Update on the Evaluation and Management of Heart Failure

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New Approach to the Classification of Heart Failure

	Stage	Patient Description
A	High risk for developing heart failure (HF)	• Hypertension • CAD • Diabetes mellitus • Family history of cardiomyopathy
B	Asymptomatic HF	• Previous MI • LV systolic dysfunction • Asymptomatic valvular disease
C	Symptomatic HF	• Known structural heart disease • Shortness of breath and fatigue • Reduced exercise tolerance
D	Refractory end-stage HF	• Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

Carvedilol is indicated for use in patients with mild to severe chronic HF and in patients with HTN.
Hunt SA et al. *J Am Coll Cardiol.* 2001;38:2101–2113.

Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class

ACC/AHA HF Stage[1]	NYHA Functional Class[2]
A At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with hypertension or coronary artery disease)	None
B Structural heart disease but without symptoms of heart failure	I Asymptomatic
C Structural heart disease with prior or current symptoms of heart failure	II Symptomatic with moderate exertion
	III Symptomatic with minimal exertion
D Refractory heart failure requiring specialized interventions	IV Symptomatic at rest

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Identifying the Patient With Heart Failure

- Symptoms*
  - Exertional dyspnea or fatigue
  - Orthopnea, paroxysmal nocturnal dyspnea
- Physical findings†
  - Elevated jugular venous pressure, third heart sound, laterally displaced apical impulse, rales, edema, cardiomegaly on chest X-ray
- Assess cardiac function
  - Echocardiography or radionuclide ventriculography may be used to assess ejection fraction

*Patients may limit activity to avoid symptoms.
†Any of these findings is consistent with heart failure and LV dysfunction and may serve as a warning sign.

Types of Left Heart Failure

- Systolic dysfunction EF<40
- Diastolic dysfunction EF>50
- Both

Causes of Left Heart Failure

- CAD n(2/3 of total)
- Congestive/Dilated Cardiomyopathy
- Valve disease (often diastolic dysfunction)
- Hypertension (often diastolic dysfunction)
- Arrhythmias
- Thyrotoxicosis
- Toxic (including alcohol)

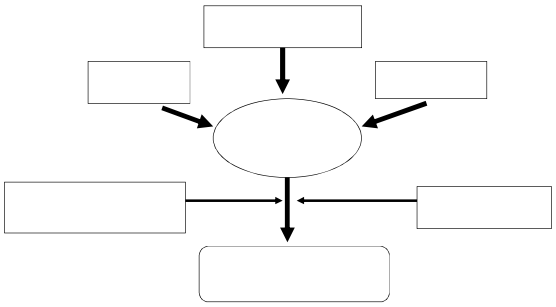
Causes of Left Heart Failure (cont.)

- Myocarditis
- Obesity
- Sarcoidosis
- Amyloidosis
- Hemochromatosis

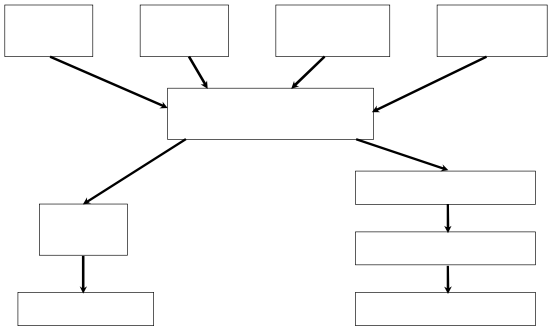
Causes of Right Heart Failure

- Left HF (can have biventricular failure)
- Pulmonary Disease
- Coronary Artery Disease
- Valve Disease

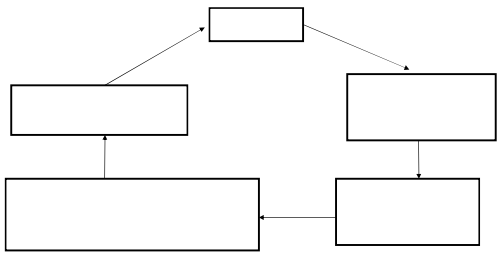
Determinants of Ventricular Function



Left Ventricular Dysfunction



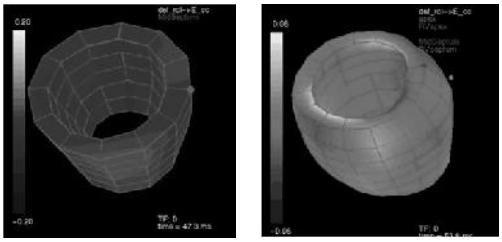
Vicious Cycle of Heart Failure



Compensatory Mechanisms

Ventricular Remodeling

Alterations in the heart's size, shape, structure, and function brought about by the chronic hemodynamic stresses experienced by the failing heart.



Curry CW, et al. Mechanical dyssynchrony in dilated cardiomyopathy with intraventricular conduction delay as depicted by 3D tagged magnetic resonance imaging. Circulation 2000 Jan 4;101(1):E2.

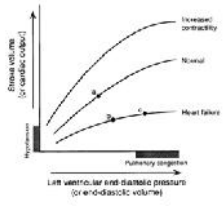
Compensatory Mechanisms

Frank-Starling Mechanism

a. At rest, no HF

b. HF due to LV systolic dysfunction

c. Advanced HF



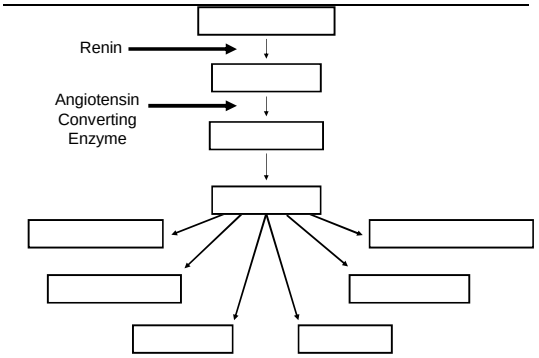
Compensatory Mechanisms

Neurohormonal Activation

Many different hormone systems are involved in maintaining normal cardiovascular homeostasis, including:

- Sympathetic nervous system (SNS)
- Renin-angiotensin-aldosterone system (RAAS)
- Vasopressin (a.k.a. antidiuretic hormone, ADH)

Compensatory Mechanisms: Renin-Angiotensin-Aldosterone (RAAS)



Neurohormonal Responses to Impaired Cardiac Performance

Initially Adaptive, Deleterious if Sustained

Response	Short-Term Effects	Long-Term Effects
Salt and Water Retention	Augments Preload	Pulmonary Congestion, Anasarca
Vasoconstriction	Maintains BP for perfusion of vital organs	Exacerbates pump dysfunction (excessive afterload), increases cardiac energy expenditure
Sympathetic Stimulation	Increases HR and ejection	Increases energy expenditure

Jaski, B, MD: Basics of Heart Failure: A Problem Solving Approach

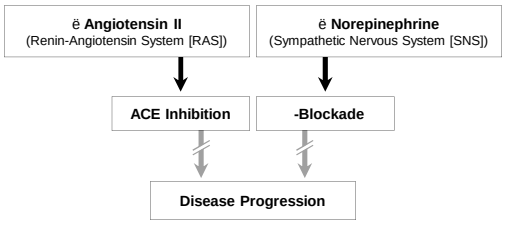
Diagnostic Tests

- Echocardiogram – systolic & diastolic function, valve disease, pericardial disease
- EKG
- CBC
- Chest X-ray
- Electrolytes
- May also include Thyroid panel, Lipids, BNP, CAD evaluation

B Type Naturetic Peptide

- Produced by cardiac ventricles
- Useful diagnostically; 98% negative predictive value & 95% accuracy
- Therapeutic value: vasodilation, decreases aldosterone and norepinephrine levels; increases diuresis and naturesis

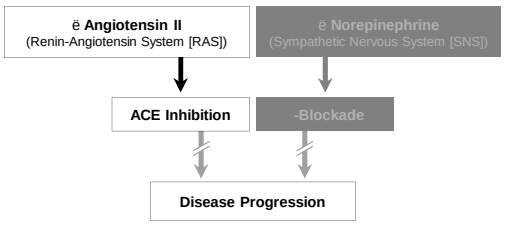
Two Systems—Two Therapies



Steering Committee and Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. *Am J Cardiol*. 1999;83(Suppl 2A):1A–38A.

Focus on the Renin-Angiotensin System

Two systems—Two therapies



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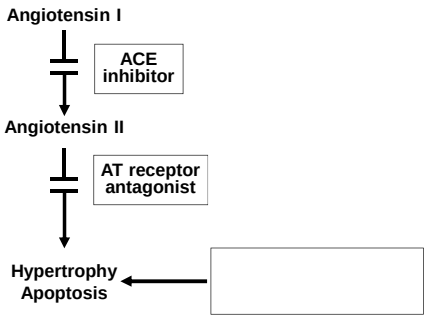
RAS Pathophysiology



Pharmacologic treatment of Systolic HF

- Systolic HF refers to those patients whose EF is < 40%
- It occurs due to a process described as remodeling
- Remodeling occurs as the myocytes respond to injury by dilating or developing hypertrophy
- As this process occurs the myocytes become more spherical in shape which leads to a fall in cardiac output

Drugs for Heart Failure

- Diuretics
- Ace Inhibitors
- Beta Blockers
- Digoxin
- Spironolactone
- Vasopeptidase Inhibitor
- Inotropes

Diuretics

Diuretics

- Used to relieve fluid retention
- May improve exercise tolerance
- Facilitate the use of other drugs indicated for heart failure
- Patients can be taught to adjust their diuretic dose based on changes in body weight
- Electrolyte depletion a frequent complication
- Should never be used alone to treat heart failure
- Higher doses of diuretics are associated with increased mortality

Diuretic Therapy (*quickly relieves Sx)*

- Loop - furosamide, Bumetanide Bumex), Torsamide (Demadex)
- Distal Tubule - metalazone (zaroxolyn), Thiazide, Spironolactone (aldactone) - newer indication & physiologic rationale

Clinical Use of Diuretics

- IV diuretics (either bolus or continuous infusion) are more potent for unstable or severe disease.
- With acute pulmonary edema with acute MI, IV furosemide induces venodilation, which may reduce cardiac filling pressures prior to the onset of diuresis
- If a patient becomes resistant to one loop diuretic, switching to a different loop diuretic may overcome the resistance
- If such strategy does not work, adding metolazone 30 minutes before a loop diuretic is usually effective

Clinical Use of Diuretics

- Sliding scale for weight gain
- Avoid volume depletion (decreased BP; BUN/creatinine ratio >30)
- Avoid NSAIDs
- Absorption variable (Demadex “vs” Furosemide)
- Watch K+ and Mg++ levels

Precautions with Diuretics

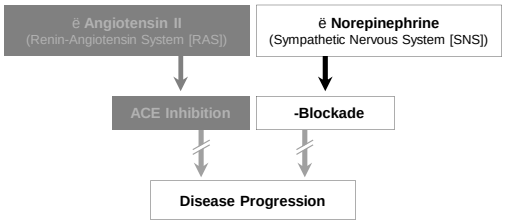
- Higher dosages of loop diuretics may lead to prerenal syndrome if overdiuresed, causing elevation in BUN, creatinine and K+
- Recheck blood presssure and electrolytes in 1 to 2 weeks
- Recheck electrolytes with use of metolazone recommended in 5 days. Usually need K+ supplement increase or addition.
- To prevent diuretic resistance , maintain patients on the lowest effective loop diuretic dosage
- A potassium-sparing diuretic can be consisered along with a loop diuretic.
- Remember, Spironolactone & Eplerenone also conserve K+

ACE Inhibitors Mechanism of Action

- Blocks conversion of angiotensin I to II
- Increases kinins and therefore increases prostaglandin synthesis
- Improves endothelial function
- Benefits therefore:
  - decrease symptoms; improve functional class,
  - decrease risk of hospitalization & death

ACE Inhibition Only Addresses Half the Problem

Two systems—Two therapies



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ACEI Side effects

•Hyperkalemia

Worsening renal insufficiency

Hypotension

ACEI

- ACEIs should be started at low doses and slowly titrated up to target dose
- Renal function and K+ should be monitored 1-2 weeks after initiating therapy or after dose increase
- If the patient cannot tolerate the target dose then intermediate doses should be used
- Abrupt withdrawal of the drug may lead to clinical deterioration
- It may take 1-2 months before the benefits of therapy are seen

Drug	Initial Daily Dose	Maximum Dose
Captopril	6.25mg TID	50mg TID
Enalapril	2.5mg BID	10-20mg BID
Lisinopril	2.5-5mg Daily	20-40mg Daily
Perindopril	2mg Daily	8-16mg Daily
Ramipril	1.25-2.5mg Daily	10mg Daily
Trandolapril	1mg Daily	4mg Daily

Morbidity and Mortality Risk Remains High in HF Patients on ACE Inhibitors Alone

- Despite the benefits of ACE inhibitors…
  - Mortality ↓ by 20%–25% (*P*<.001)
  - Death plus hospitalization ↓ by 30%–35% (*P*<.001)[1]
- …patients still require aggressive therapy because as many as:
  - 50% will die within 5 years[2]
  - 30% may be rehospitalized for CHF within 3 months[3]
  - The cost of hospitalization for HF is twice that for all forms of cancer[4]

[1]Garg R, Yusuf S. *JAMA*. 1995;273:1450–1456; [2]AHA. *2001 Heart and Stroke Statistical Update*. 2000; [3]Young JB, Mills RM. *Clinical Management of Heart Failure*. Caddo, Okla: Professional Communications, Inc. 2001:24; [4]Steering Committee and Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. *Am J Cardiol*. 1999;83(Suppl 2A):1A–39A.

Angiotensin Receptor Blockers (ARB)

- Not as thoroughly studied as ACE1
- Recommended when ACE intolerant because of cough, angioedema or anuric renal failure
- Use in combination with ACE being studied; not yet used in HF with ACE and Bblockers already in use (Val-Heft study)

ACC/AHA Guidelines on the Role of ARBs in HF

Several clinical trials with ARBs failed to show mortality benefit in heart failure

- ARBs should not be considered equivalent or superior to ACE inhibitors in the treatment of HF
- ARBs should not be used for the treatment of HF in patients who have had no prior use of an ACE inhibitor
- β-Blockers, rather than ARBs, should be added to therapy for patients with HF who are taking an ACE inhibitor until further data are available

Hunt SA et al. *J Am Coll Cardiol.* 2001;38:2101–2113.

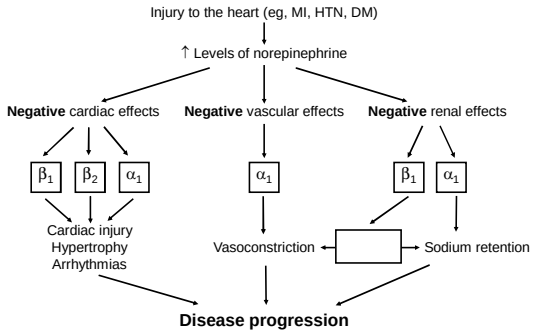
ARB's

Drug Name	Initial Dose	Maximum Dose
Candesartan	4 to 8 mg Daily	32mg Daily
Losartan	25-50mg Daily	50 to 100mg Daily
Valsartan	20 to 40 mg BID	160mg BID

ACE-I's & ARB's Together?

- There have been 2 studies looking at adding an ARB to those patients already taking an ACE-I.
- Both studies showed a decrease in hospitalization
- One study showed a mortality benefit while the other study showed no effect on mortality
- So the general thought is that you could use the two drugs together if the patient was still symptomatic on other optimal therapy
- However, the patient's BP, K+, and renal function would need to be monitored very carefully

Norepinephrine Exerts Negative Effects Through $_1$-, $_2$-, and ~$_1$-Receptors



Beta Blockers

- Currently there are 3 beta blockers approved for the management of systolic HF
  - Bisoprolol
  - Carvedilol (Coreg)
  - Sustained released metoprolol (succinate)
    - Toprol XL

Effect of -Blockade on Outcomes in Heart Failure

Study	Drug	HF Severity	Target Dosage (mg/day)	Outcome
US Carvedilol[1]	carvedilol	mild/ moderate	6.25 to 25* bid	↓65% mortality (*P*=.001)
CIBIS-II[2]	bisoprolol‡	moderate/ severe	10 qd	↓34% mortality (*P*<.0001)
MERIT-HF[3]	metoprolol succinate	mild/ moderate	200 qd	↓34% mortality (*P*=.0062)
COPERNICUS[4]	carvedilol	severe	25 bid	↓35% mortality (*P*=.0014)

*50 mg bid if >85 kg.

[1]Colucci WS et al. *Circulation*. 1996;94:2800–2806.
[2]CIBIS II Investigators and Committees. *Lancet*. 1999;353:9–13.
[3]MERIT-HF Study Group. *Lancet*. 1999;353:2001–2007.
[4]Packer M et al. *N Engl J Med*. 2001;344:1651–1658.

‡*HF NOT AN APPROVED INDICATION*

Dosing for -Blockers in Heart Failure

Adapted from *The Medical Letter*, June 26, 2000

Drug	Starting Dosage	Target Dosage
Carvedilol	3.125 mg bid	6.25 to 25 mg bid
Metoprolol CR/XL	12.5 to 25 mg qd	200 mg qd

Considerations with Beta Blocker Use

- Carvedilol, metoprolol most common. Atenolol is renally excreted
- No BB with ISA
- Start low; push diuretic if fluid retention occurs
- Fatigue usually resolves. Use with ACE generally maximized
- For symptomatic hypotension reduce diuretic then ACE and lastly, BB

Beta Blocker Side Effects

- Hypotension
- Bradycardia & heart block
- Fatigue (another frustrating symptom, that I encourage patients to try and ride out)
- Patients with reactive airway disease may not tolerate beta blockers because of the effects on their airways

Pharmacologic Management

Digoxin

- Enhances inotropy of cardiac muscle
- Reduces activation of SNS and RAAS
- Controlled trials have shown long-term digoxin therapy:
  - Reduces symptoms
  - Increases exercise tolerance
  - Improves hemodynamics
  - Decreases risk of HF progression
  - Reduces hospitalization rates for decompensated HF
  - Does not improve survival

Digoxin

- Recent clinical trials have shown that patients with HF actually have better benefit from Dig when their serum levels are kept between .5-1
- Patients with serum levels closer to 2 did not have better outcomes and the risk of toxicity is much higher
- It's also thought that over the long-term these higher levels of Dig may actually be harmful

Digoxin - DIG, PROVED & RADIANCE Trials

- Use of dig decreases overall risk of rehospitalization, no effect on mortality
- Don't push dose
- Serum level of uncertain value
- SE: arrhythmia, nausea, visual changes, confusion
- Improves symptoms and exercise tolerance

Digoxin side effects

- Bradycardia and heart blocks and lots of ugly arrhythmias
- Anorexia, Nausea, & Vomiting
- Visual disturbances, disorientation, and confusion
- These are all signs of Dig toxicity

Aldosterone Antagonists - RALES trial

- Provides long term suppression of aldosterone which may not be achieved with ACEI
- Spironolactone 12.5 to 25mg qd
- 30% reduction in death
- Raises K+ (depleted with diuretics)
- slightly improves diuresis
- 10% incidence of gynecomastia

HF Associated with Hypertension

- With preserved systolic function - primarily in elderly women;
- may be related to aging having a greater impact on diastolic function than on systolic performance
- Rate of ventricular filling decreases due in part to structural changes (fibrosis) and decline in active relaxation (due to increase in afterload)
- exacerbated by dec. in beta-adrenergic receptor density & decline in peripheral vasodilator capacity

Diastolic Dysfunction - Principles of Treatment

- Few clinical trials available; presence of comorbid conditions reasons for treatment with essentially the same drug classes
- Based on control of physiological factors (BP, HR, blood volume and myocardial ischemia)
  - increases in SBP slows myocardial relaxation
  - tach shortens vent. Filling time and CP
  - diuretics decrease circulating blood volume to decrease vent. filling pressure and pulmonary hypertension to improve breathlessness

Aldosterone

•Causes sodium and water retention

•Endothelial inflammation & dysfunction

•Increased myocardial fibrosis & tissue stiffness which causes further remodeling

•There's a significant correlation between increased aldosterone and decreased LVEF

•So blocking aldosterone may be beneficial in managing systolic HF

Side Effects of Aldosterone Antagonists

The major side effect of Aldosterone antagonists is HYPERKALEMIA

This can be very dangerous and K+ levels need to be followed closely when patients are started on Aldosterone Antagonists

Often times K+ supplements may need to be discontinued

Other side effects include diarrhea, cramping, GI upset, confusion, lethargy, gynecomastia, and rash

Aldosterone Antagonists

Drug Name	Initial Dose	Maximum Dose
Spironolactone	12.5-25mg Daily	25mg Daily or BID
Eplerenone	25mg Daily	50mg Daily

All 3 RAAS Blockers Together?

- The current recommendation is to NOT use all 3 drugs together (ACE, ARB, Aldosterone antagonist).
- This creates too high a risk for hyperkalemia and renal insufficiency.

Patient Teaching

- I tell patients that the aldosterone antagonists are being used to help decrease the remodeling in the heart and not as a diuretic.
- I find patients reluctant to take another diuretic so I emphasize that yes these drugs can cause diuresis that is not why we are using it.

Patient Teaching

•I tell patients these medications are used to help lower their BP & to slow down the progression of their disease

•Depending on the patient, I sometimes talk to them about ventricular remodeling and how these medications can actually decrease remodeling.

•These medications can be taken at anytime of the day and without regard to meals

•If they also take a beta blocker, they can take their ACE/ARB at noon or HS to avoid hypotension from both meds

Patient Teaching

- It's important for patients to understand that initially they may feel worse when a beta blocker is started and they just have to be patient
- It's also important to tell patients that these medications can't be stopped suddenly without physician supervision due to rebound hypertension and tachycardia

Isosorbide and Hydralazine

- These medications may be used in combination for those patients who are unable to take either an ACEI or an ARB
- They may also be added to the patient's regimen if the patient is still symptomatic on other recommended therapy
- This combination seems to be especially effective in African Americans

Isosorbide

- Vasodilator which may decrease dyspnea at night and during exercise and may actually improve exercise tolerance
- There is new evidence that it might also decrease LV remodeling and improve symptoms
- Side effects include headache and hypotension
- Tolerance may develop so they need a nitrate free period

Hydralazine

- Arterial vasodilator
- Used with isosorbide to promote both venous and arterial dilation
- It also helps reduce the development of nitrate tolerance
- Main side effects are GI upset
- No studies looking at the effects of hydralzaine alone in HF

Other pharmacologic agents

- Statin Medications

  If CAD or Diabetes is present achieving LDL goals is important and the use of statins may be indicated

- Anticoagulants
  - There is no indication to use anticoagulants in HF unless atrial fibrillation is present or the patient has a known thrombus
  - However, many patients with HF have atrial fibrillation and therefore should be on an anticoagulant

Other pharmacologic agents

- Anitplatelet agents
  - There is still some controversy regarding the use of ACEIs and Aspirin therapy
  - The current recommendation is that the 2 may be used together in those patients who have an indication for aspirin therapy
  - Plavix does not interfere with ACEIs and could be used in place of Aspirin for those patients with known CAD

Other pharmacologic agents

- Antiarrhythmic agents
  - Many antiarrhythmic agents suppress LV function and should not be used in patients with systolic HF
  - Some drugs that should not be used include flecainide and propafenone
  - The drug that is used most often in patients with systolic HF is amiodorone and is used for both atrial and ventricular arrhythmias
  - Multaq has a black box warning for patients with NYHA Class IV or patients with Class II-III with recent decompensation requiring

Other pharmacologic agents

- Nitrates
  - If the patient with HF also has CAD and has symptoms of angina nitrates may also improve LV function
  - Ranexa has also shown to have benefit in patients with LV dysfunction and does not lower BP

Conclusions: ACC/AHA Recommendations

- Patients at high risk for heart failure (eg, patients with HTN, CAD, DM, family history of cardiomyopathy)
  - Treat systolic and diastolic hypertension according to guidelines
    - An appropriate HTN regimen frequently consists of several drugs used in combination
    - When such a HTN regimen is devised, drugs that are useful for the treatment of both HTN and HF are preferred (eg, diuretics, ACE inhibitors, and β-blockers)
  - Encourage smoking cessation; treat lipid disorders; discourage alcohol intake
- Patients with heart failure
  - Treat with ACE inhibition* and β-blockade*
  - Diuretics and digitalis as required
  - Withdraw drugs known to adversely affect patient's clinical status

*Unless contraindicated.

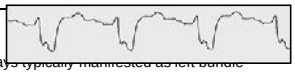
Clinical Consequences of IVCDs

- Abnormalities in electromechanical coupling which can be expressed as a wide QRS
  - QRS duration increases with heart failure progression.[1]
- Prolonged QRS is an independent or contributing risk factor for mortality in HF patients[2,3,4,5]

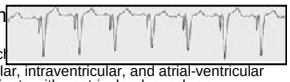
[1] Wilensky RL, Yudelman P, Cohen AI, Fletcher RD, Atkinson J, Virmani R, Roberts WC.
[2] Shamin W, Francis DP, Yousufuddin M, et al.
[3] Aaronson K, Swartz J, Chen T-M, et al.
[4] Xiao H, Ror C, Fujimoto S, Gibson D.
[5] Schoeller R, Andresen D, et al.

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 synch
    - Modification of interventricular, intraventricular, and atrial-ventricular activation sequences in patients with ventricular dysynchrony
    - Complement to optimal medical therapy

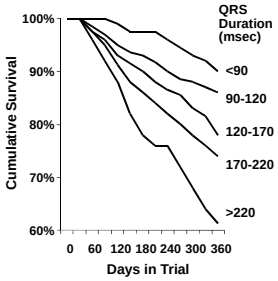


[1] Tavazzi L. Eur Heart J 2000;21:1211-1214

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].

Clinical Trials

- AVID,CIDS,CASH – evaluated persons who had survived VF or hemodynamically compromising VT in the setting of LVD, or syncopy with inducible VT at EP testing. ICD conferred a survival benefit

Clinical Trials

- MADIT & MUSTT – primary prevention trials (SCD) – improved survival in patients with CAD, LVFx, sustained VT & inducible VT
- MADIT II trial – reported improved survival in pts with prior MI & LVEF $\leq$ 30 who received an ICD – decreased mortality by 31%
- DEFINITE –defibs in nonischemic cardiomyopathy – ICD decreased mortality by 34%
- *SCD-Heft trial designed to evaluate mortality benefit in patients with either ischemic or nonischemic heart failure

Hypothesis and Primary Endpoint

- To determine, by intention-to-treat analysis, if amiodarone or a conservatively programmed shock-only ICD reduces all-cause mortality compared to placebo* in patients with either ischemic or non-ischemic NYHA Class II and III CHF and EF ≤ 35%.

*Double-blind for drug therapy

Enrollment Scheme

DCM ± CAD and CHF

↓

EF ≤ 35%

↓

NYHA Class II or III

↓

6 minute walk, Holter

↓

R

Placebo Amiodarone ICD

Study Drug Dosing

- Outpatient administration
- < 800 mg qd for week 1
- < 400 mg qd for weeks 2–4
- Chronic dose is weight dependent
  - 200mg/d if < 150 lbs
  - 300mg/d if 150-200 lbs
  - 400mg/d if > 200 lbs

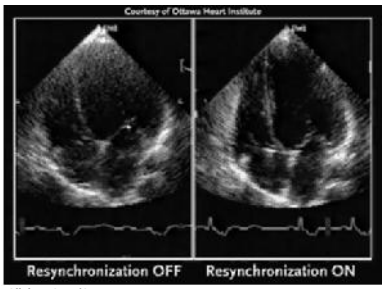
SCD-HeFT: Conclusions

- In class II or III CHF patients with EF ≤ 35% on good background drug therapy, the mortality rate for placebo-controlled patients is 7.2% per year over 5 years
- Simple, shock-only ICDs decrease mortality by 23%
- Amiodarone, when used as a primary preventative agent, does not improve survival

Discussion

- Should all patients with EF ≤ .35 have an ICD implant?
- Are there subgroups who benefit (or not benefit)?
- Does this support the use of CRT-D over CRT therapy?
- Can our health care system afford this?

Clinical Consequences of Ventricular Dysynchrony

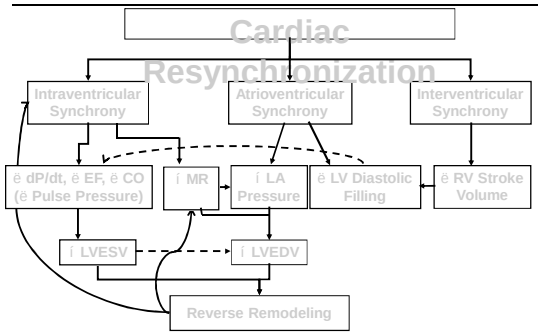


Click to Start/Stop

- 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]

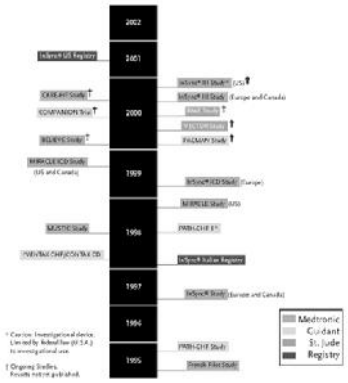
[1] Grines CL, Bashore TM, Boudoulas H, et al. Circulation 1989;79:845-853.
[2] Xiao, HB, Lee CH, Gibson DG. Br Heart J 1991;66:443-447.
[3] Xiao HB, Brecker SJD, Gibson DG. Br Heart J 1992;68:403-407.
[4] Yu C-M, Chau E, Sanderson JE, et al. Circulation. 2002;105:438-445.

Summary of Proposed Mechanisms



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

HF and CRT Clinical Studies – Observational and Randomized



CRT Therapy Trials

- PATH-CHF I, II, MUSTIC, &MIRACLE trials – functional benefits of CRT
- InSync (MIRACLE) ICD and the Contak CD trials – demonstrated that CRT provided functional improvements (QOL, functional status, & exercise capacity) comparable to the CRT benefits observed in the non-ICD patients
- COMPANION – CRT-D with OMRx decreased mortality aby 36% compared with OMRx alone; CRT with OMRx decreased mortality by 24% compared with OMRx alone

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 á 0.05)
é 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
[5] Abraham W, Fisher W, Smith A, et al. N Engl J Med. 2002;346:1845-1853
[6] Leon A. NASPE Scientific Sessions – Late Breaki
Clinical Trials. May 2002; Medtronic Inc. data on fi

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)	+	é	
MIRACLE[5] (n=453)	+	+	+
MIRACLE ICD[6] (n=364)	é	+	+

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

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)	é	é	é LVEDD,LVESD é Filling Time
MIRACLE[5] (n=453)	+	+	+ LVEDD, + LVEDV, LVESV
MIRACLE ICD[6] (n=362)	é	+	+ LVESV, + LVEDV

+ Statistically significant improvement with CRT (p á 0.05)
é 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
[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

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)	+	+	+	é

+ Statistically significant improvement with CRT (p á 0.05)
é 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

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

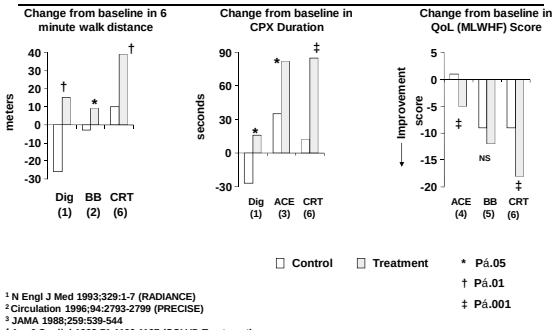
MUSTIC[2]
- Sinus Rhythm Group: 7 times fewer hospitalizations for HF (12 month F/U)
- AF Group: 4 times fewer hospitalizations for HF (12 m/fu)

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

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



[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

Trials Summary

- CRT when combined with optimal medical therapy for HF is safe and improves cardiac performance
- Resynchronization therapy improves QOL and functional capacity and reduces symptoms for patients with HF who have a prolonged QRS
- When CRT is partnered with ICD therapies more lives are saved as patients are also protected from death due to VT/VF

Cardiac Resynchronization Therapy

Patient and Device Selection, Implant and Follow-up Overview

Indications for the Medtronic InSync® Cardiac Resynchronization System

- Medtronic's InSync 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 ≥ 130 ms
  - LV ejection fraction ≤ 35%
  - Symptomatic despite stable, optimal medical

Indications for the Medtronic InSync® ICD Cardiac Resynchronization System

- Medtronic's InSync 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 ≥ 130 ms
  - LV ejection fraction ≤ 35%
  - Symptomatic despite stable, optimal medical therapy

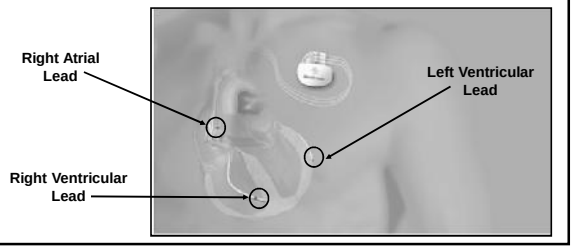
Implant Process Overview

- 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

Achieving Cardiac Resynchronization

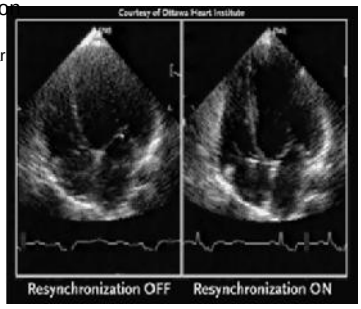
Mechanical Goal: Atrial-synchronized bi-ventricular pacing

- 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



Achieving Cardiac Resynchronization

- Improved Contraction Pattern
  - Organized ventricular activation sequence



Courtesy of Ottawa Heart Institute

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

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.

Case Studies

The results presented in these case studies are specific to these individual patients. Patient results will vary, not every response is the same.

Case Study: Ischemic Cardiomyopathy

Patient:

- 57 year-old white male
- Ischemic cardiomyopathy
- NYHA Class III heart failure

Cardiovascular History/Diagnostic Evaluation:

- **Anterior myocardial infarction, 1995. Cardiac catheterization - single vessel coronary artery disease, S/P failed-PTCA (balloon angioplasty) with emergency coronary artery bypass graft surgery 1995.**
- **Aortic valve replacement 1995.**
- **Echo, Nov 1998 – Severe LV dysfunction, EF less than 20%. LV dilatation.**
- **ECG, Nov 1998 – asymptomatic sinus bradycardia, 55 beats per minute. RBBB. QRS duration 152 msec.**
- **Right hemispheric CVA, 1998.**
- **Hyperlipidemia.**
- **No indication for pacemaker or ICD; No history of atrial arrhythmias**

Courtesy of Dr. Eric Burton, Southwest Florida Heart Group, Fort Myers

Case Study: Ischemic Cardiomyopathy (continued)

Baseline Cardiac Medications:

- **ACE inhibitor: lisinopril 20 mg once per day**
- **Beta blocker: carvedilol 25 mg twice daily**
- **Diuretic: furosemide 40 mg twice daily**
- **Digoxin 0.25 mg once per day**
- **Nitrate: isosorbide mononitrate 30 mg once per day**
- **Aspirin 81 mg once per day**
- **Anticoagulant: warfarin sodium (as directed).**
- **Lipid lowering: atorvastatin calcium 10 mg once per day**

Cardiac Resynchronization Therapy:

- **The patient received an InSync cardiac resynchronization device (InSync Model 8040) Nov 1998 while enrolled in the MIRACLE trial.**
- **The patient was randomized to the control "OFF" arm and began receiving cardiac resynchronization therapy three months later in Feb 1999*.**

***Patient was enrolled in the initial phase in which patients were randomized for three months**

Courtesy of Dr. Eric Burton, Southwest Florida Heart Group, Fort Myers

Case Study: Ischemic Cardiomyopathy (continued)

Cardiac Resynchronization Therapy Results:

	Baseline (Nov 1998)	12-Month Evaluation after Implant (Nov 1999)
Quality of Life Score	65	50
NYHA Class	III	II
Six-Minute Walk	319 meters	391 meters
Peak VO_2	12.2 ml/kg/min	13.9 ml/kg/min
Peak Exercise Time	619 seconds	702 seconds
EF (core lab calc)	23%	28%
QRS Duration	160 ms	120 ms
Symptoms	Unable to walk room-to-room, unable to carry on daily activities; sleeping average of 22 hours a day.	Walks at least one mile a day, remodeling home, sleeps 6-8 hours a night, working part-time, and recently helped build a mission church in Nicaragua.

Courtesy of Dr. Eric Burton, Southwest Florida Heart Group, Fort Myers

Case Study: Non-Ischemic Cardiomyopathy

Patient:

- 71-year-old white female
- Idiopathic dilated cardiomyopathy
- NYHA Class III heart failure

Cardiovascular History/Diagnostic Evaluation:

- **Cardiac catheterization, Jan 2000 - global hypokinesis with EF 25-30%, normal LV filling pressures. Luminal coronary atherosclerosis.**
- **Echo, Jan 2000 - left atrial size 3.6 cm. Dilated left ventricle with LVEDD 58 mm. EF 30-35%. Anterior wall akinetic, no significant valvular abnormalities.**
- **ECG, March 2000 - normal sinus rhythm, left axis deviation, LBBB, QRS 160 msec.**
- **Hyperlipidemia**
- **No indication for pacemaker or ICD; No history of atrial arrhythmias**

Courtesy of Dr. David DeLurgio, Crawford Long Hospital, Atlanta, G

Case Study: Non-Ischemic Cardiomyopathy (continued)

Baseline Cardiac Medications:

- **ACE inhibitor: enalapril maleate 10 mg once per day**
- **Beta blocker: carvedilol 6.25 mg once per day**
- **Diuretic: furosemide 40 mg once per day**
- **Digoxin 0.125 mg once per day**
- **Aspirin 81 mg once per day**
- **Potassium replacement: 20 mEq once per day**

Cardiac Resynchronization Therapy:

- **The patient received an InSync cardiac resynchronization device (InSync Model 8040) March 2000 while enrolled in the MIRACLE trial.**
- **The patient was randomized to the control "OFF" group and began receiving cardiac resynchronization therapy six months after the implant.**

Courtesy of Dr. David DeLurgio, Crawford Long Hospital, Atlanta, G

Case Study: Non-Ischemic Cardiomyopathy

Cardiac Resynchronization Therapy Results:

	Baseline (March 2000)	12-Month Evaluation after Implant (March 2001)
Quality of Life Score	82	4
NYHA Class	III	I
Six-Minute Walk	259 meters	335 meters
Peak VO_2	15.7 ml/kg/min	16.39 ml/kg/min
Peak Exercise Time	215 seconds	478 seconds
EF (core lab calc)	34%	39%
QRS Duration	160 ms	160 ms
Symptoms	Exertional dyspnea with chest discomfort, extreme fatigue with any exercise, palpitations, 2-pillow orthopnea, paroxysmal nocturnal dyspnea, inability to do housework.	Able to do daily housework, laundry, cooking, vacuuming without shortness of breath. No limitation in activity and regularly goes dancing.

Courtesy of Dr. David DeLurgio, Crawford Long Hospital, Atlanta, G

Multidimensional Patient Care with InSync Sentry CRT-D

- **Cardiac Resynchronization Therapy (CRT)**
- **Protection from sudden cardiac death (Defibrillator)**
- **Continuous tracking of:**
  - **Fluid status**
  - **Frequency or quantity of AT/AF**
  - **Activity**
  - **Heart rate variability**
  - **Day and night heart rate**
  - **Percent pacing**

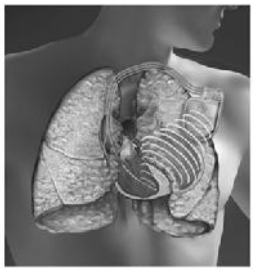
OptiVol ™ Fluid Status Monitoring using Intrathoracic Impedance

Definition of Impedance

Resistance to flow of electrical current measured in Ohms

Worsening Heart Failure ⇨ **Pulmonary Congestion** ⇨ **Decreased Intrathoracic Electrical Impedance**

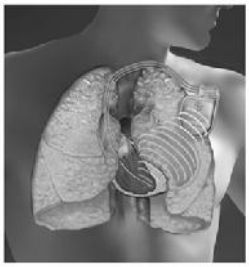
Concept



Impedance

Normal Lungs
As the lungs clear, intrathoracic

Concept

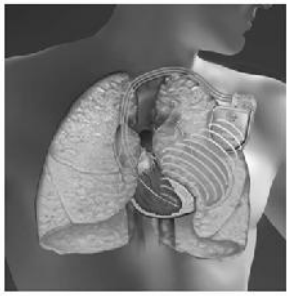


Impedance

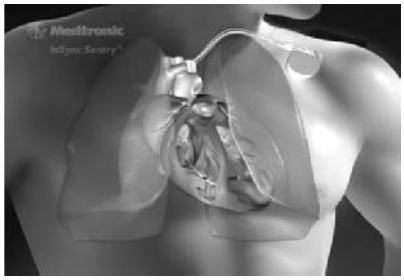
Pulmonary Congestion
As fluid accumulates in the lu
impedance decreases

OptiVol Ē Intrathoracic Impedance Measurements

- The impedance is measured from the device can to the RV Coil every 20 minutes from noon until 5 pm
- Identical impedance measurement to current daily subthreshold measurement
- No manual measurement functionality available



Intrathoracic Impedance Measured with InSync Sentry

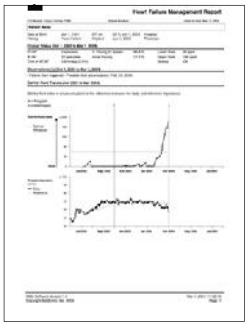


OptiVol™ Fluid Status Monitoring

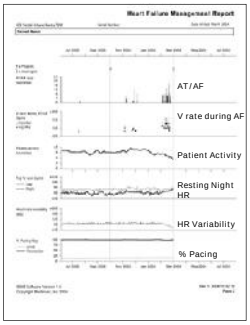
- **Tracks intrathoracic impedance changes**
  - Compares Daily Impedance to the patient's own Reference Impedance
  - Tracks fluid accumulation over time
  - Allows programming to a threshold that is clinically relevant for the patient
- **Algorithm designed to detect with good sensitivity while minimizing false positives**

Insight into Patient Status

OptiVol Fluid Trends



Additional Trends to Assess Patient Status



Summary – Patient Selection Criteria

- Cardiac Resynchronization therapy(MADIT II, Miracle,etc)
- Moderate to severe HF (NYHA III/IV
- QRS width ≥ 130ms
- LVEF ≤ 35%
- Symptomatic despite sable, OMRx
- ICD (SCD-Heft)
- LVEF ≤ 35%
- Class II or III ischemic or non-ischemic cardiomyopathy

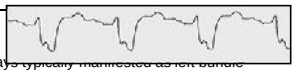
Clinical Consequences of IVCDs

- Abnormalities in electromechanical coupling which can be expressed as a wide QRS
  - QRS duration increases with heart failure progression.[1]
- Prolonged QRS is an independent or contributing risk factor for mortality in HF patients[2,3,4,5]

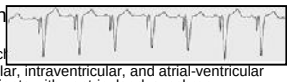
[1] Wilensky RL, Yudelman P, Cohen AI, Fletcher RD, Atkinson J, Virmani R, Roberts WC.
[2] Shamin W, Francis DP, Yousufuddin M, et al.
[3] Aaronson K, Swartz J, Chen T-M, et al.
[4] Xiao H, Ror C, Fujimoto S, Gibson D.
[5] Schoeller R, Andresen D, et al.

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 synch
    - Modification of interventricular, intraventricular, and atrial-ventricular activation sequences in patients with ventricular dysynchrony
    - Complement to optimal medical therapy

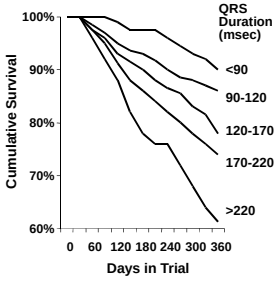


[1] Tavazzi L. Eur Heart J 2000;21:1211-1214

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].

Clinical Trials

- AVID,CIDS,CASH – evaluated persons who had survived VF or hemodynamically compromising VT in the setting of LVD, or syncopy with inducible VT at EP testing. ICD conferred a survival benefit

Clinical Trials

- MADIT & MUSTT – primary prevention trials (SCD) – improved survival in patients with CAD, LVFx, sustained VT & inducible VT
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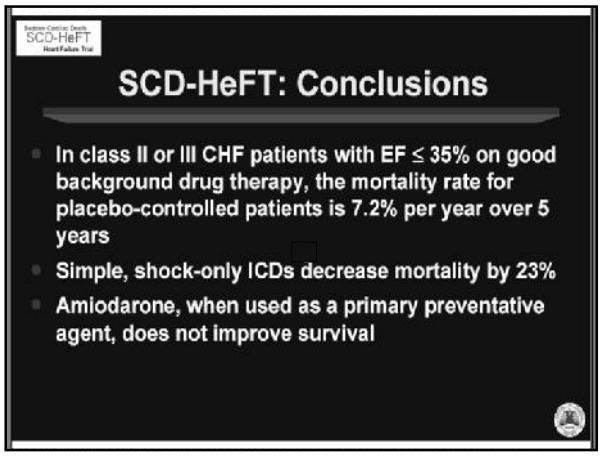
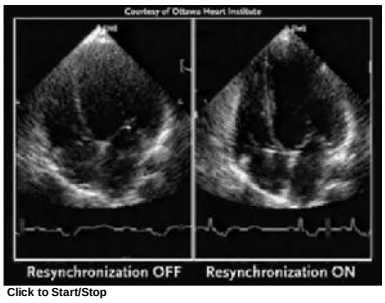


Discussion

- Should all patients with EF ≤ .35 have an ICD implant?
- Are there subgroups who benefit (or not benefit)?
- Does this support the use of CRT-D over CRT therapy?
- Can our health care system afford this?

Clinical Consequences of Ventricular Dysynchrony

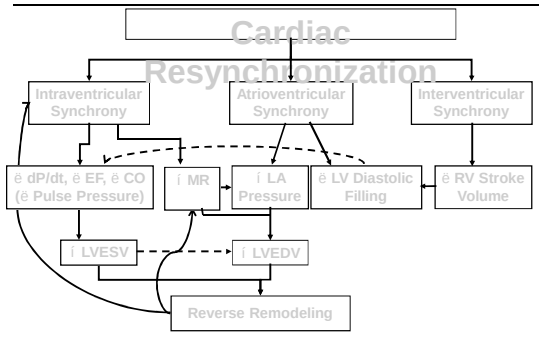


Click to Start/Stop

- 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]

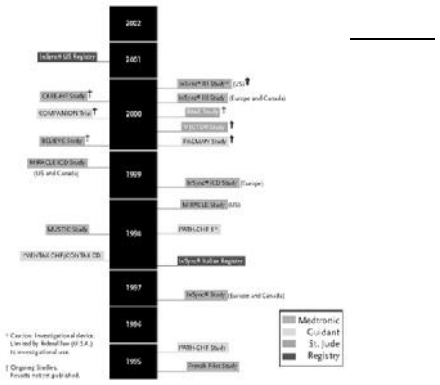
[1] Grines CL, Bashore TM, Boudoulas H, et al. Circulation 1989;79:845-853.
[2] Xiao, HB, Lee CH, Gibson DG. Br Heart J 1991;66:443-447.
[3] Xiao HB, Brecker SJD, Gibson DG. Br Heart J 1992;68:403-407.
[4] Yu C-M, Chau E, Sanderson JE, et al. Circulation. 2002;105:438-445.

Summary of Proposed Mechanisms



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

HF and CRT Clinical Studies – Observational and Randomized



CRT Therapy Trials

- PATH-CHF I, II, MUSTIC, &MIRACLE trials – functional benefits of CRT
- InSync (MIRACLE) ICD and the Contak CD trials – demonstrated that CRT provided functional improvements (QOL, functional status, & exercise capacity) comparable to the CRT benefits observed in the non-ICD patients
- COMPANION – CRT-D with OMRx decreased mortality aby 36% compared with OMRx alone; CRT with OMRx decreased mortality by 24% compared with OMRx alone

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 á 0.05)
é 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
[5] Abraham W, Fisher W, Smith A, et al. N Engl J Med. 2002;346:1845-1853
[6] Leon A. NASPE Scientific Sessions – Late Breaki Clinical Trials. May 2002; Medtronic Inc. data on fi

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)	+	é	
MIRACLE[5] (n=453)	+	+	+
MIRACLE ICD[6] (n=364)	é	+	+

+ Statistically significant improvement with CRT (p á 0.05)
é 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
[5] Abraham W, Fisher W, Smith A, et al. N Engl J Med. 2002;346:1845-1853
[6] Leon A. NASPE Scientific Sessions – Late Breakin Clinical Trials. May 2002; Medtronic Inc., data on f

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)	é	é	é LVEDD,LVESD é Filling Time
MIRACLE[5] (n=453)	+	+	+ LVEDD, + LVEDV, LVESV
MIRACLE ICD[6] (n=362)	é	+	+ LVESV, + LVEDV

+ Statistically significant improvement with CRT (p á 0.05)
é 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
[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

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

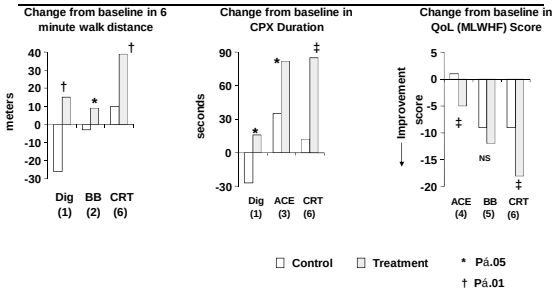
MUSTIC[2]
- Sinus Rhythm Group: 7 times fewer hospitalizations for HF (12 month F/U)
- AF Group: 4 times fewer hospitalizations for HF (12 m/fu)

MIRACLE[3]
- Number of HF-hospitalizations significantly reduced (p = 0.02)

MIRACLE ICD[4]
- Study did not meet HF-hospitalizations significantly reduced (p = 0.25)

[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

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



[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

Trials Summary

- CRT when combined with optimal medical therapy for HF is safe and improves cardiac performance
- Resynchronization therapy improves QOL and functional capacity and reduces symptoms for patients with HF who have a prolonged QRS
- When CRT is partnered with ICD therapies more lives are saved as patients are also protected from death due to VT/VF

Cardiac Resynchronization Therapy

Patient and Device Selection, Implant and Follow-up Overview

Indications for ICD

- moderate to severe heart failure (NYHA Class III/IV)
- LV ejection fraction ≤ 35%
- Symptomatic despite stable, optimal medical therapy

Indications ® ICD Cardiac Resynchronization

- :
  - Standard ICD indication
  - Moderate to severe heart failure (NYHA Class III/IV)
  - QRS ≥ 130 ms
  - LV ejection fraction ≤ 35%
  - Symptomatic despite stable, optimal medical therapy

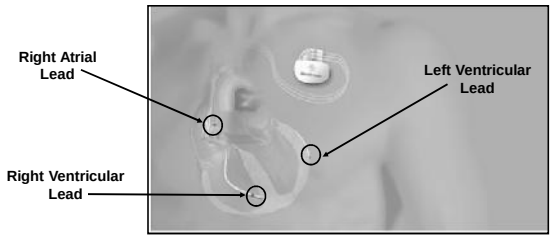
Implant Process Overview

- 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

Achieving Cardiac Resynchronization

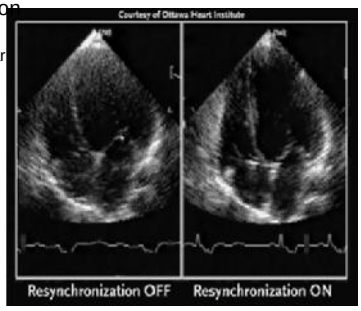
Mechanical Goal: Atrial-synchronized bi-ventricular pacing

- 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



Achieving Cardiac Resynchronization

- Improved Contraction Pattern
  - Organized ventricular activation sequence



Courtesy of Ottawa Heart Institute

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

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.

Case Studies

The results presented in these case studies are specific to these individual patients. Patient results will vary, not every response is the same.

Case Study: Ischemic Cardiomyopathy

Patient:

- 57 year-old white male
- Ischemic cardiomyopathy
- NYHA Class III heart failure

Cardiovascular History/Diagnostic Evaluation:

- **Anterior myocardial infarction, 1995. Cardiac catheterization - single vessel coronary artery disease, S/P failed-PTCA (balloon angioplasty) with emergency coronary artery bypass graft surgery 1995.**
- **Aortic valve replacement 1995.**
- **Echo, Nov 1998 – Severe LV dysfunction, EF less than 20%. LV dilatation.**
- **ECG, Nov 1998 – asymptomatic sinus bradycardia, 55 beats per minute. RBBB. QRS duration 152 msec.**
- **Right hemispheric CVA, 1998.**
- **Hyperlipidemia.**
- **No indication for pacemaker or ICD; No history of atrial arrhythmias**

Courtesy of Dr. Eric Burton, Southwest Florida Heart Group, Fort Myers

Case Study: Ischemic Cardiomyopathy (continued)

Baseline Cardiac Medications:

- **ACE inhibitor: lisinopril 20 mg once per day**
- **Beta blocker: carvedilol 25 mg twice daily**
- **Diuretic: furosemide 40 mg twice daily**
- **Digoxin 0.25 mg once per day**
- **Nitrate: isosorbide mononitrate 30 mg once per day**
- **Aspirin 81 mg once per day**
- **Anticoagulant: warfarin sodium (as directed).**
- **Lipid lowering: atorvastatin calcium 10 mg once per day**

Cardiac Resynchronization Therapy:

- **The patient received an InSync cardiac resynchronization device (InSync Model 8040) Nov 1998 while enrolled in the MIRACLE trial.**
- **The patient was randomized to the control "OFF" arm and began receiving cardiac resynchronization therapy three months later in Feb 1999*.**

***Patient was enrolled in the initial phase in which patients were randomized for three months**

Courtesy of Dr. Eric Burton, Southwest Florida Heart Group, Fort Myers

Case Study: Ischemic Cardiomyopathy (continued)

Cardiac Resynchronization Therapy Results:

	Baseline (Nov 1998)	12-Month Evaluation after Implant (Nov 1999)
Quality of Life Score	65	50
NYHA Class	III	II
Six-Minute Walk	319 meters	391 meters
Peak VO_2	12.2 ml/kg/min	13.9 ml/kg/min
Peak Exercise Time	619 seconds	702 seconds
EF (core lab calc)	23%	28%
QRS Duration	160 ms	120 ms
Symptoms	Unable to walk room-to-room, unable to carry on daily activities; sleeping average of 22 hours a day.	Walks at least one mile a day, remodeling home, sleeps 6-8 hours a night, working part-time, and recently helped build a mission church in Nicaragua.

Courtesy of Dr. Eric Burton, Southwest Florida Heart Group, Fort Myers

Case Study: Non-Ischemic Cardiomyopathy

Patient:

- 71-year-old white female
- Idiopathic dilated cardiomyopathy
- NYHA Class III heart failure

Cardiovascular History/Diagnostic Evaluation:

- **Cardiac catheterization, Jan 2000 - global hypokinesis with EF 25-30%, normal LV filling pressures. Luminal coronary atherosclerosis.**
- **Echo, Jan 2000 - left atrial size 3.6 cm. Dilated left ventricle with LVEDD 58 mm. EF 30-35%. Anterior wall akinetic, no significant valvular abnormalities.**
- **ECG, March 2000 - normal sinus rhythm, left axis deviation, LBBB, QRS 160 msec.**
- **Hyperlipidemia**
- **No indication for pacemaker or ICD; No history of atrial arrhythmias**

Courtesy of Dr. David DeLurgio, Crawford Long Hospital, Atlanta, G

Case Study: Non-Ischemic Cardiomyopathy (continued)

Baseline Cardiac Medications:

- **ACE inhibitor: enalapril maleate 10 mg once per day**
- **Beta blocker: carvedilol 6.25 mg once per day**
- **Diuretic: furosemide 40 mg once per day**
- **Digoxin 0.125 mg once per day**
- **Aspirin 81 mg once per day**
- **Potassium replacement: 20 mEq once per day**

Cardiac Resynchronization Therapy:

- **The patient received an InSync cardiac resynchronization device (InSync Model 8040) March 2000 while enrolled in the MIRACLE trial.**
- **The patient was randomized to the control "OFF" group and began receiving cardiac resynchronization therapy six months after the implant.**

Courtesy of Dr. David DeLurgio, Crawford Long Hospital, Atlanta, G

Case Study: Non-Ischemic Cardiomyopathy

Cardiac Resynchronization Therapy Results:

	Baseline (March 2000)	12-Month Evaluation after Implant (March 2001)
Quality of Life Score	82	4
NYHA Class	III	I
Six-Minute Walk	259 meters	335 meters
Peak VO_2	15.7 ml/kg/min	16.39 ml/kg/min
Peak Exercise Time	215 seconds	478 seconds
EF (core lab calc)	34%	39%
QRS Duration	160 ms	160 ms
Symptoms	Exertional dyspnea with chest discomfort, extreme fatigue with any exercise, palpitations, 2-pillow orthopnea, paroxysmal nocturnal dyspnea, inability to do housework.	Able to do daily housework, laundry, cooking, vacuuming without shortness of breath. No limitation in activity and regularly goes dancing.

Courtesy of Dr. David DeLurgio, Crawford Long Hospital, Atlanta, G

Multidimensional Patient Care with InSync Sentry CRT-D

- **Cardiac Resynchronization Therapy (CRT)**
- **Protection from sudden cardiac death (Defibrillator)**
- **Continuous tracking of:**
  - **Fluid status**
  - **Frequency or quantity of AT/AF**
  - **Activity**
  - **Heart rate variability**
  - **Day and night heart rate**
  - **Percent pacing**

Summary – Patient Selection Criteria

- Cardiac Resynchronization therapy(MADIT II, Miracle,etc)
- Moderate to severe HF (NYHA III/IV
- QRS width ≥ 130ms
- LVEF ≤ 35%
- Symptomatic despite sable, OMRx
- ICD (SCD-Heft)
- LVEF ≤ 35%
- Class II or III ischemic or non-ischemic cardiomyopathy