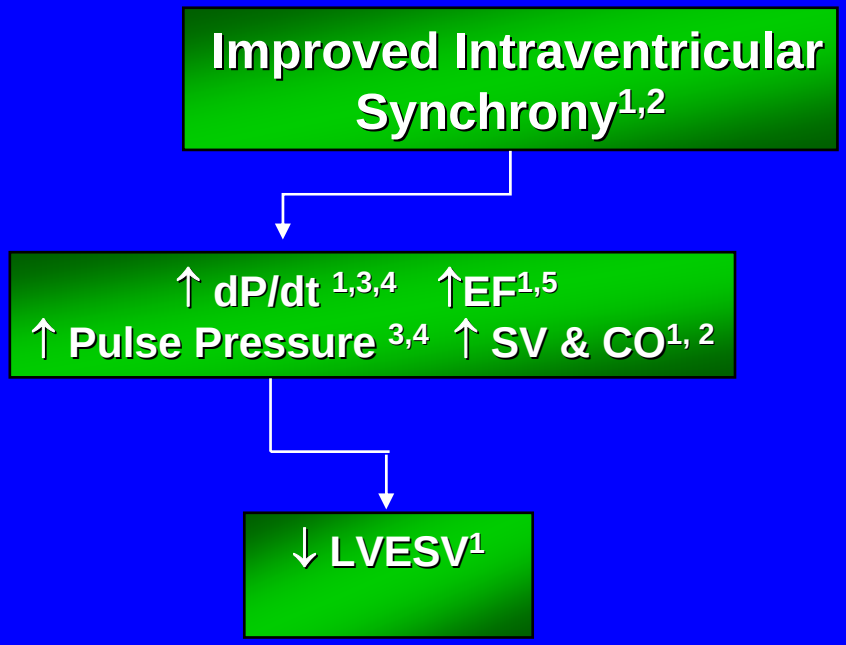
Summary of Proposed Mechanisms



Yu C-M, Chau E, Sanderson J, et al. *Circulation* 2002;105:438-445

- **These paragraphs highlight some of the key findings from Yu's study (see slide reference).**
- **Intraventricular synchrony**
- As a result of improved synchrony, systole becomes more effective and therefore, ejection fraction (EF), cardiac output (CO) and other parameters of cardiac function are improved. Left ventricular end-systolic volume (LVESV) is reduced. Mitral regurgitation (MR) attributable to distortion of the mitral apparatus is reduced by synchronizing the contractions and left atrial (LA) pressure is reduced. LV end-diastolic pressure and volume (LVEDV) are decreased.
- **Atrioventricular synchrony**
- A second mechanism is the shortening of the isovolumic contraction time (IVCT) after optimization of the atrioventricular delay. The effective diastolic filling time is increased, which in turn increases the stroke volume. In addition, LA pressure is reduced due to decreases in presystolic mitral regurgitation.
- **Interventricular synchrony**
- A less important mechanism is the improvement of interventricular synchrony between the right and left ventricles. This benefit may mediate through ventricular interdependence. This results in the gain in RV cardiac output, thereby augmenting the LV filling, resulting in overall improved cardiac function. The end effect of reverse remodeling will additionally improve cardiac synchrony and decrease secondary mitral regurgitation, forming a positive feedback loop.
- **Benefits are dependent upon pacing**
- Withholding pacing resulted in loss of cardiac improvements. Improvement in diastolic filling time, isovolumic contraction time, and myocardial performance index (MPI) were lost immediately since they were largely dependent upon control of AV synchrony. Benefits on ejection fraction and cardiac output were lost over 4 weeks which suggest strongly that pacing is the cause of LV remodeling. Improvements in Quality of Life score and walking distance were maintained for at least 4 weeks after pacing was suspended. **These observations provide strong evidence that cardiac resynchronization therapy is the cause of LV reverse remodeling.**

Proposed Mechanisms: Improved Intraventricular Synchrony



[1] Yu C-M, Chau E, Sanderson J, et al. *Circulation* 2002;105:438-445
[2] Søgaard P, Kim W, Jensen H, et al. *Cardiology* 2001;95:173-182
[3] Kass D Chen-Huan C, Curry C, et al. *Circulation* 1999;99:1567-73
[4] Auricchio A, Ding J, Spinelli J, et al. *J Am Coll Cardiol* 2002;39:1163-1169
[5] Stellbrink C, Breithardt O, Franke A, et al. *J Am Coll Cardiol* 2001;38:1957- 65

- **Improved intraventricular synchrony is proposed as the one mechanism providing the largest contribution.**

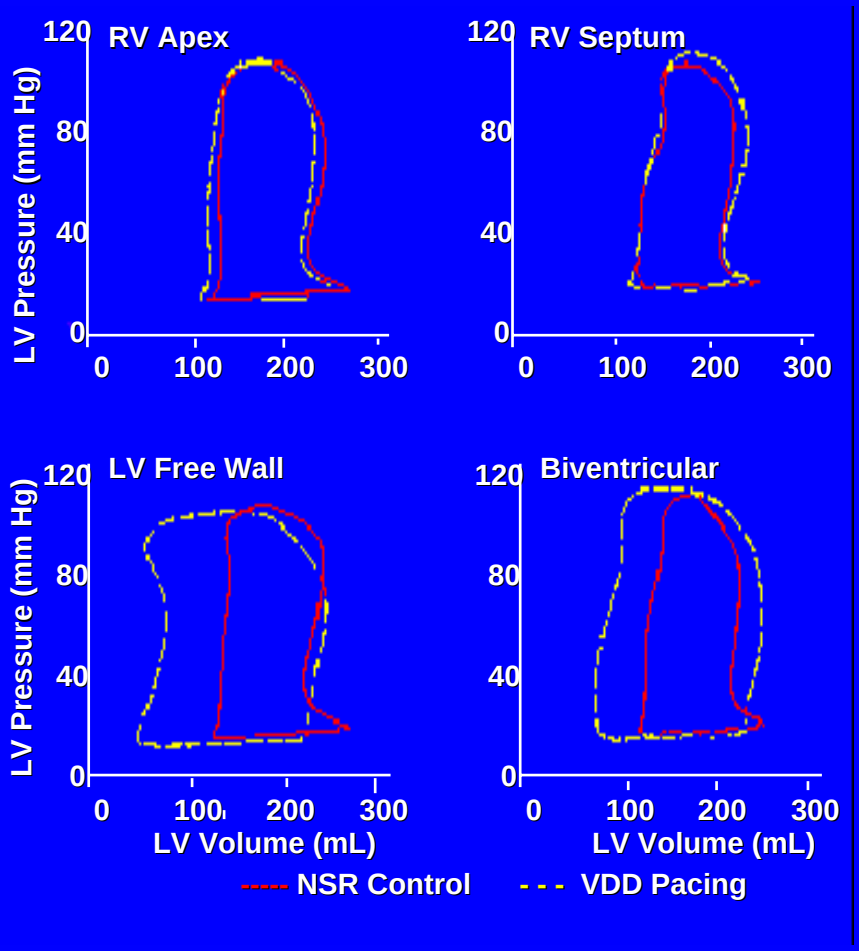
- **[1] Yu C-M, Chau E, Sanderson J, Fan K, Tang M, Fung W, Lin H, Kong S, Lam Y, Hill M, Lau C. Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-445.**
- Yu et al studied changes in the time to peak regional sustained systolic contraction (T_s) before and after pacing, using Tissue Doppler echocardiography. At baseline, there was marked regional variation in T_s among the LV segments and between the left and right ventricles. T_s was earliest in the basal anteroseptal segment, and latest in the basal lateral segment. After biventricular pacing, the difference in T_s between the two regions was abolished. Also, there was marked regional variation in the T_s among all LV segments at baseline which was abolished after pacing therapy. Biventricular pacing improved the synchronicity of the LV by delaying the T_s in segments with initially early peaked, sustained systolic contraction so that all the regions of the LV had synchronized systolic contraction.
- This improved intraventricular synchrony led to increases in dP/dt, LVEF, and cardiac output (CO) secondary to improved systole which in turn led to a decrease in Left Ventricular End Systolic Volumes (LVESV).

- **[2] Sogaard P, Kim W, Jensen Henrik, Mortensen P, Pedersen A, Kristensen B, Egeblad H. Impact of acute biventricular pacing on left ventricular performance and volumes in patients with severe heart failure. *J Am Coll Cardiol* 2001;38:1957–1965** Study of 25 patients with QRS >120 ms, NYHA class III or IV on standard medical HF therapy. Tissue velocity imaging (TVI) and 3-dimensional echocardiography was used to evaluate the effect of acute bi-V pacing on LV performance and volumes in patients with severe HF and BBB. Bi-V pacing significantly improved extent of contracting myocardium in synchrony by 15.4% and the duration of contraction synchrony by 17% ($p<0.05$ for both). LVEDV and LVESV decreased by 7 +/- 4.5% and 13 +/- 6% ($p<0.01$) and EF increased by 22.8 +/- 9% ($p<0.01$). Conclusion: Bi-V pacing improves LV systolic performance and reduces LV volumes during short-term treatment.

- **[3] Kass D, Chen-Huan C, Curry C, Talbot M, Berger R, Fetics B, Nevo E. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999;99:1567-1573**
- **[4] Auricchio A, Ding J, Spinelli J, Kramer A, Salo R, Hoersch W, KenKnight B,Klein H for PATH-CHF Study Group. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. *J Am Coll Cardiol* 2002;39:1163–1169**
- **[5] Stellbrink C, Breithardt O, Franke A, Sack S, Bakker P, Auricchio A, on behalf of PATH-CHF Investigators, Pochet T, Salo R, Kramer A, Spinelli J, on behalf of CPI Guidant Congestive Heart Failure Research Group. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol* 2001;38:1957–1965**

Proposed Mechanisms: Improved Intraventricular Synchrony

PV loop tracings at right illustrate BiV/LV pacing produces: greater stroke work (area) and increased stroke volume (width), and a reduced systolic volume



Adapted from Kass et al.

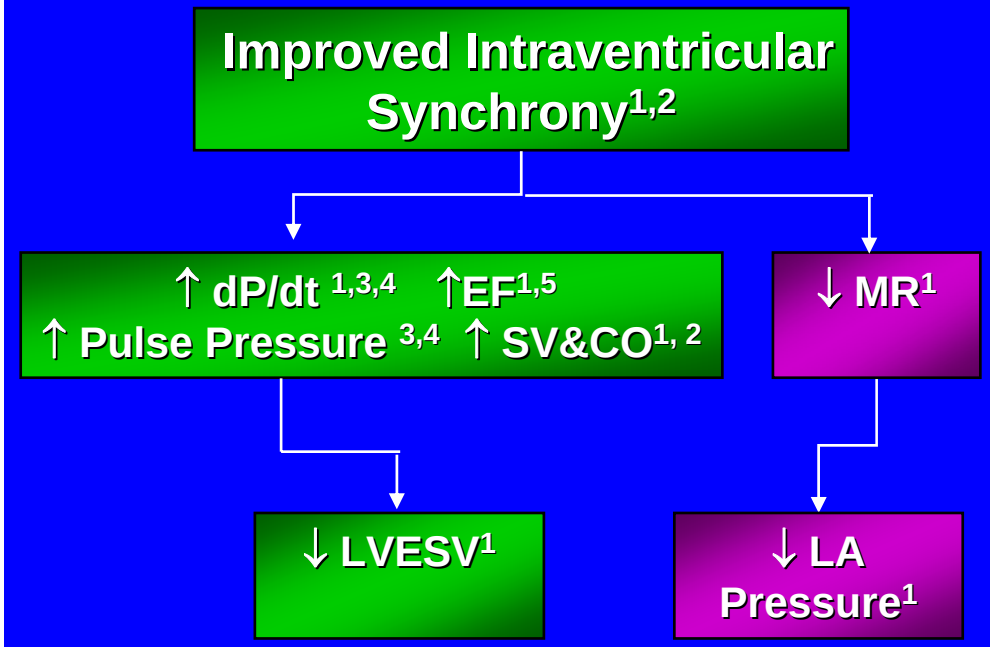
Kass D Chen-Huan C, Curry C, et al. *Circulation* 1999;99:1567-73

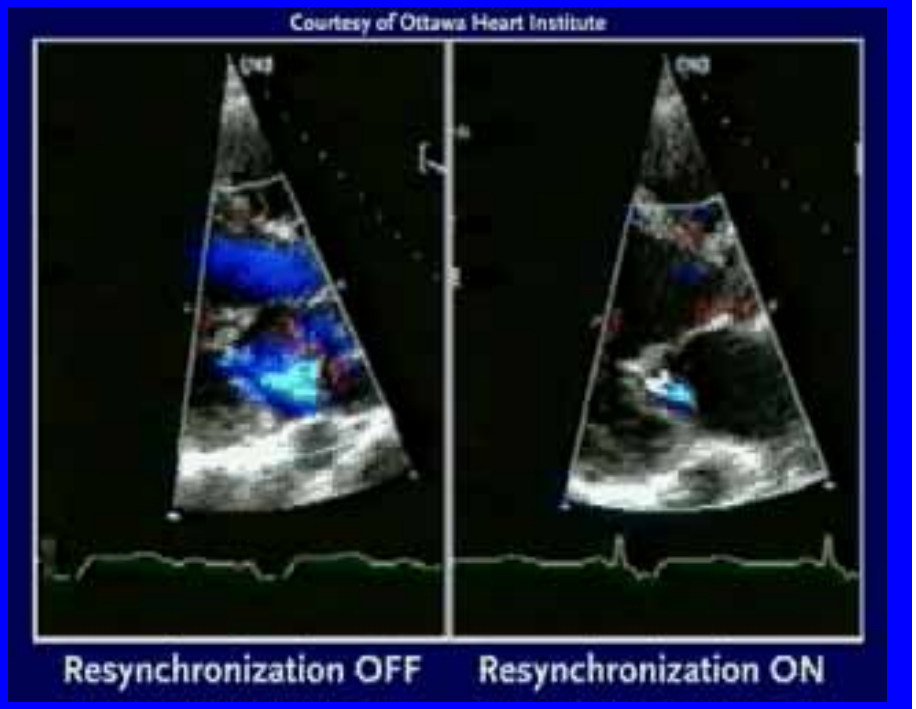
- In addition, David Kass at Johns Hopkins showed that LV or BiV pacing decreased end systolic volumes.

- PV loops displayed here are from a single patient with LBBB in Kass's acute study. In these PV loops, the red line indicates normal sinus rhythm (NSR) control and the yellow line indicates VDD pacing. It is also noteable that each site shown here was at the optimal AV interval. Minimal changes were seen with RV pacing, but increased stroke work and lowered end systolic volumes were seen with LV or BiV pacing.

- **Kass D, Chen-Huan C, Curry C, Talbot M, Berger R, Fetics B, Nevo E. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999;99:1567-1573**

Proposed Mechanisms: Improved Intraventricular Synchrony





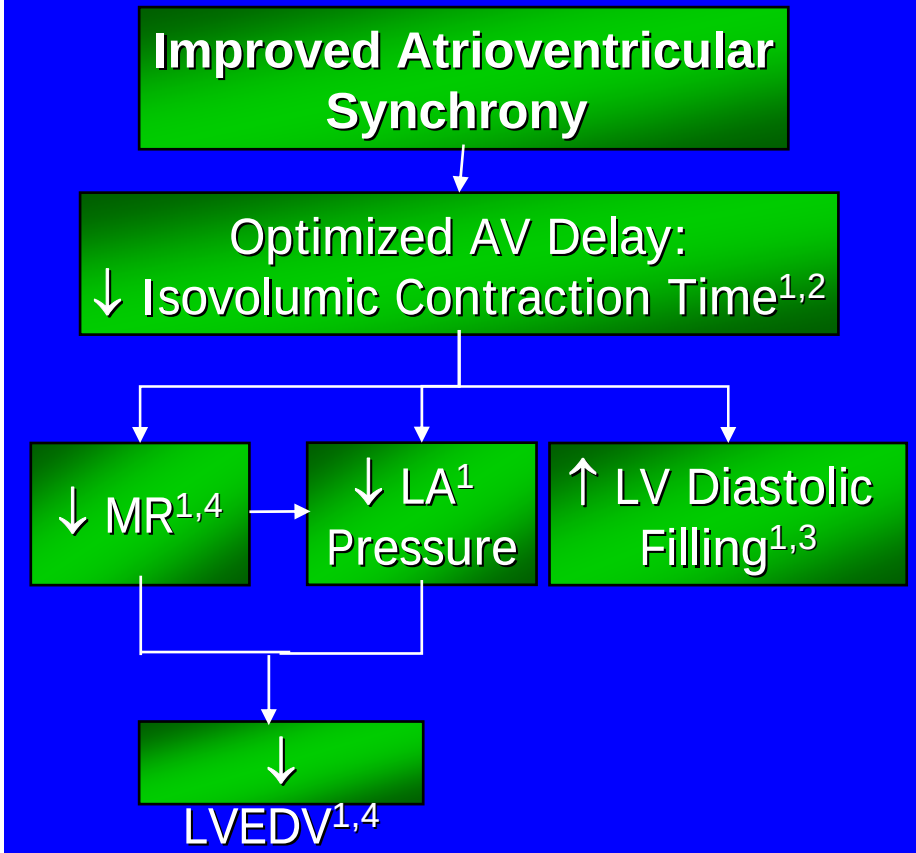
Click to Start/Stop

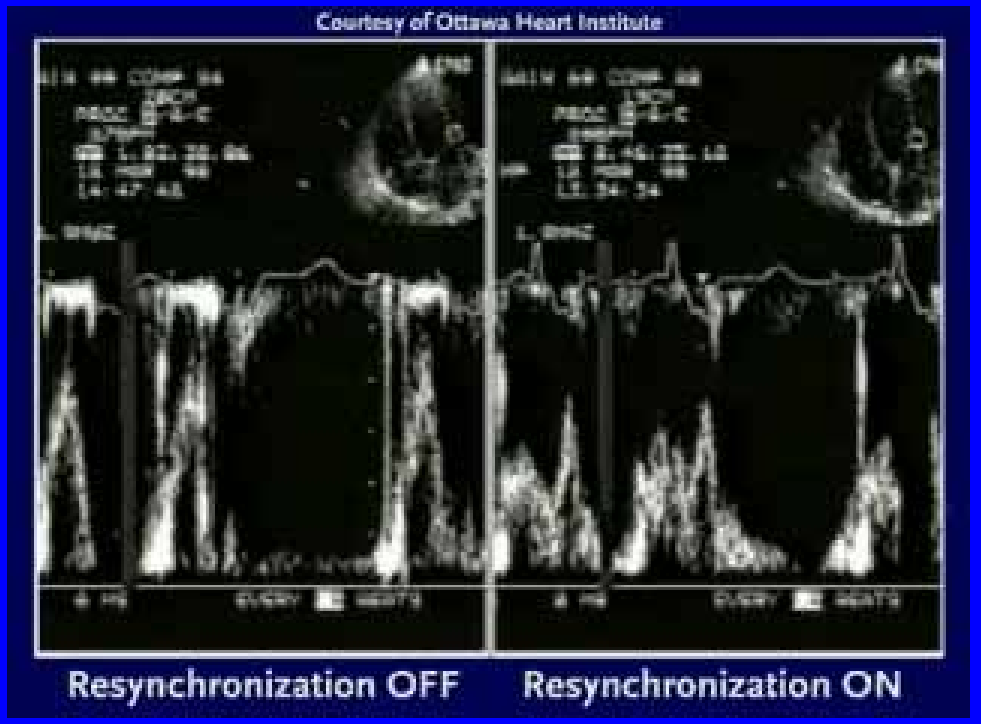
[1] Yu C-M, Chau E, Sanderson J, et al. *Circulation* 2002;105:438-445
[2] Søgaard P, Kim W, Jensen H, et al. *Cardiology* 2001;95:173-182
[3] Kass D Chen-Huan C, Curry C, et al. *Circulation* 1999;99:1567-73
[4] Auricchio A, Ding J, Spinelli J, et al. *J Am Coll Cardiol* 2002;39:1163-1169
[5] Stellbrink C, Breithardt O, Franke A, et al. *J Am Coll Cardiol* 2001;38:1957- 65

- We have discussed how improvement in the intraventricular synchrony improves cardiac function. Now, let's discuss mitral regurgitation.
- Yu et al found that mechanical mitral regurgitation (MR) decreased due to improved LV synchronicity, secondary to decreased distortion of the mitral valve during systole. This decrease in mitral regurgitation led to decreased left-atrial pressure, which led to a decrease in left ventricular end diastolic volume (LVEDV)[1].
- **Yu C-M, Chau E, Sanderson J, Fan K, Tang M, Fung W, Lin H, Kong S, Lam Y, Hill M, Lau C.P. Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-445.**

- Video Filename: "mitral-regurg.avi."
- The animation can be started by positioning the mouse-cursor over the image and clicking once. To stop or restart the animation video at anytime, click once on the image.
- Note in the video clips, that with cardiac resynchronization off, the mitral regurgitation (blue jet seen filling the left atrium) is significant. When cardiac resynchronization is turned on, the mitral regurgitation has markedly decreased.

Proposed Mechanisms: Improved Atrioventricular Synchrony





Click to Start/Stop

[1] Yu C-M, Chau E, Sanderson J, et al. *Circulation* 2002;105:438-445
[2] Kindermann M, Frohlig G, Doerr T, et al. *Pacing Clin Electrophysiol* 1997; 20(I):2453-2462
[3] Breithardt O, Stellbrink C, Franke A, et al. *Am Heart J* 2002;143:34-44
[4] Søgaard P, Kim W, Jensen H, et al. *Cardiology* 2001;95:173-182

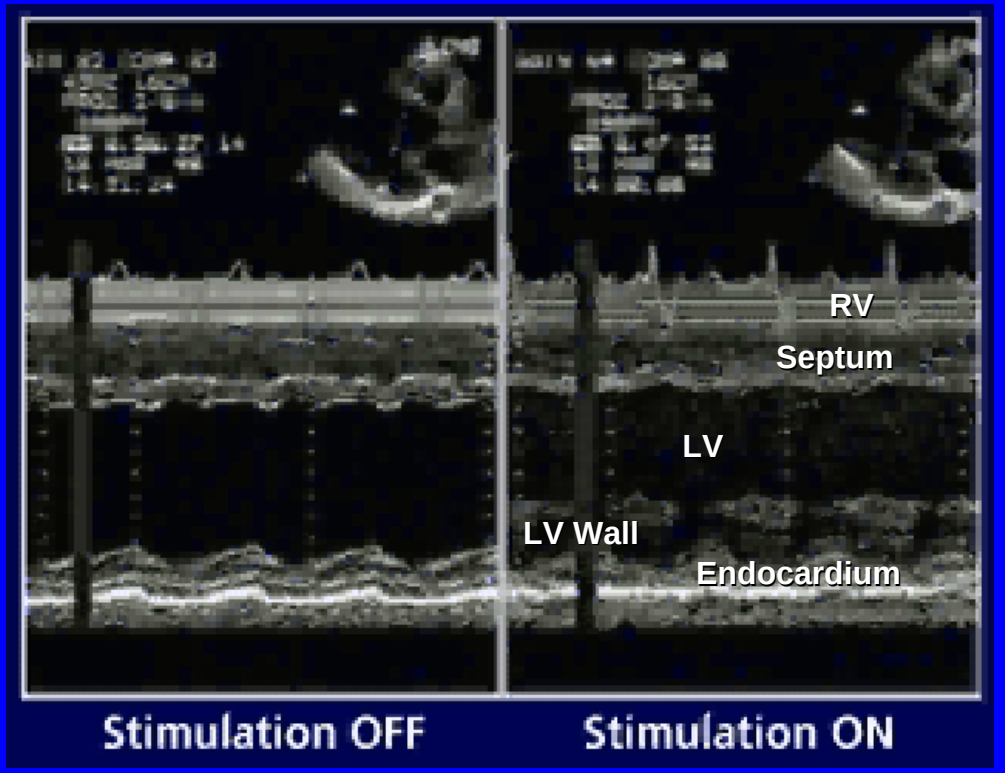
- Optimization of the AV interval is thought to have a positive, albeit less significant than intraventricular synchrony, effect on improved hemodynamics.
- Yu et al. found that an optimized AV delay effectively reduced the extended isovolumic contraction time (IVCT) observed in this patient population without change in the contraction time or isovolumic relaxation time. This reduction in IVCT reduced the time available for pre-systolic mitral regurgitation, and allowed more time during the cardiac cycle for left ventricular diastolic filling. This reduced MR (wasted presystolic time after atrial filling) with an accompanying reduction in LA pressure resulted in an acute reduction in left ventricular end-diastolic volume.
- **Yu C-M, Chau E, Sanderson J, Fan K, Tang M, Fung W, Lin H, Kong S, Lam Y, Hill M, Lau C.P. Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-445.**
- **Kindermann M, Frohlig G, Doerr T, Schieffer H. Optimizing the AV delay in DDD pacemaker patients with high degree AV block: mitral valve doppler versus impedance cardiography. *Pacing Clin Electrophysiol* 1997; 20(l):2453-2462**
- **Breithardt O, Stellbrink C, Franke A, Balta O, Diem B, Bakker P, Sack S, Auricchio A, for the PATH-CHF Study Group, and Pochet T, Salo R, for the Guidant Congestive Heart Failure Research. Acute effects of cardiac resynchronization therapy on left ventricular Doppler indices in patients with congestive heart failure. *Am Heart J* 2002;143:34-44**
- Study of 32 pts w/ advanced HF (59±6 yrs, NYHA III, QRS>120 ms,PR interval>150 ms) 4 wks after implant of cardiac resynchronization therapy (CRT) system. Doppler echocardiography in 3 separate CRT modes (RV, LV,and BV stimulation) at 3 different atrioventricular delays (short, intermediate, and long). CRT resulted in significant improvement of Doppler parameters such as filling time (313±11 baseline to 363±54 ms BV), aortic velocity time integral (23.2±7.4 cm to 26.8±8.8 cm LV),and myocardial performance index (MPI; 1.21±0.51 to 0.85±0.34 BV). Most improvement observed w/ LV and BV stimulation at short and intermediate atrioventricular delays (80-120 ms), independent of ischemic or idiopathic origin. Discussion of effect of AV delay, effect of pacing site, effects on systolic time intervals and MPI, diastolic vs. systolic Doppler parameters, response to CRT according to HF, and the limitations of the study.
- **Sogaard P, Kim W, Jensen Henrik, Mortensen P, Pedersen A, Kristensen B, Egeblad H. Impact of acute biventricular pacing on left ventricular performance and volumes in patients with severe heart failure. *J Am Coll Cardiol* 2001;38:1957–1965.**
- Study of 25 patients with QRS >120 ms, NYHA Class III or IV on standard medical HF therapy. Tissue velocity imaging (TVI) and 3-dimensional echocardiography was used to evaluate the effect of acute bi-V pacing on LV performance and volumes in patients with severe HF and BBB. Bi-V pacing significantly improved extent of contracting myocardium in synchrony by 15.4% and the duration of contraction synchrony by 17% ($p<0.05$ for both). LVEDV and LVESV decreased by 7 +/- 4.5% and 13 +/- 6% ($p<0.01$) and EF increased by 22.8 +/- 9% ($p<0.01$). Conclusion: Bi-V pacing improves LV systolic performance and reduces LV volumes during short-term treatment.

- Video Filename: “mitral-flow.avi.”
- The animation can be started by positioning the mouse-cursor over the image and clicking once. To stop or restart the animation video at anytime, click once on the image.
- Note on the video clips. With resynchronization Off, the E and A-waves are fused and the diastolic filling time is short. With

Proposed Mechanisms: Improved Interventricular Synchrony

Improved Interventricular Synchrony[1,2]

↑ RV Stroke Volume[1] → **↑ LV Diastolic Filling[1]**



Courtesy of Ottawa Heart Institute

[1] Yu C-M, Chau E, Sanderson J, et al. *Circulation* 2002;105:438-445
[2] Kerwin W, Botvinick E, O'Connel W, et al. *JACC* 2000;35:1221-7

- The last proposed mechanism, improved interventricular synchrony, appears to be the least important mechanism and has been the least studied. The benefit may be due to ventricular interdependence.[1] When both ventricles contract appropriately with respect to the "shared" septum, the net result is improved forward flow. This improved ventricular contraction results in improved perfusion and return of blood to the heart for appropriate diastolic filling (overall system improvement).
- **Yu C-M, Chau E, Sanderson J, Fan K, Tang M, Fung W, Lin H, Kong S, Lam Y, Hill M, Lau C.P. Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-445.**
- According to Yu's article, in the RV there was also delay in the the time to peak sustained systolic contraction (T_s) to a magnitude similar to that of the septum during biventricular pacing, resulting in simultaneous peak contraction with the LV (i.e interventricular synchrony was also achieved).
- The still images of the M-mode echos above illustrate how the LV freewall contracts toward a stable septum with cardiac resynchronization On versus away from the septum with cardiac resynchronization Off.
- **Kerwin W, Botvinick E, O'Connell W, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dysynchrony. *J Am Coll Cardiol* 2000;35:1221-7.**
- 13 pts with DCM, NYHA Class II-IV HF, IVCD, and sinus rhythm underwent multiple gated equilibrium blood pool scintigraphy to determine if BiV pacing would improve synchrony of RV and LV contraction and thus result in improved LVEF. The study showed that the degree of interventricular dysynchrony present in NSR correlated with LVEF. During BiV pacing, interventricular contractile synchrony improved overall. The degree of interventricular dysynchrony present in NSR correlated with the magnitude of improvement in synchrony during BiV pacing. LVEF increased in all 13 pts during BiV pacing and correlated significantly with improvement in RV/LV synchrony during BiV pacing. Conclusion: Improvement in interventricular synchrony during BiV pacing correlate with acute improvement in LVEF.
- In this still echo picture, note with resynchronization OFF, the LV wall moves away from the interventricular septum during systole. With resynchronization ON, the LV wall moves toward the interventricular septum

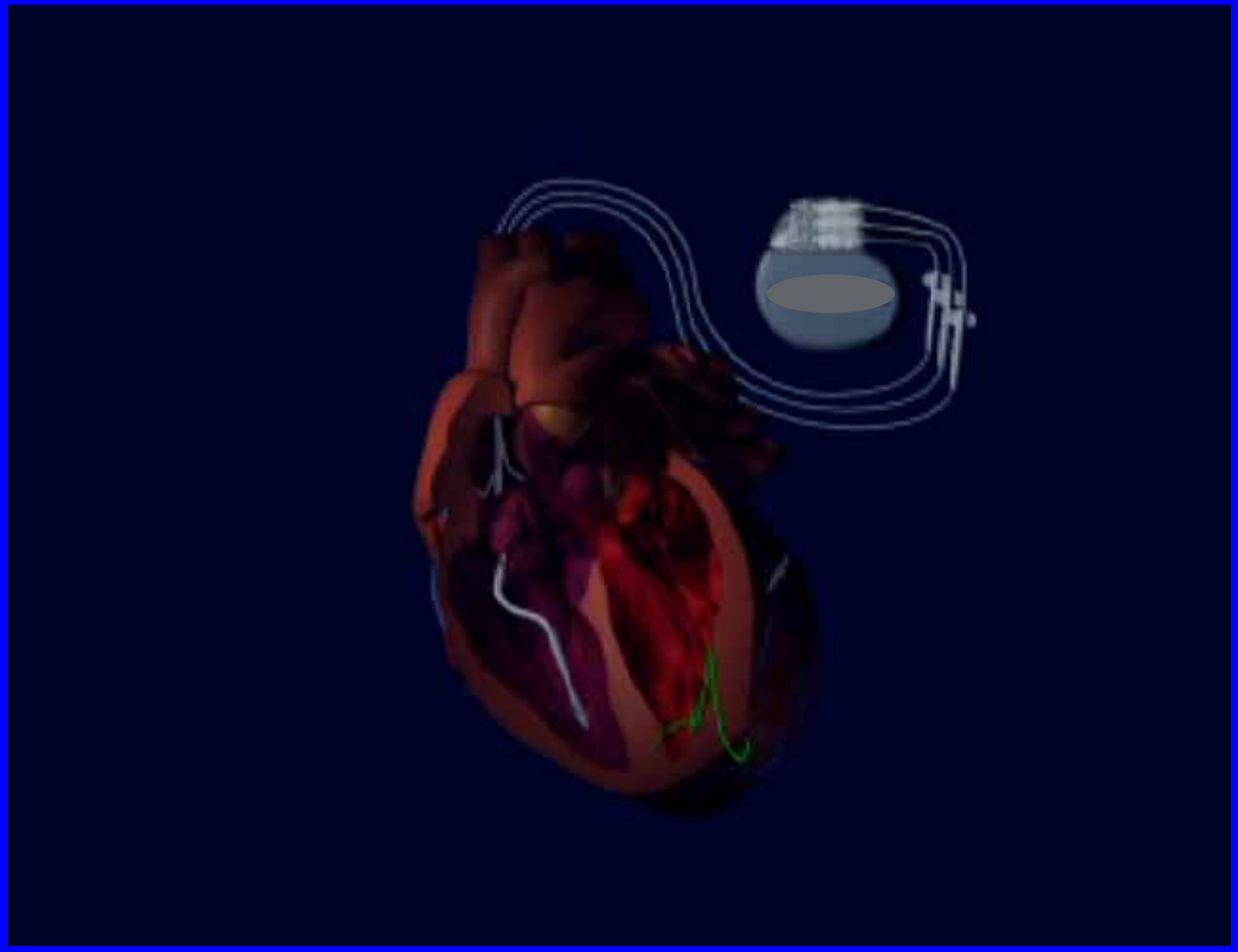
Achieving Cardiac Resynchronization

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

- **A specially designed pacing lead is passed through the coronary sinus into a cardiac vein on the left lateral freewall.**
- A standard pacing lead is placed in the right atrium. If the patient is indicated for an ICD and receives a device that combines both VT/VF therapies with cardiac resynchronization, a standard defibrillation lead is placed in the right ventricle. Otherwise a standard pacing lead is in placed in the right ventricle.

Cardiac Resynchronization



Click to Start/Stop

- The animation illustrates cardiac resynchronization. During resynchronization, notice the stabilization of the septal wall and the restoration of a more coordinated ventricular systolic contraction. A dilated heart with ventricular dysynchrony appears toward the end of the video to further highlight the paradoxical septal wall motion that occurs when CRT therapy is not applied.

- Animation Filename: “Clip3-CardiacResynch.mpg.” The animation can be started by positioning the mouse-cursor over the image and clicking once. To stop or restart the animation video at anytime, click once on the image.

Is Cardiac Resynchronization Pro-arrhythmic?

VT/VF Events: Non-ICD Indicated Patients with wide QRS

- 20 class III/IV HF patients implanted with bi-ventricular pacemakers

  Finding: Significant decrease in ventricular ectopic counts and total VT duration in both groups

  Finding: Significant decrease in ventricular salvo counts in SR group

Conclusion: Cardiac Resynchronization does NOT appear to increase ectopic ventricular activity in Non-ICD indicated patients

Walker S, Levy T, Rex S, et al. *Am J Cardiol* 2000;86231-233.

- **Walker S, Levy T, Rex S, Brant S, Allen J, Ilsley C, Paul V. Usefulness of suppression of ventricular arrhythmia by biventricular pacing in severe congestive cardiac failure. *Am J Cardiol* 2000;86:231-233.**

- Holter analysis of 20 NYHA Class III/IV, 8 in chronic AF undergoing HIS ablation, and both RV and LV leads implant; 12 in normal sinus rhythm and RA, RV and LV leads place. Compared ectopic events during BiV and control (no pacing for NSR, RV pacing for AF). Randomized cross-over design. Results from NSR group shown here. Similar results for chronic AF pts not shown.

Is Cardiac Resynchronization Pro-arrhythmic?

VT/VF Events: ICD-Indicated Patients with wide QRS

- 32 patients (sub-analysis Ventak CHF study)[1]

  Finding: Mean number of episodes was 0.6 during Bi-V pacing, versus 1.4 during no-pacing period (p=0.035)

- 26 patients (33% in the InSync ICD worldwide study) [2]

  Finding: Experienced at least one episode of spontaneous VT/VF during bi-ventricular pacing

  Consistent with published data: 32% (96/300) ICD patients experienced at least 1 episode during non-biV pacing; mean follow-up of 1.7 months[1]

Conclusion: Cardiac Resynchronization does NOT appear to be pro-arrhythmic in ICD indicated patients

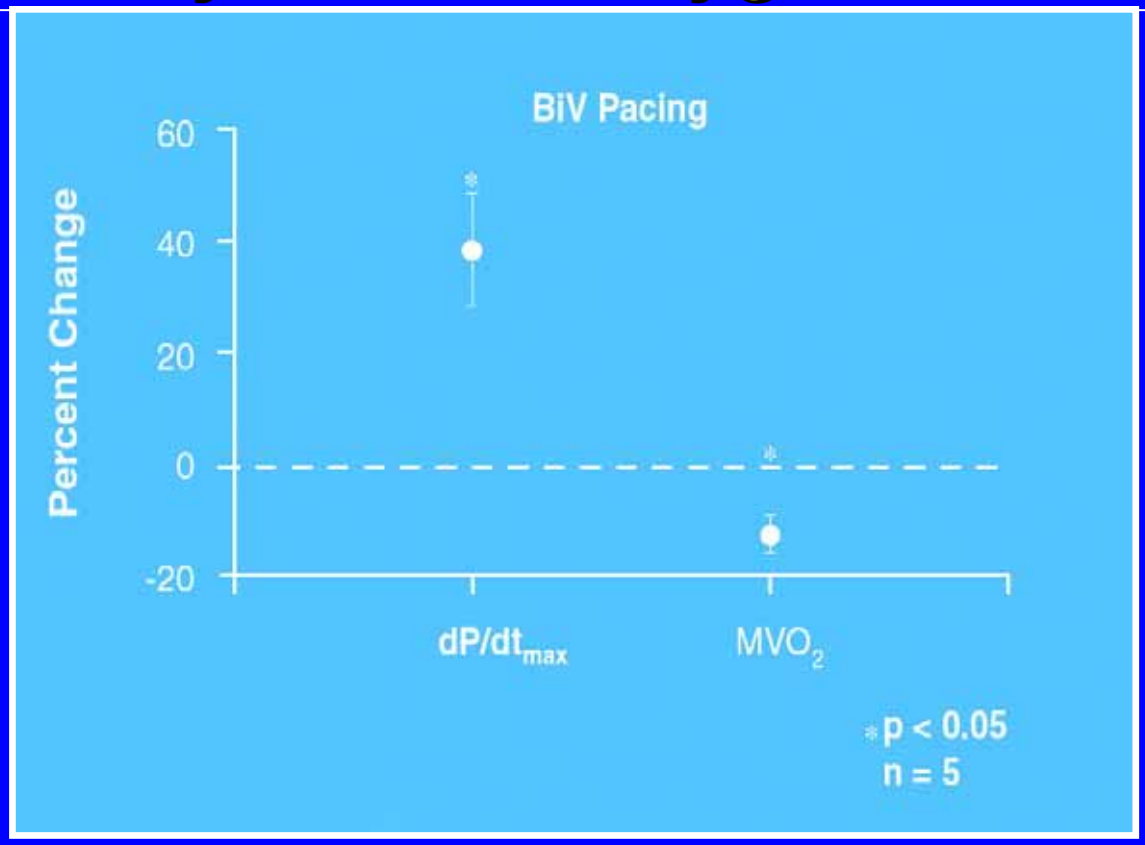
[1] Higgins S, Yong P, Scheck D, et al. *J Am Coll Cardiol* 2000;36:824-827.
2 Kuhlkamp V, et al., for the InSync 7272 ICD World Wide Investigators. *J Am Coll Cardiol 2002*;39;790-797

- **Higgins S, Yong P, Scheck D, McDaniel M, Bollinger F, Vadecha M, Desai S, Meyer D for the Ventak CHF Investigators. Biventricular pacing diminishes the need for implantable defibrillator therapy. *J Am Coll Cardiol* 2000;36:824-827.**

- Analysis of 32 of 54 pts with HF and ICD indications enrolled in randomized Ventak CHF study in the US. Study was a 3 month crossover design. 13/32 (41%) received appropriate therapy for VT at least once during the 6 month period. 5/32 (16%) had at least 1 episode while programmed o BiV, 11/32 (34%), had at least 1 episode while programmed to no pacing, and 3/32 (9%) received therapy in both periods. The mean number of episodes in the BiV pacing period was 0.6±2.1 compared with 1.4±3.5 in the no pacing period, p=0.035.
- **Kuhlkamp V, et al. for the InSync 7272 ICD World Wide Investigators. Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy. *J Am Coll Cardiol* 2002;39:790-797.**

- Analysis of 84 pts with HF and standard ICD indications enrolled in InSync ICD European study. Patients were required to have symptomatic heart failure despite appropriate therapy, LVEF < 35%, QRS > 130 ms and LVEDD > 55 mm. 81 patients were successfully implanted with an LV lead. Of the patients, 26 experienced 472 episodes of spontaneous sustained ventricular tachyarrhythmias. 339 episodes in 17 patients were detected in the VT zone, 107 episodes in 8 patients in the fast VT zone and 26 episodes in 8 patients in the VF zone. Double-counting of sensed events did NOT occur. 26 patients (33%) experienced at least one episode of sustained VT or VF.

Cardiac Resynchronization Does Not Increase Myocardial Oxygen Consumption



Adapted from: Nelson G, Berger R, Fetics B, et al. *Circulation*. 2000;102:3053-3059.

Improved systolic function without increasing energy consumption.

- This slide illustrates that cardiac resynchronization therapy does NOT increase myocardial oxygen consumption. Heart function is improved by a more efficient, rather than stronger, contraction.

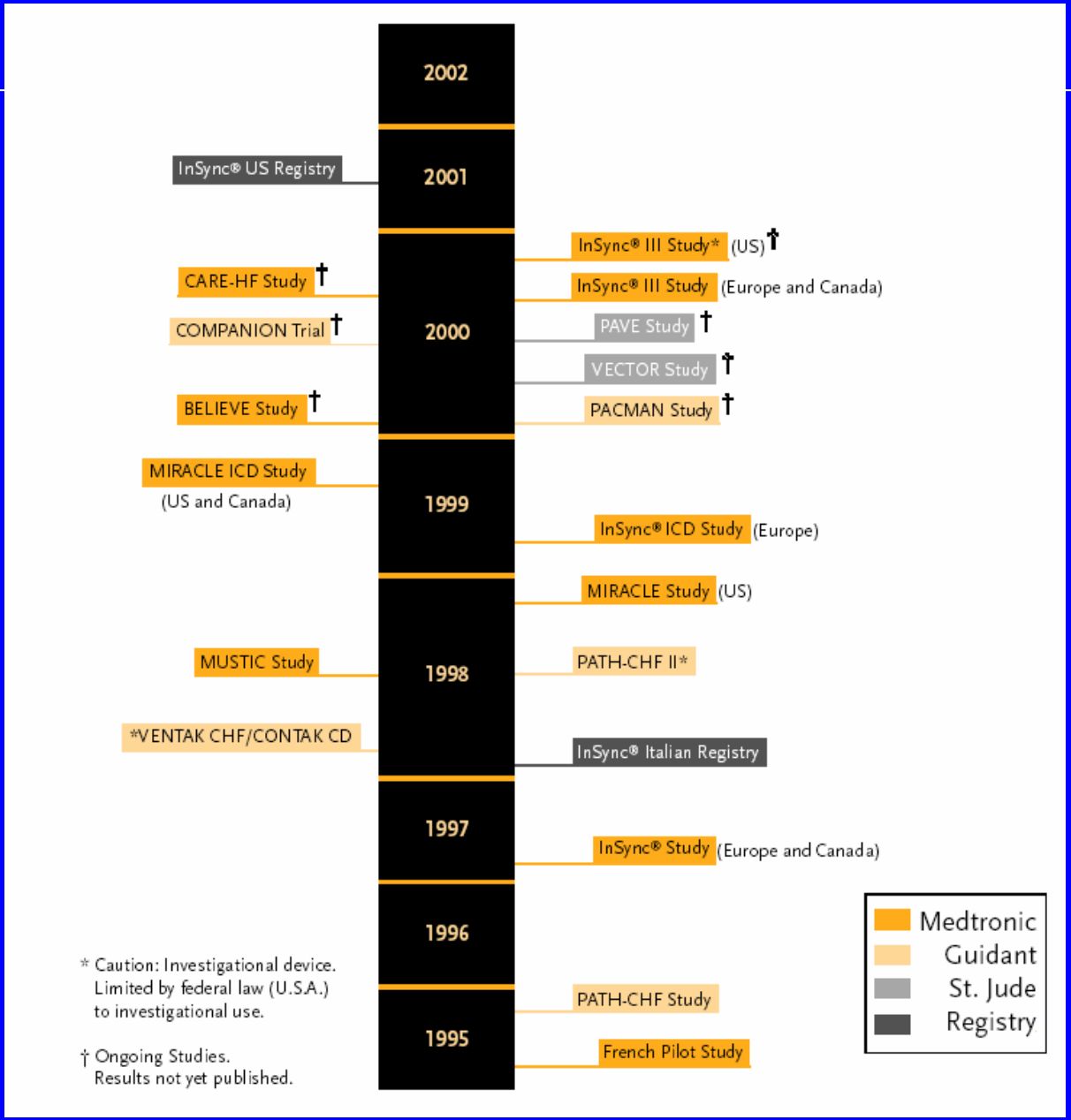
- Adapted from: Nelson G, Berger R, Fetics B. et al. *Circulation*. 2000;102:3053-3059.

- The above graph shows the percent changes seen in mechanical and energetic parameters as a result of cardiac resynchronization through biventricular pacing. This data clearly depicts an improvement in a measure of systolic function (dP/dt_{max}) without increasing energy consumption.

Results from Clinical Studies

- Concordance of Proof - Summary of Results from Various Trials
- Comparison with Heart Failure Drug Trials

HF and CRT Clinical Studies – Observational and Randomized



- Note: This graphic is not all-inclusive of all studies and all device manufacturers. It lists some of the larger or key studies to date.
- Early studies of CRT have demonstrated improvement in patient symptoms and exercise capacity, but have been limited by small numbers of enrolled patients, uncontrolled or poorly controlled study designs and unblinded or single-blinded nature of follow-up.
- **1995-1997:** Mechanistic and longer-term observational studies
- **1998-1999:** Randomized, placebo-controlled studies to assess exercise capacity, functional capacity and Quality of Life
- **2000-2002:** Randomized trials to assess combined mortality and hospitalization

CRT Improves Quality of Life Score and NYHA Functional Class

	QoL	NYHA
PATH-CHF[1] (n=41)	+	+
InSync (Europe)[2] (n=103)	+	+
InSync ICD (Europe)[3] (n=84)	+	+
MUSTIC[4] (n=67)	+	
MIRACLE[5] (n=453)	+	+
MIRACLE ICD[6] (n=364)	+	+

+	Statistically significant improvement with CRT ($p \leq 0.05$)
↔	Not statistically significant or No statistical analysis performed on data
Blank	Indicates test neither performed nor reported

[1] Auricchio A. Stellbrink C, Sack S., et al. *J Am Coll Cardiol* 2002;39:2026-2033

[2] Gras D, Leclercq C, Tang A, et al. *Eur J Heart Failure* 2002;4:311-320

[3] Kuhlkamp V. *JACC* 2002;39:790-797

[4] Linde C, Leclercq C, Rex S, et al. *J Am Coll Cardiol* 2002;40:111-118

[5] Abraham W, Fisher W, Smith A, et al. *N Engl J Med.* 2002;346:1845-1853

[6] Leon A. *NASPE Scientific Sessions – Late Breaking Clinical Trials.* May 2002; Medtronic Inc. data on file

- Follow-up data from both controlled and uncontrolled studies document symptomatic improvement in patients treated with cardiac resynchronization therapy. Most notably, MUSTIC, MIRACLE and MIRACLE ICD trials document that cardiac resynchronization is safe, well tolerated by patients, and clinically beneficial. These studies reported improvements in patient Quality of Life, exercise capacity, and NYHA functional class for patients receiving cardiac resynchronization therapy as well as improvement in many echocardiagraphic parameters.

CRT Improves Exercise Capacity

	6 Min Walk	Peak VO_2	Exercise Time
PATH-CHF[1] (n=41)	+	+	
InSync (Europe)[2] (n=103)	+		
InSync ICD (Europe)[3] (n=84)	+		
MUSTIC[4] (n=67)	+	↔	
MIRACLE[5] (n=453)	+	+	+
MIRACLE ICD[6] (n=364)	↔	+	+

+	Statistically significant improvement with CRT ($p \leq 0.05$)
↔	Not statistically significant or No statistical analysis performed on data
Blank	Indicates test neither performed nor reported

[1] Auricchio A. Stellbrink C, Sack S., et al. *J Am Coll Cardiol* 2002;39:2026-2033

[2] Gras D, Leclercq C, Tang A, et al. *Eur J Heart Failure* 2002;4:311-320

[3] Kuhlkamp V. *JACC* 2002;39:790-797

[4] Linde C, Leclercq C, Rex S, et al. *J Am Coll Cardiol* 2002;40:111-118

[5] Abraham W, Fisher W, Smith A, et al. *N Engl J Med.* 2002;346:1845-1853

[6] Leon A. *NASPE Scientific Sessions – Late Breaking Clinical Trials.* May 2002; Medtronic Inc., data on file

- Key Message: Results from studies, both observational and randomized, controlled are concordant in their finding that CRT improves exercise capacity measured parameters.
- Note: A subset of the MIRACLE and MIRACLE ICD patients provided paired data for these parameters.

CRT Improves Cardiac Function/Structure

	LVEF	MR	Other
PATH-CHF[1] (n=41)			+ LVEDP + LV dP/dt_{max}
InSync (Europe)[2] (n=103)	+		+ Filling Time
InSync ICD (Europe)[3] (n=84)	+		+ Filling Time
MUSTIC[4] (n=67)	↔	↔	↔ LVEDD,LVESD ↔ Filling Time
MIRACLE[5] (n=453)	+	+	+ LVEDD, + LVEDV, LVESV
MIRACLE ICD[6] (n=362)	↔	+	+ LVESV, + LVEDV

+	Statistically significant improvement with CRT ($p \leq 0.05$)
↔	Not statistically significant or No statistical analysis performed on data
Blank	Indicates test neither performed nor reported

[1] Auricchio A. Stellbrink C, Sack S., et al. *J Am Coll Cardiol* 2002;39:2026-2033

[2] Gras D, Leclercq C, Tang A, et al. *Eur J Heart Failure* 2002;4:311-320

[3] Kuhlkamp V. *JACC* 2002;39:790-797

[4] Linde C, Leclercq C, Rex S, et al. *J Am Coll Cardiol* 2002;40:111-118

[5] Abraham W, Fisher W, Smith A, et al. *N Engl J Med.* 2002;346:1845-1853

[6] Young J. *ACC Scientific Sessions – Late Breaking Clinical Trials III.* March 2002; Medtronic Inc., data on file

- Key Message: Results from studies, both observational and randomized, controlled are concordant in their finding that CRT improves many secondary efficacy endpoints measured by echocardiographic parameters.
- The MIRACLE ICD data reported here was presented at the 2002 ACC Scientific Sessions (n=362 here, rather than n=364 reported by Dr. Leon at the 2002 NASPE scientific session.)
- Note: A subset of the MIRACLE and MIRACLE ICD patients provided paired data for the echo parameters.

Cardiac Resynchronization Outcomes Sustained for at least 12 months

	NYHA	QoL	6 Minute Walk	Peak VO_2
InSync European and Canadian Study[1] (n=67, followed to 12 months)	+	+	+	
PATH-CHF Study[2] (n=29, followed to 12 months)	+	+	+	+
MUSTIC Study[3] (n=42 in sinus rhythm group, n=33 in atrial fibrillation group followed to 12 months)	+	+	+	↔

+	Statistically significant improvement with CRT ($p \leq 0.05$)
↔	No statistically significant improvement with CRT
Blank	Indicates test neither performed nor reported

[1] Gras D, Leclercq C, Tang A, et al. *Eur J Heart Fail* 2002;4:311-320
[2] Auricchio A. Stellbrink C, Sack S., et al. *J Am Coll Cardiol* 2002;39:2026-2033
[3] Linde C, Leclercq C, Rex S, et al. *J Am Coll Cardiol* 2002;40:111-118

- Results from the InSync prospective observational multi-center European and Canadian study (67 patients followed to 12 months), the PATH-CHF (multi-center, patient-blinded, sequential-treatment, randomized, crossover) study (29 patients followed to 12 months), and the MUSTIC (multicenter, randomized, controlled; 75 patients followed to 12 months) showed sustained long term improvements in NYHA functional class, quality of life and 6 minute walk distance.
- Peak VO_2 improvements were sustained in the the PATH-CHF study but no statistically significant improvement between control and therapy groups was measured in the MUSTIC study at 12 months.

Cardiac Resynchronization Benefits Relative to Hospitalization

PATH-CHF[1]

- 1 year prior to implant, 22 patients hospitalized for HF with average stay of 18.5 days
- One year following implant, 9 patients hospitalized for HF with average stay of 4.5 days

MUSTIC[2]

- Sinus Rhythm Group: 7 times fewer hospitalizations for HF (12 month F/U)
- AF Group: 4 times fewer hospitalizations for HF (12 m/fu)

MIRACLE[3]

- Number of HF-hospitalizations significantly reduced ($p = 0.02$)

MIRACLE ICD[4]

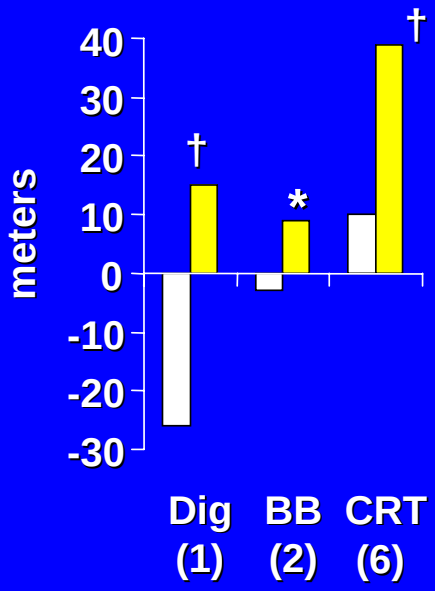
- Length of stay for HF-hospitalizations significantly reduced ($p = 0.05$)

[1] Auricchio A. Stellbrink C, Sack S., et al. *J Am Coll Cardiol* 2002;39:2026-2033
[2] Linde C, Leclercq C, Rex S, et al. *J Am Coll Cardiol* 2002;40:111-118
[3] Abraham W, Fisher W, Smith A, et al. *N Engl J Med.* 2002;346:1845-1853
[4] Leon A. DeLurgioD, Smith A, et al. *PACE* 2002;25(4), Part II:647

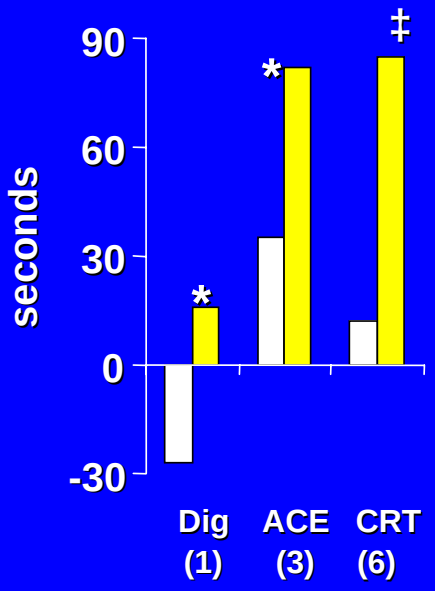
- Heart failure related hospitalizations were studied and recorded in the trials listed on this slide. Each of these studies documented either reduced hospitalization or reduced length of stay for patients receiving cardiac resynchronization therapy.
- Note: P-values were not calculated for the PATH-CHF and MUSTIC trial data.

Comparison with Drug Trials: Digoxin, ACE-I and Beta-blocker Therapies

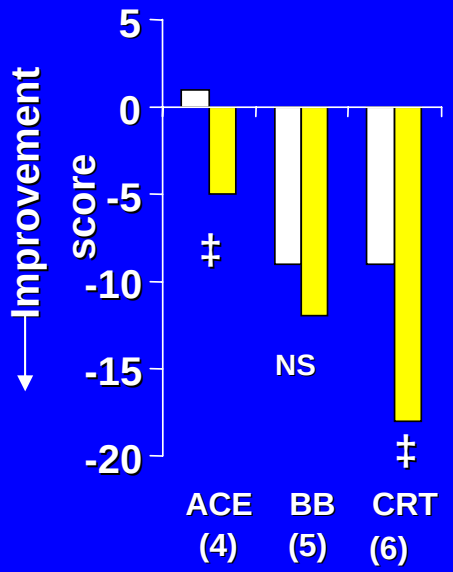
Change from baseline in 6 minute walk distance



Change from baseline in CPX Duration



Change from baseline in QoL (MLWHF) Score



Control Treatment

* P≤.05

† P≤.01

‡ P≤.001

[1] *N Engl J Med* 1993;329:1-7 (RADIANCE)
[2] *Circulation* 1996;94:2793-2799 (PRECISE)
[3] *JAMA* 1988;259:539-544
[4] *Am J Cardiol* 1993;71:1106-1107 (SOLVD Treatment)
[5] *J Cardiac Failure* 1997;3:173-179
[6] *N Engl J Med.* 2002;346:1845-1853

- **Key points: 1) CRT is used as an adjunct with these medications to treat heart failure. 2) CRT provides the same or greater level of improvement in these endpoints. It is important to point out that those patients receiving cardiac resynchronization therapy were on optimal medical therapy (MIRACLE trial – 90% on ACEI, 60% on beta-blockers).**

- These graphs show results from randomized, controlled trials of ACE-I , beta-blockers, and CRT for heart failure related to changes in 6 minute walk, QoL (MLWHF), and exercise duration.

- In the first graph, note the patients on Digoxin and those receiving CRT significantly improved ($p \leq .01$) their 6 minute hall ($p \leq .01$) their 6 minute hall walk over control compared to those patients on beta blockers.

- In the second graph, the CRT patients (MIRACLE – 90% already on an ACEI) could perform longer on CPX testing ($P<0.001$) over control compared to those on Digoxin and an ACEI.

- In the third graph, patients on an ACE inhibitor and receiving CRT had a highly significant change ($p \leq .001$) in their QoL score (marked improvement since score went down). Patients on Beta blockers improved but when compared to the control, it was not significant.

- **Key Message:** Cardiac resynchronization therapy shows an incremental benefit over medical therapy on these HF endpoints. Note that these drugs were approved by the FDA because they improved survival or combined survival and hospitalization.

Cardiac Resynchronization Therapy

Patient and Device Selection, Implant and Follow-up Overview

Indications for Cardiac Resynchronization System

- Resynchronization system is indicated for the reduction of HF symptoms in patients that meet the following criteria:
  - Moderate to severe heart failure (NYHA Class III/IV)
  - QRS $\geq$ 130 ms
  - LV ejection fraction $\leq$ 35%
  - Symptomatic despite stable, optimal medical therapy

Indications for the ICD Cardiac Resynchronization System

- Resynchronization ICD system is indicated for the reduction of HF symptoms in patients that meet the following criteria:
  - Standard ICD indication
  - Moderate to severe heart failure (NYHA Class III/IV)
  - QRS $\geq$ 130 ms
  - LV ejection fraction $\leq$ 35%
  - Symptomatic despite stable, optimal medical therapy

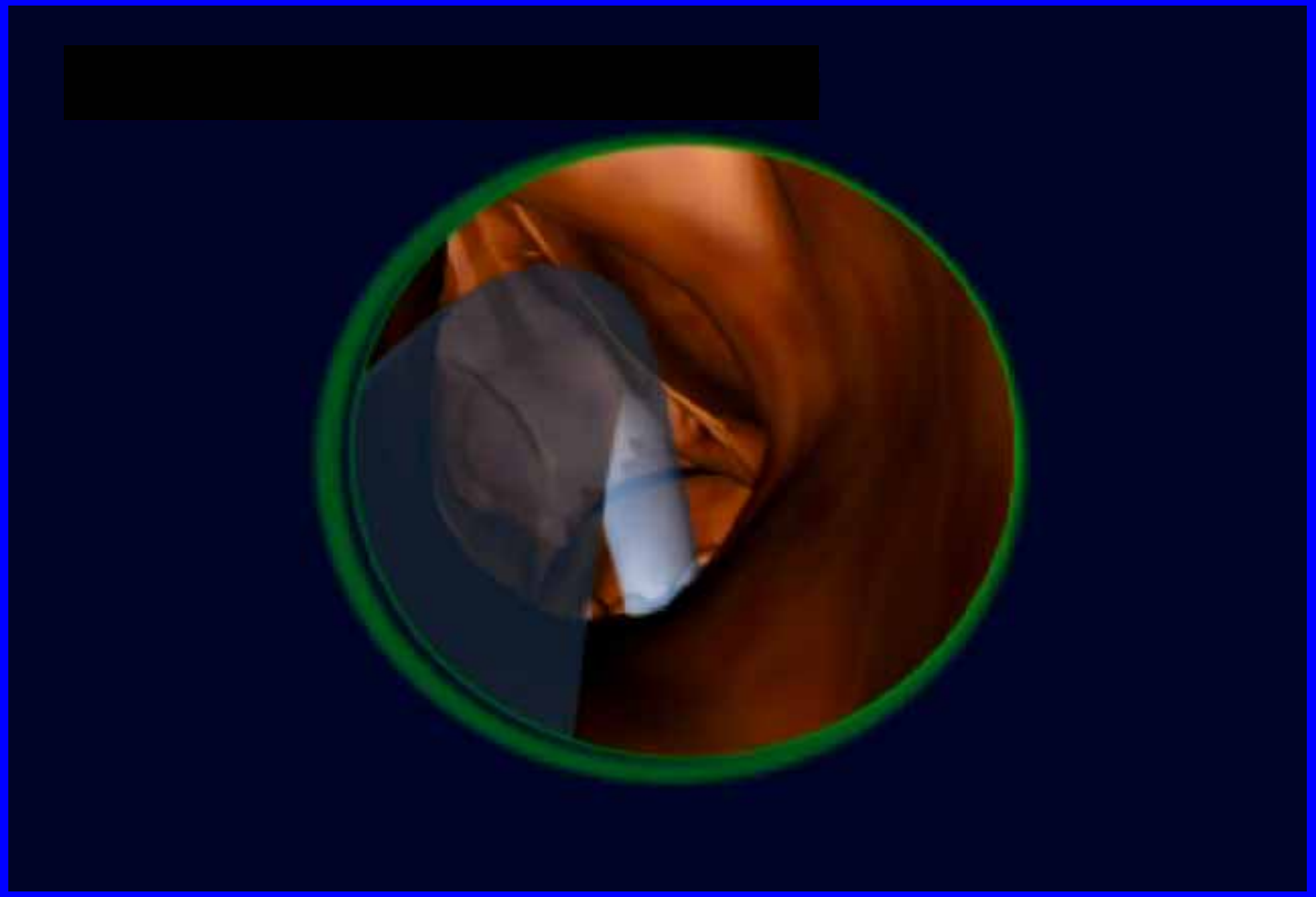
- The indications listed are the approved labeling as determined by the FDA.
- **Indications:**
- The ICD system is intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias, and for the reduction of the symptoms of moderate to severe heart failure (NYHA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy (as defined in the clinical trials section), and have a left ventricular ejection fraction less than or equal to 35% and a QRS duration greater than or equal to 130 ms.
- **Contraindications:**
- The ICD system is contraindicated in:
- - Patients whose ventricular tachyarrhythmias may have transient or reversible causes.
- - Patients with incessant VT or VF
- - Patients who have a unipolar pacemaker
- **Warnings/Precautions:**
- - Changes in patient's disease and/or medications may alter the efficacy of the device's programmed parameters.
- - Patients should avoid sources of magnetic and electromagnetic radiation, including MRI, ditheramy, and electrosurgical units, to avoid possible underdetection, inappropriate therapy delivery, and/or electrical reset of the device.
- - Certain programming and device operations may not provide cardiac resynchronization.
- - Do not place transthoracic defibrillation paddles directly over the device.
- *See the appropriate technical manuals for detailed information regarding instructions for use, indications, contraindications, warnings and precautions, and potential adverse events.*

Implant Process Overview

- Insertion of three leads (RA, RV, LV)
  - Standard pacing lead in right atrium
  - Standard pacing or defibrillation lead in right ventricle
  - Left heart lead placed transvenously in a cardiac vein branch, on the LV freewall (accessed via the coronary sinus)
- Implantation of cardiac resynchronization device
  - Similar to standard pacemaker or ICD implant procedure
- Measurement of final thresholds and programming of device

- Implantation involves placement of a device into the upper chest along with three leads. The implant is typically done under local anesthesia with the patient sedated. Three leads are implanted: Standard transvenous pacing leads are placed in the right atrium and ventricle, while a specially designed transvenous left ventricular lead is inserted into the distal cardiac vein via the coronary sinus.
- The goal is to place the LV lead in a mid-cardiac position on the left lateral freewall with good physical and electrical separation from the RV lead. This separation helps to optimize resynchronization to correct the ventricular contraction pattern.

Animation – LV Lead Placement



Click to Start/Stop

- This animation shows the placement of a left heart lead via the coronary sinus. On-screen annotations are included during the playing of the video clip.
- Animation Filename(s): “Clip2-AttainLV.mpg.”
- The animation can be started by positioning the mouse-cursor over the image and clicking once. To stop or restart the animation video at anytime, click once on the image.

Follow-up Care (Brief Overview)

- Standard medical management of HF as defined by practice guidelines and clinician judgment
- Standard device follow-up as defined by practice guidelines and clinician judgment
  - Goal is to achieve 100% biventricular pacing to deliver therapy
  - AV interval optimization is recommended to achieve maximum diastolic filling time

- Standard medical management of heart failure patients as well as device management should continue as defined by practice guidelines and clinician judgment.
- Typically a physician who specializes in implantable devices should monitor the device operation. At follow-up, close attention should be paid to the ventricular high rate diagnostics from the device since advanced HF patients have a significant risk of developing ventricular arrhythmias. The rate histogram can be evaluated the first month to ensure cardiac resynchronization is being applied throughout the range of patient activities.
- Special considerations may need to be taken to ensure coordination of medical management with device operation.
  - Interrogation of device information and lead status occur per device guidelines.
  - Diagnostic information reviewed for presence of potential arrhythmias (AT/AF, VT/VF).
  - Rate Histograms to evaluate appropriateness of CR therapy (percentage of V-pacing) throughout the range of patient activity.

In Summary

Cardiac Resynchronization therapy offers an adjunctive approach for treating selected patients with ventricular dysynchrony and moderate to severe heart failure who remain symptomatic despite optimal, stable medical therapy.