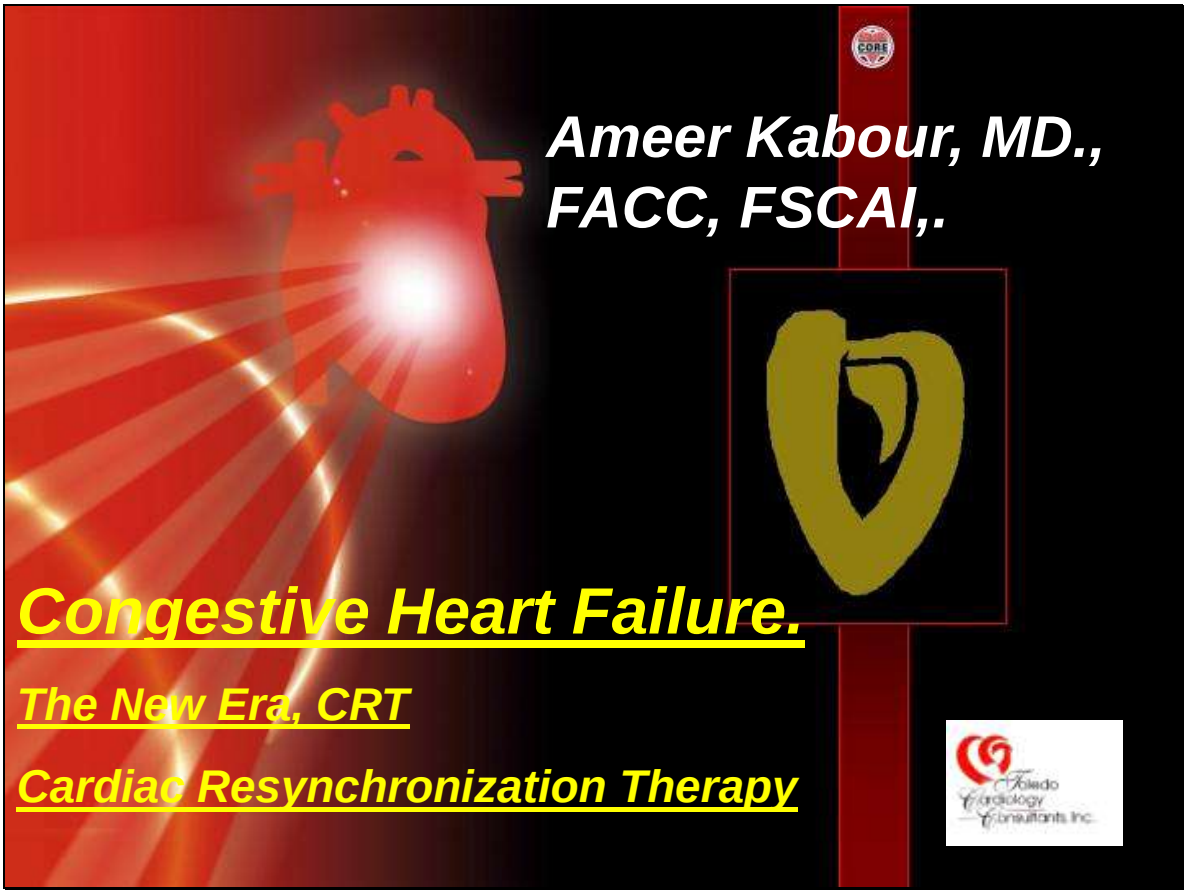
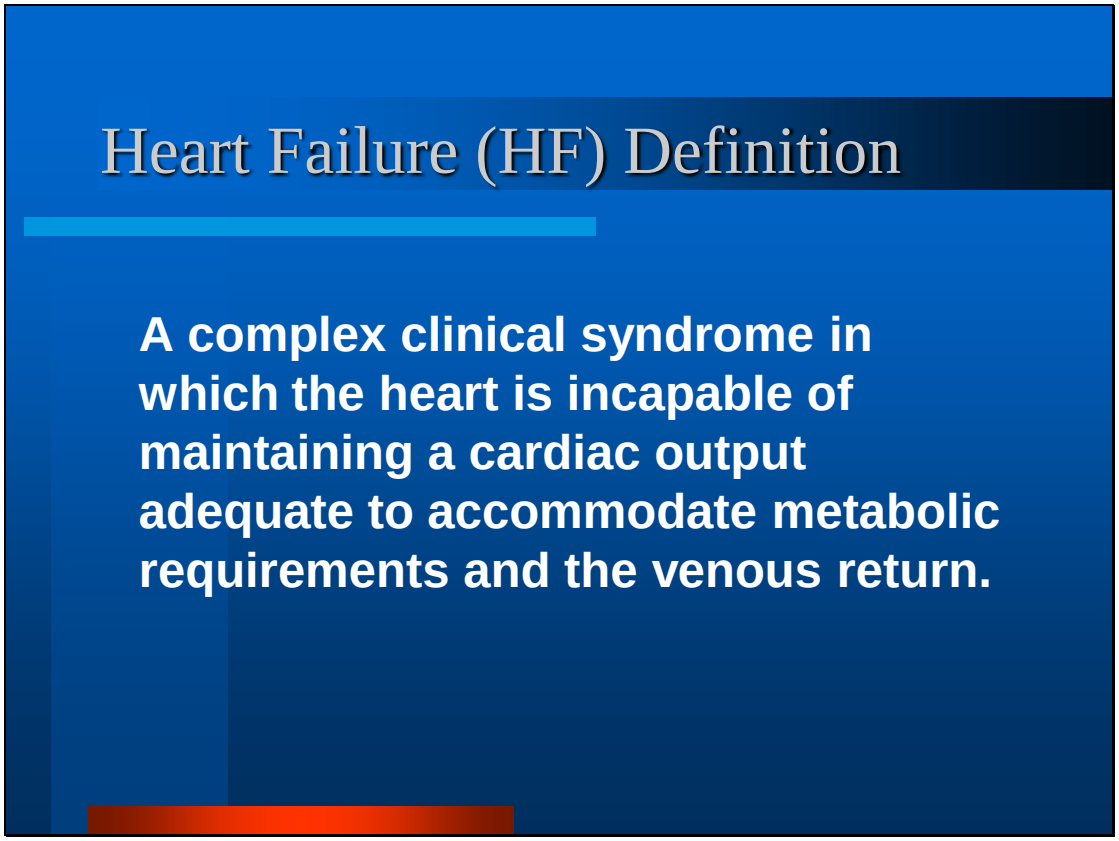
Slide 1


Ameer Kabour, MD.,
FACC, FSCAI,.
Congestive Heart Failure.
The New Era, CRT
Cardiac Resynchronization Therapy
Toledo Cardiology Consultants Inc.

Slide 2

Part I:
Etiology and Pathophysiology of Heart Failure

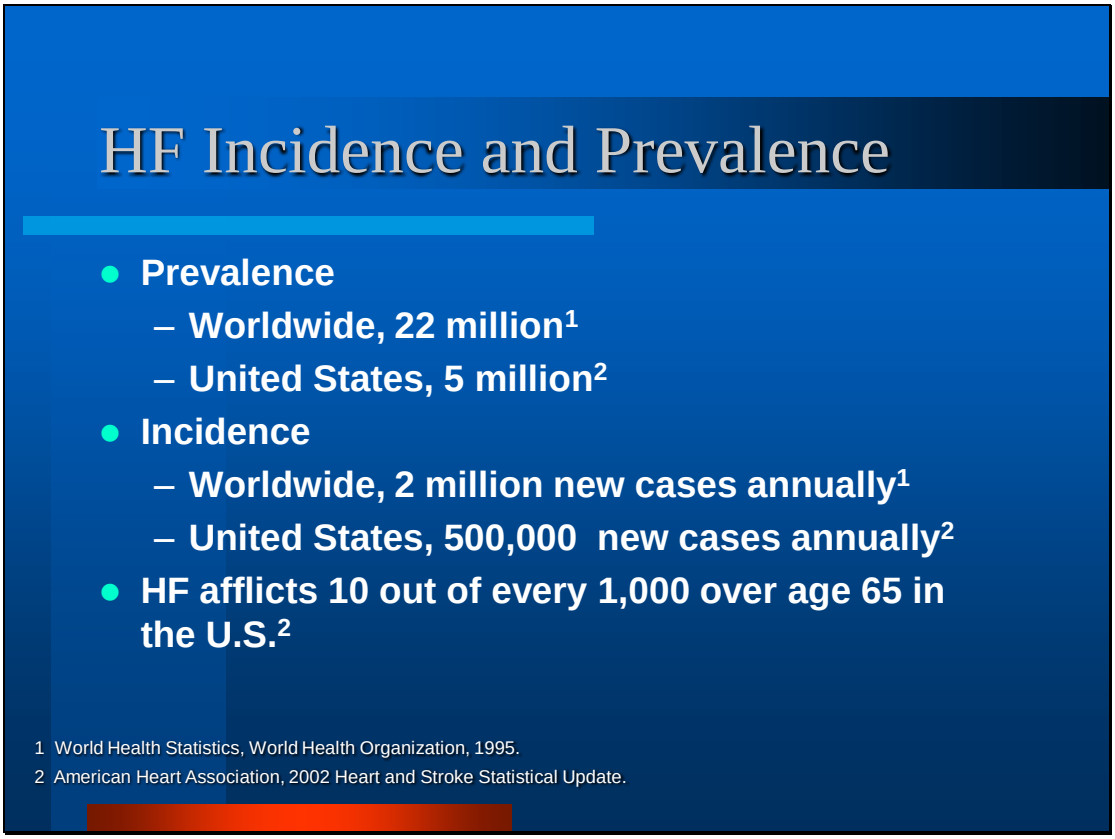
Slide 3



Under normal circumstances, the heart accepts blood at low filling pressures during diastole and then propels it forward at higher pressures during systole. A variety of disorders can impair the ability of the heart to meet the metabolic demands of the body. Heart failure (HF) can be defined as a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

Today, substantial healthcare resources are used to treat heart failure patients, yet heart failure patients continue to have a poor quality of life and an unacceptably high mortality rate. According to the American Heart Association, the five-year mortality rate for heart failure patients is about 50%.

Slide 4

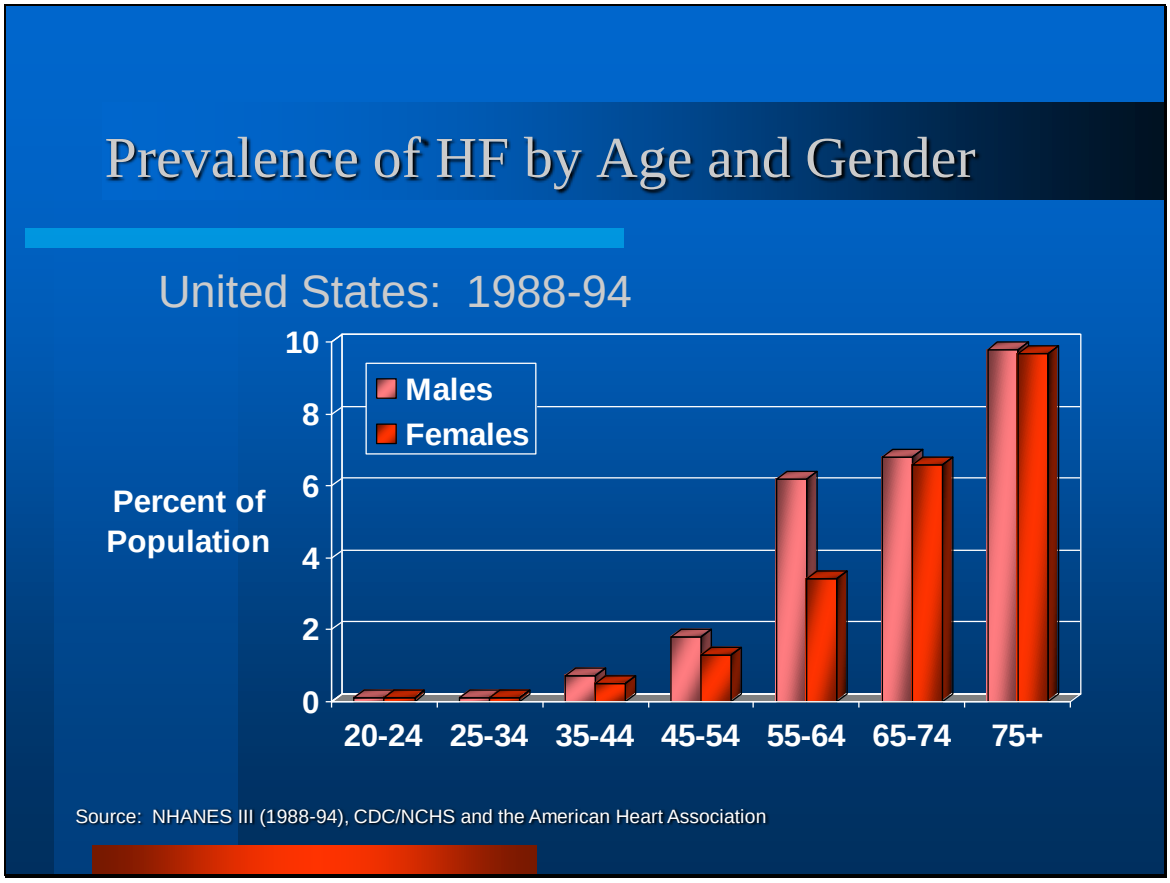


Heart failure is estimated to afflict more than 22 million people worldwide with an estimated 2 million new cases diagnosed annually.[1]
In the United States it is estimated that 5 million people have HF, with 10 out of every 1,000 over the age of 65 being afflicted.[2]
It is the only major cardiovascular disorder that is increasing in incidence and prevalence.
Other Heart Failure Statistics:

- HF patients take an average of six medications[3]
- 78% of HF patients have had at least two hospital admissions per year[3]
- Cost of HF in the U.S. is estimated to be between $10 billion and $38 billion annually[4]
- 5-year survival rate for all NYHA classes estimated at 50%[2]

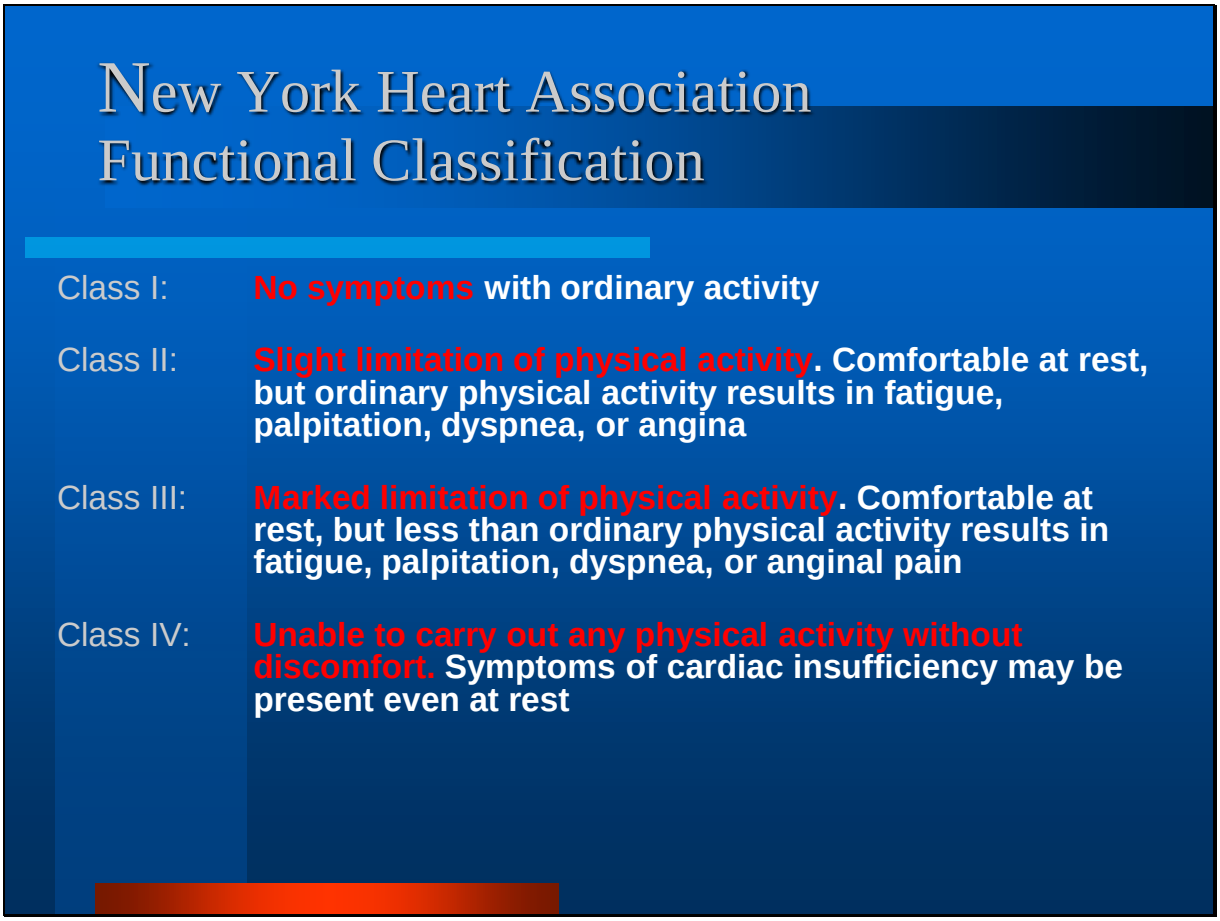
1 World Health Statistics, World Health Organization, 1995.
2 American Heart Association, 2002 Heart and Stroke Statistical Update
3 English M and Mastream M. *Crit Care Nurse Q* 1995;18:1-6.
4 Havranek EP, Abraham WT, *The Healthcare Economics of Heart Failure* 1998; 14:10-18.

Slide 5



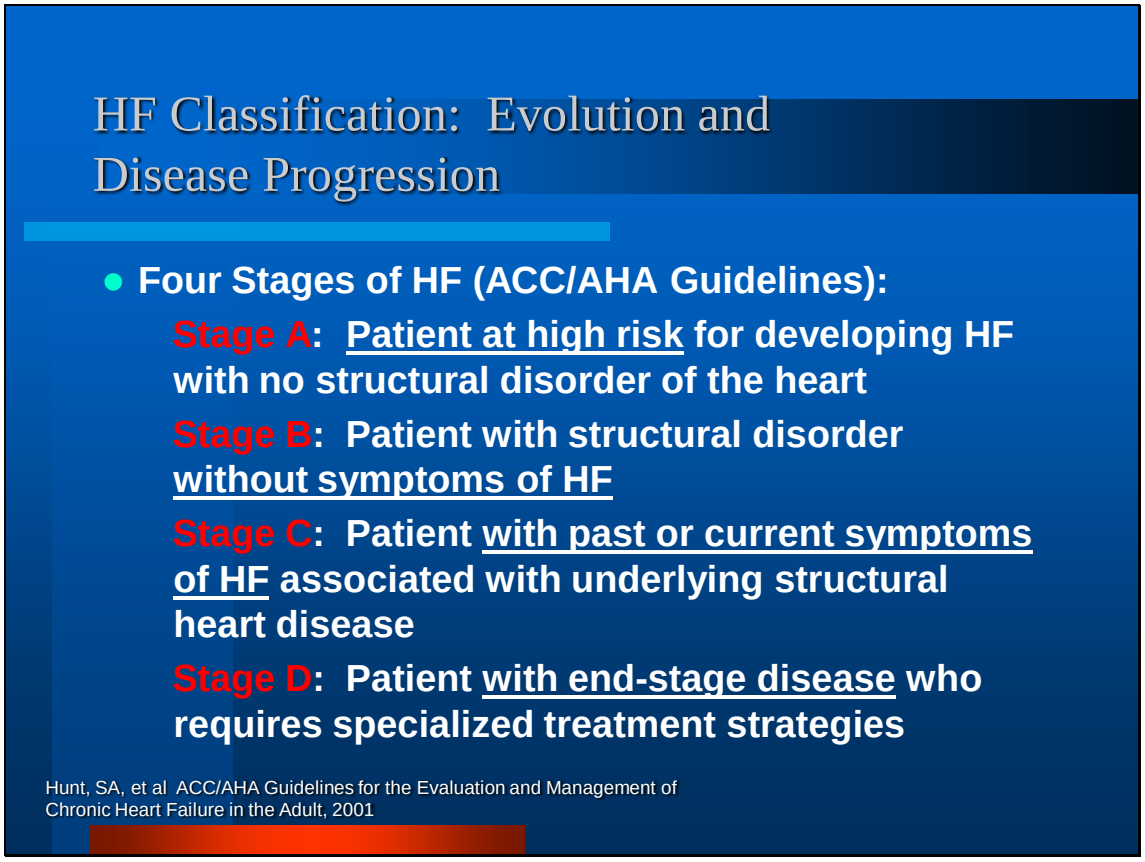
This chart shows that males have a higher incidence of developing HF compared to females until age 65. At that time, females essentially equal males in the incidence of developing HF.

Slide 6



After completing a thorough history and physical exam, physicians will commonly use the New York Heart Association (NYHA) functional classification to help describe the degree of physical disability a patient has. The NYHA class is also commonly used to determine entry criteria for patients participating in clinical research trials.

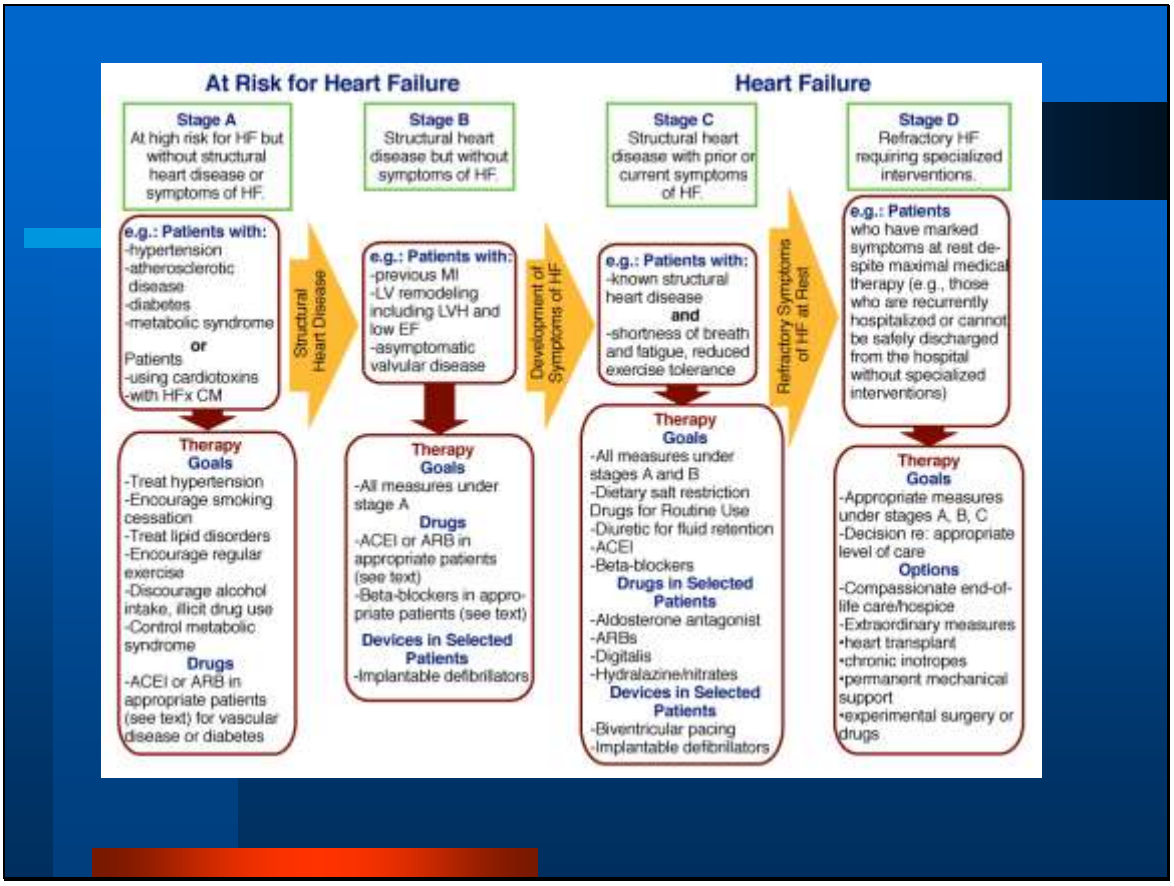
Slide 7



A new approach to the classification of HF emphasizing both the evolution and progression of the disease recognizes that there are established risk factors and structural prerequisites for the development of HF, and that therapeutic interventions performed even before the appearance of LV dysfunction or symptoms can reduce the morbidity and mortality of HF.

Hunt, SA, Baker, DW, Chin, MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2001.

Slide 8


At Risk for Heart Failure
Heart Failure
Stage A
At high risk for HF but without structural heart disease or symptoms of HF.
Stage B
Structural heart disease but without symptoms of HF.
Stage C
Structural heart disease with prior or current symptoms of HF.
Stage D
Refractory HF requiring specialized interventions.
e.g.: Patients with:
-hypertension
-atherosclerotic disease
-diabetes
-metabolic syndrome
or
Patients
-using cardiotoxins
-with HFx CM
Structural Heart Disease
e.g.: Patients with:
-previous MI
-LV remodeling including LVH and low EF
-asymptomatic valvular disease
Development of Symptoms of HF
e.g.: Patients with:
-known structural heart disease
and
-shortness of breath and fatigue, reduced exercise tolerance
Refractory Symptoms of HF at Rest
e.g.: Patients
who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)
Therapy Goals
-Treat hypertension
-Encourage smoking cessation
-Treat lipid disorders
-Encourage regular exercise
-Discourage alcohol intake, illicit drug use
-Control metabolic syndrome
Drugs
-ACEI or ARB in appropriate patients (see text) for vascular disease or diabetes
Therapy Goals
-All measures under stage A
Drugs
-ACEI or ARB in appropriate patients (see text)
-Beta-blockers in appropriate patients (see text)
Devices in Selected Patients
-Implantable defibrillators
Therapy Goals
-All measures under stages A and B
-Dietary salt restriction
Drugs for Routine Use
-Diuretic for fluid retention
-ACEI
-Beta-blockers
Drugs in Selected Patients
-Aldosterone antagonist
-ARBs
-Digitalis
-Hydralazine/nitrates
Devices in Selected Patients
-Biventricular pacing
-Implantable defibrillators
Therapy Goals
-Appropriate measures under stages A, B, C
-Decision re: appropriate level of care
Options
-Compassionate end-of-life care/hospice
-Extraordinary measures
•heart transplant
•chronic inotropes
•permanent mechanical support
•experimental surgery or drugs

Stages of Heart Failure

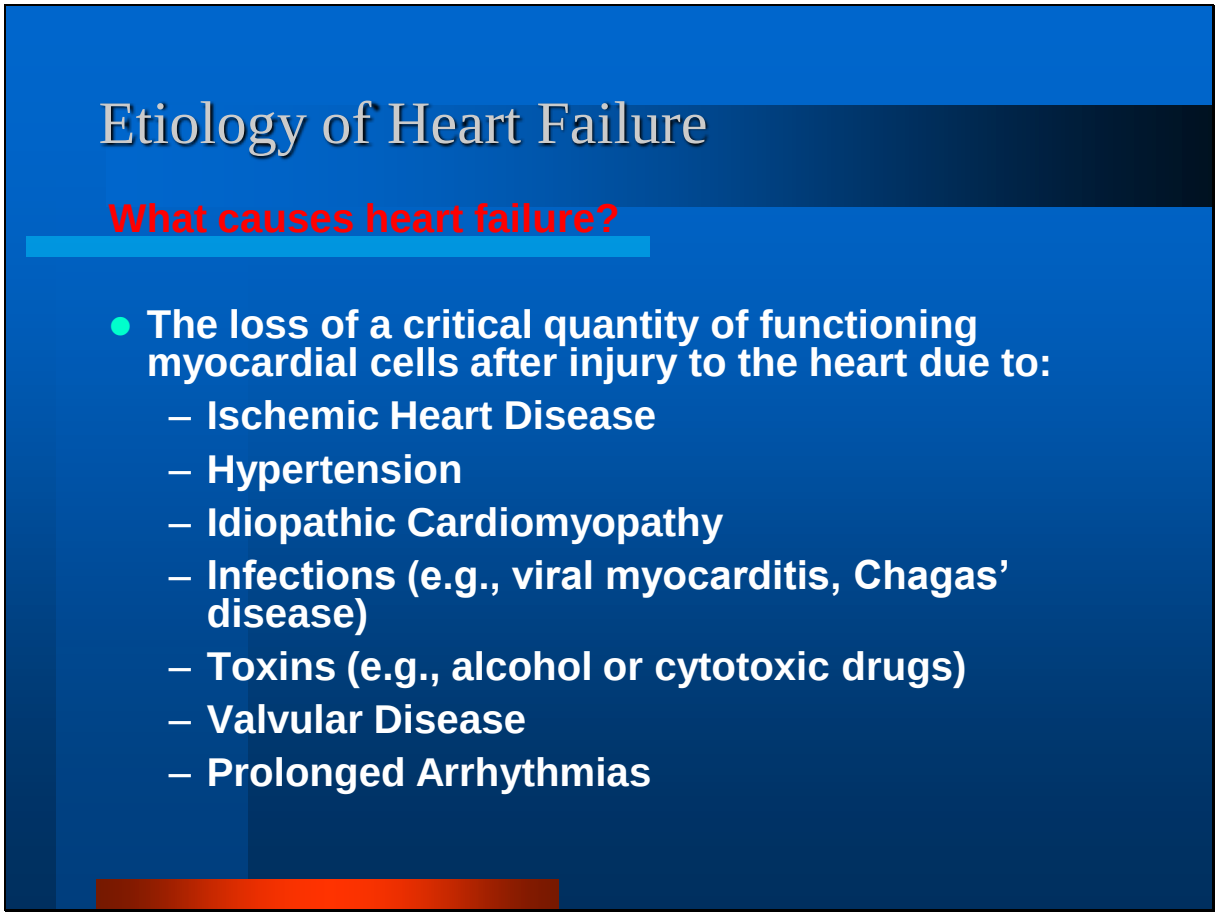
- Designed to emphasize preventability of HF
- Designed to recognize the progressive nature of LV dysfunction

Stages of Heart Failure

COMPLEMENT, DO NOT REPLACE NYHA CLASSES

- NYHA Classes - shift back/forth in individual patient (in response to Rx and/or progression of disease)
- Stages - progress in one direction due to cardiac remodeling

Slide 11

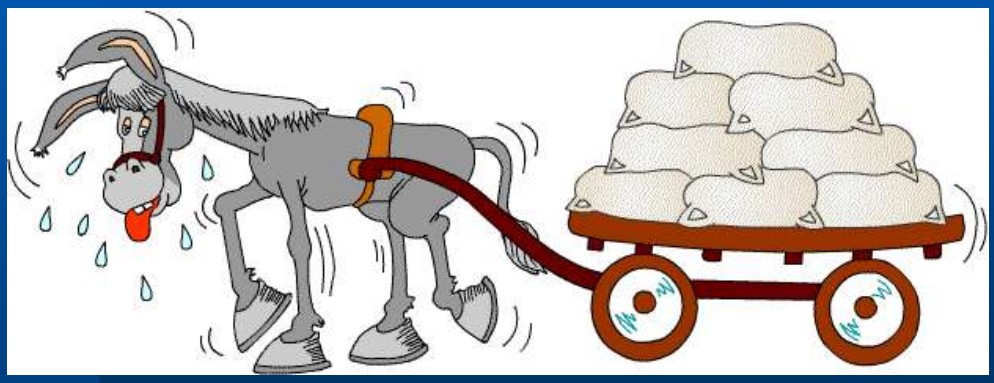


Listed above is the etiology of heart failure in order from most to least common causes.

Slide 12

The Donkey Analogy

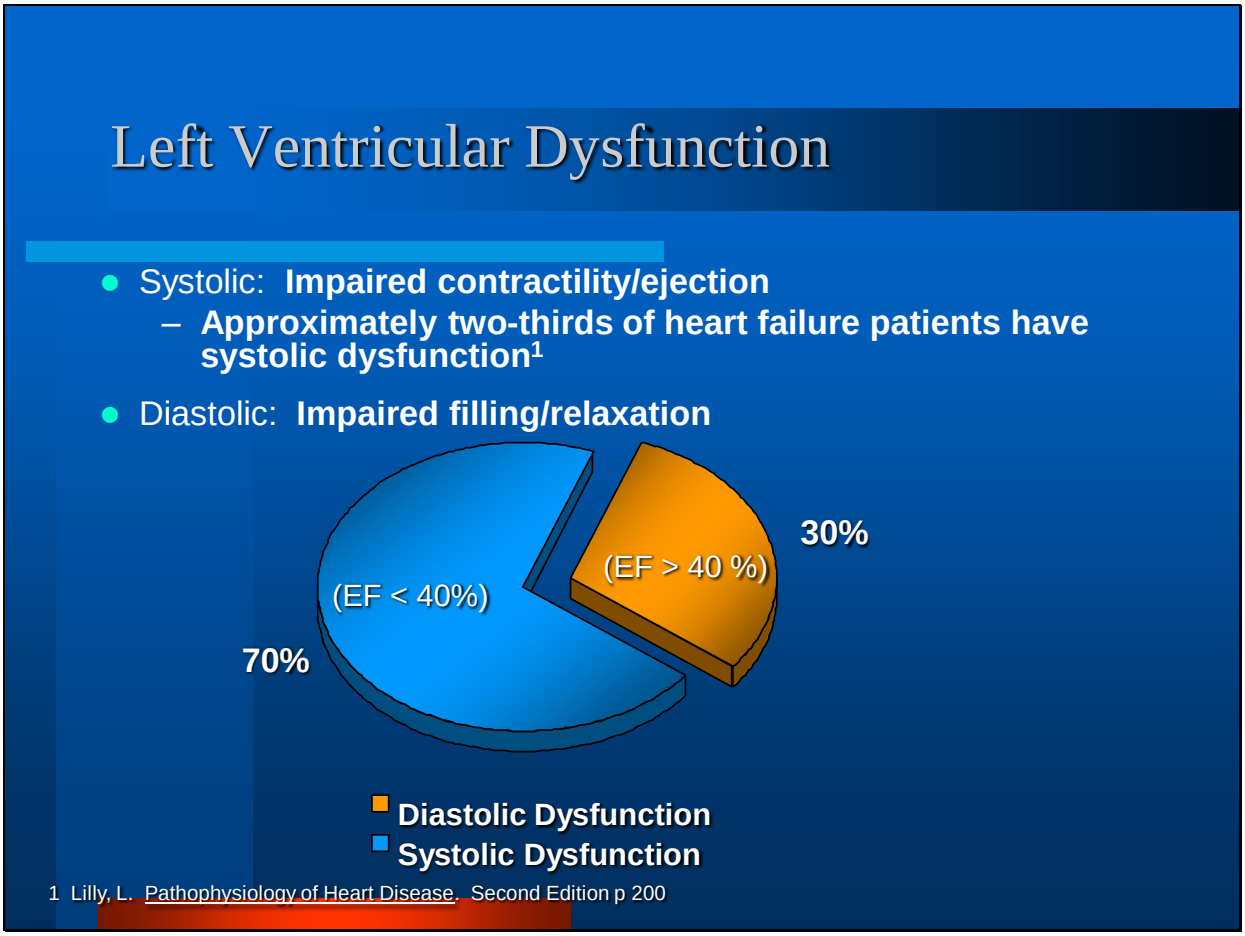
Ventricular dysfunction limits a patient's ability to perform the routine activities of daily living…



Let's compare our heart to this donkey, and our body to the wagon that this donkey has to pull every day.

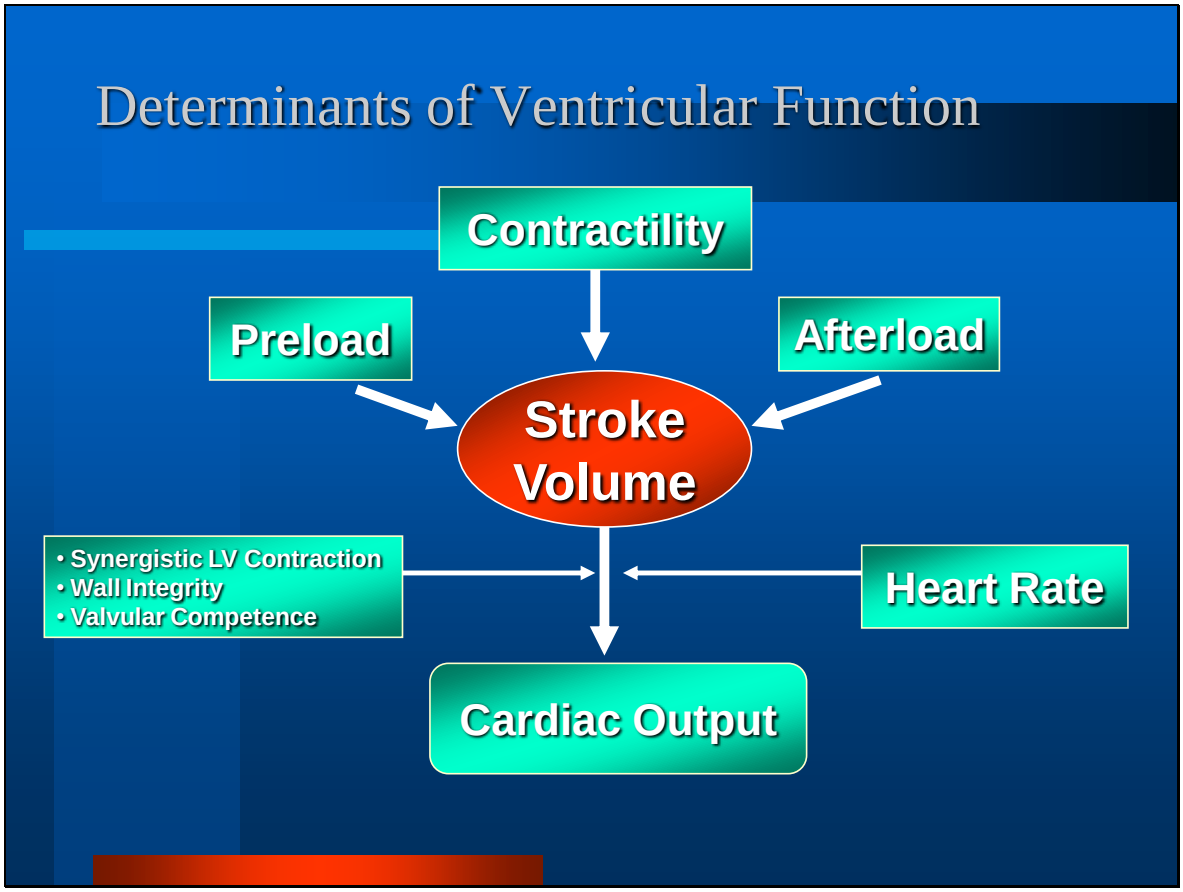
A healthy heart is like an energetic donkey, which without fatigue, pulls the wagon full of weights. Conversely, a diseased heart will have difficulty meeting metabolic demands (or pulling the wagon).

Slide 13



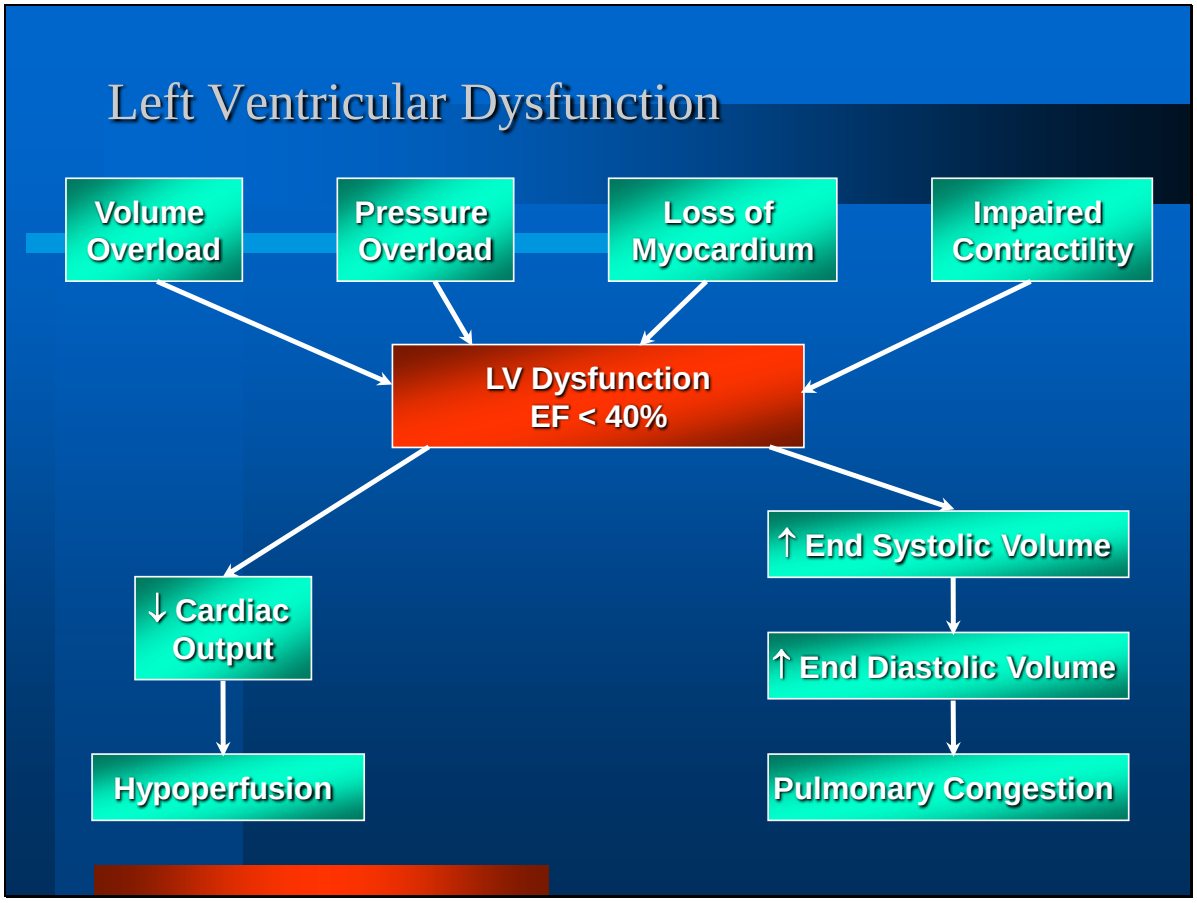
As previously seen, there are many causes of heart failure. Some diseases, however, tend to more adversely affect the heart's systolic function (ventricular contraction/ejection), while others tend to more adversely affect diastolic function (ventricular filling/relaxation). This provides a useful way of classifying heart failure from a hemodynamic standpoint. Most patients who have systolic dysfunction also have a component of diastolic dysfunction.

Slide 14



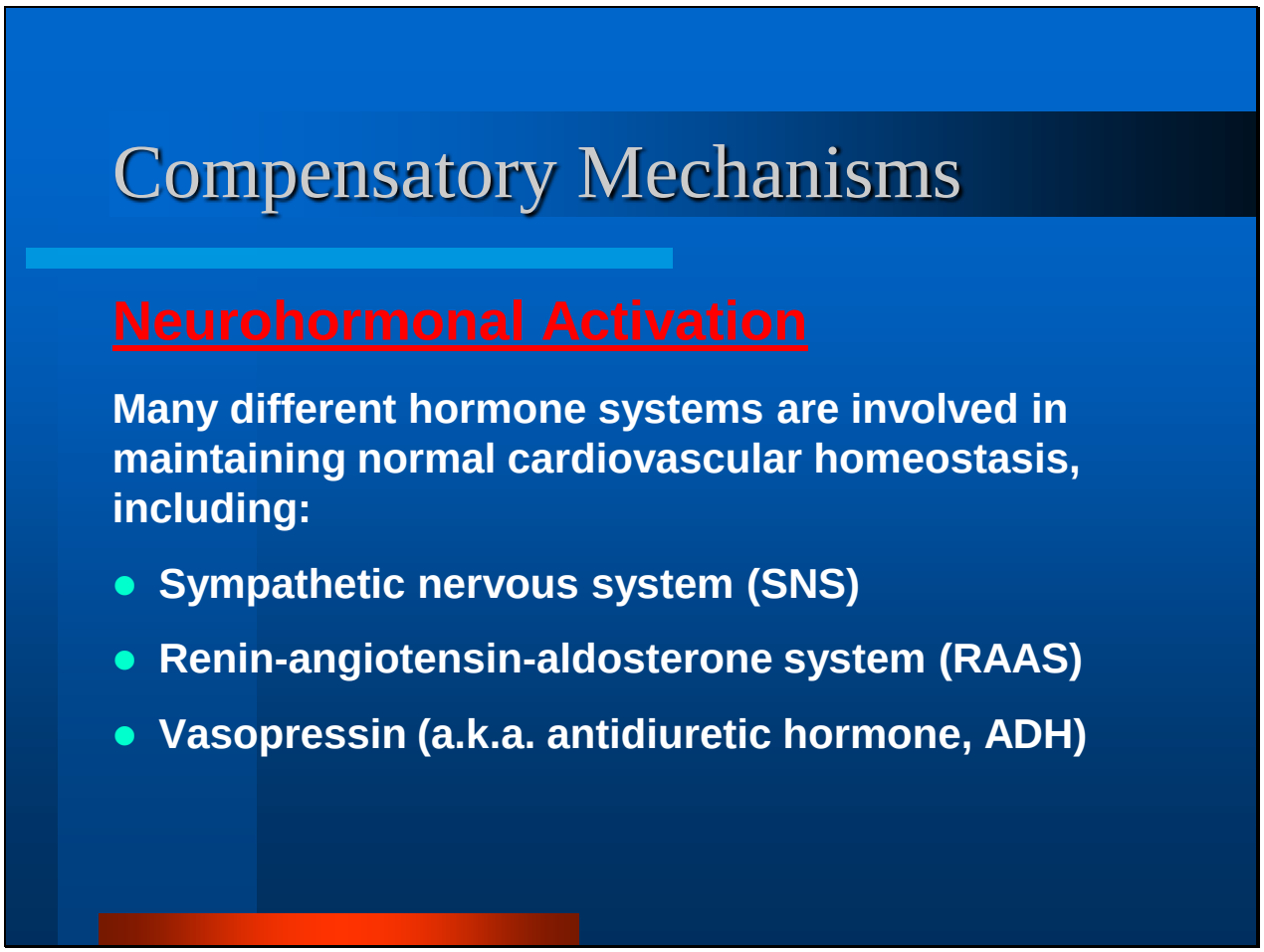
Stroke volume is affected by **preload, afterload,** and **contractility**.
Preload is the amount myocardial stretch at the end of diastole.
Afterload is the resistance that needs to be overcome for the heart to eject the blood.
There is an inverse relationship between afterload and ventricular function. As the resistance to contraction increases, the force of contraction decreases which results in a decreased stroke volume. Also, as an increase in resistance occurs, there is an increase in myocardial oxygen demand.
Contractility is the inotropic state of the heart independent of the preload and the afterload.
Synergistic LV contraction, wall integrity, and the competence of the valves also affect cardiac output.

Slide 15



LV dysfunction is defined as an ejection fraction of less than 40%. The number one cause of LV systolic dysfunction is loss of myocardium due to a myocardial infarction (MI, or heart attack).
Pressure overload due to uncontrolled hypertension is another major cause of systolic dysfunction. It is estimated that only 25% of all patients with hypertension are adequately treated.
Impaired contractility also contributes to LV dysfunction and is usually the result of drugs such as alcohol or toxins such as chemotherapy. Volume overload from valvular diseases contribute to LV dysfunction.
LV dysfunction causes decreased cardiac output, which in turn causes hypoperfusion of the body's organs. In addition, LV dysfunction causes an increase in the amount of blood left in the ventricle when the heart squeezes, and therefore, both End Systolic and End Diastolic Volumes are subsequently increased. This increase in volume leads to pulmonary congestion and the patient being short of breath.

Slide 16



Neurohormonal activation is an important compensatory mechanism involved in maintaining the mean arterial pressure.
Hormones and neurohormonal systems play a important role in maintaining normal cardiovascular hemostasis; they also play an important compensatory role in the early stages of heart failure.
First, let's start by defining what a neurohormone is.
A *hormone* is simply a biologically active substance that originates in one tissue and is transported through the bloodstream to another part of the body where it acts to either increase the activity of that tissue or stimulate the release of another hormone. Hormones that are

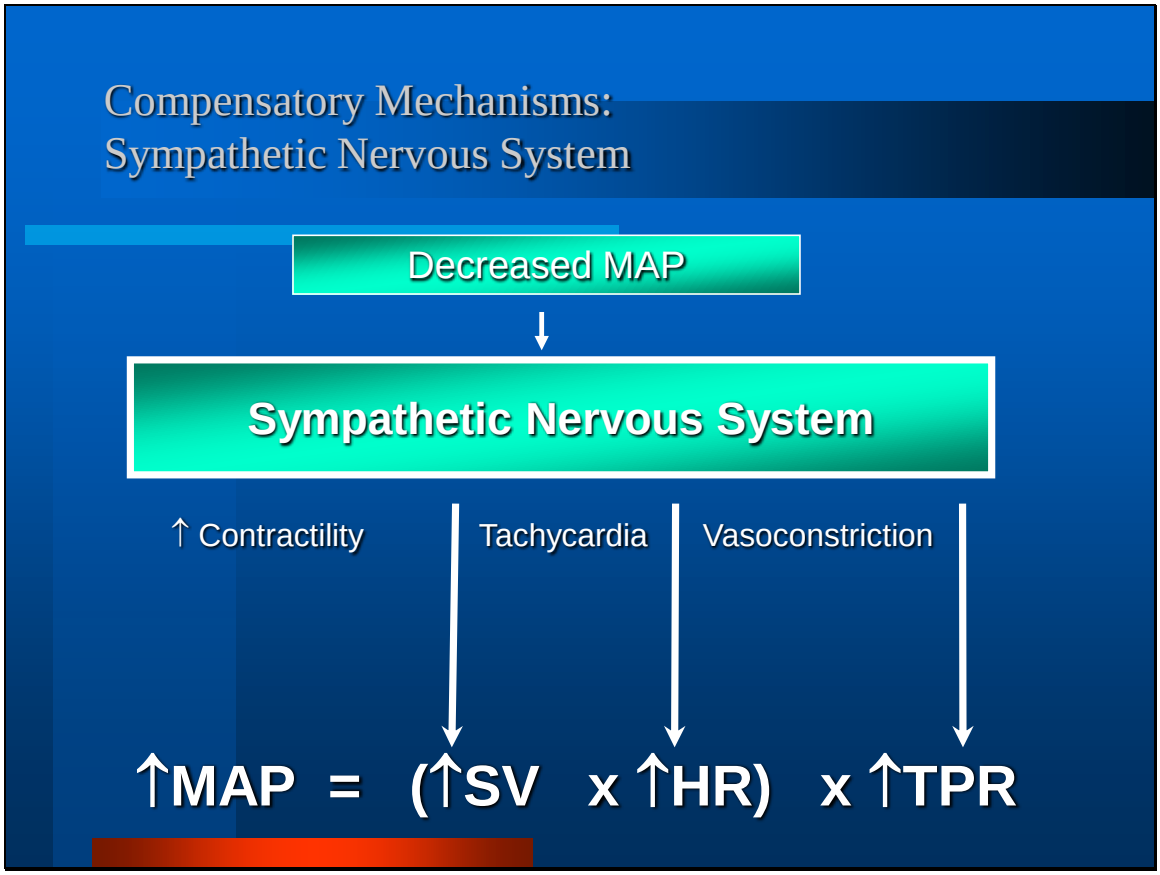
formed by neurosecretory cells and are liberated by nerve stimulation are called neurohormones.

In general, activation of the body's various neurohormonal systems serve to increase systemic vascular resistance, thereby attenuating any fall in blood pressure (recall: Blood Pressure = Cardiac Output x Total Peripheral Vascular Resistance). In addition, many neurohormones encourage salt and water retention, which increases intravascular volume and LV preload so as to maximize stroke volume via the Frank-Starling mechanism.

But as was the case with remodeling, too much of a good thing over the long-term eventually becomes detrimental to the failing heart. Because of the importance of neurohormonal activation in the cascade of events that lead to chronic heart failure, and ultimately death, the following slides will review the various neurohormones and neurohormonal systems in detail, starting with their role in maintaining normal cardiovascular hemostasis, and then later their contribution to the progression of heart failure.

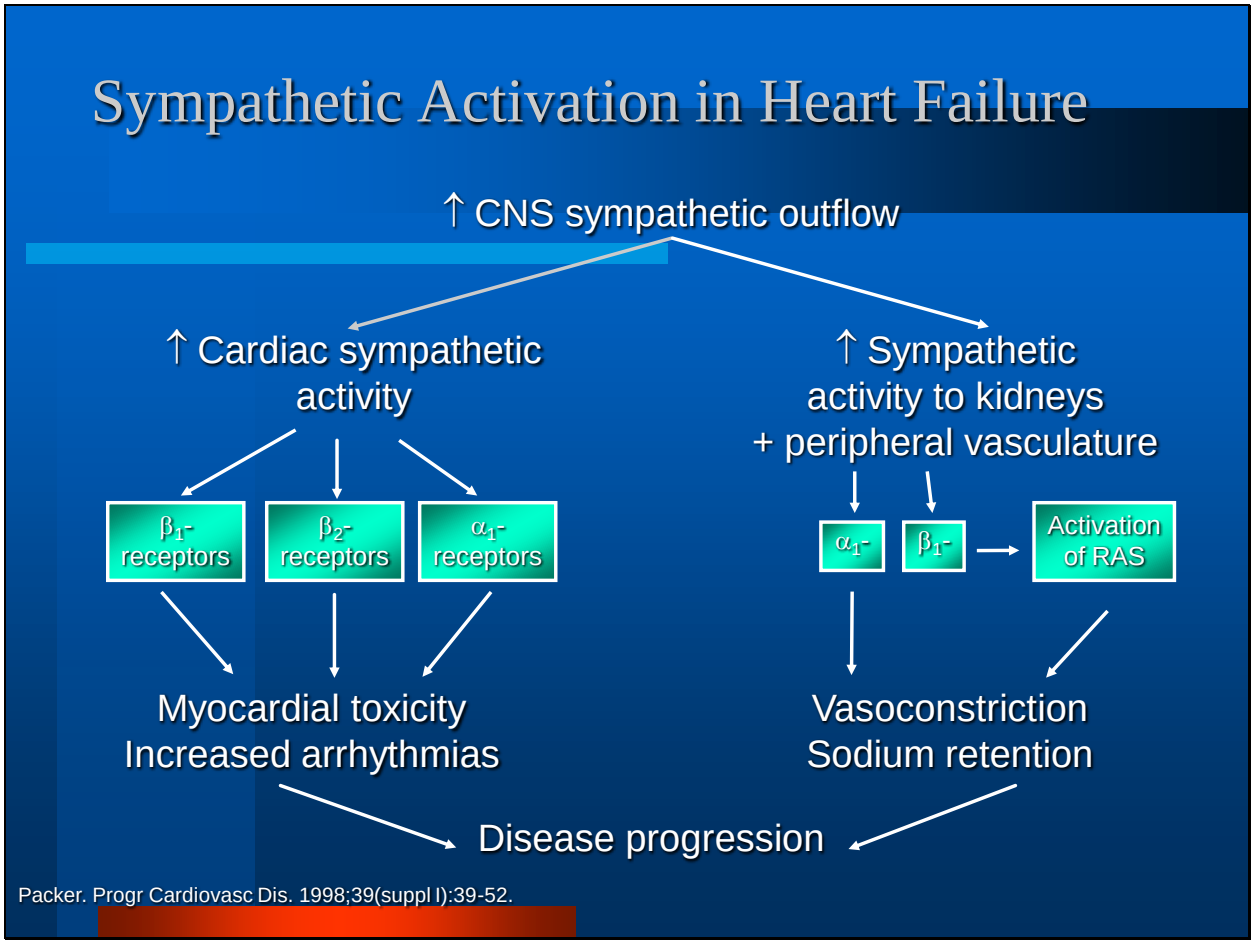
The acute effects of neurohormonal stimulation are beneficial but the long term or chronic activation of these mechanisms is detrimental.

Slide 17



The sympathetic nervous system (SNS) is stimulated due to a decrease in mean arterial pressure. Sympathetic outflow is increased to the heart and the peripheral circulation which causes an increase in the patient's heart rate and an increase in contractility. In addition, vasoconstriction occurs which increases the peripheral vascular resistance. Stroke volume is subsequently increased which in turn increases mean arterial pressure.

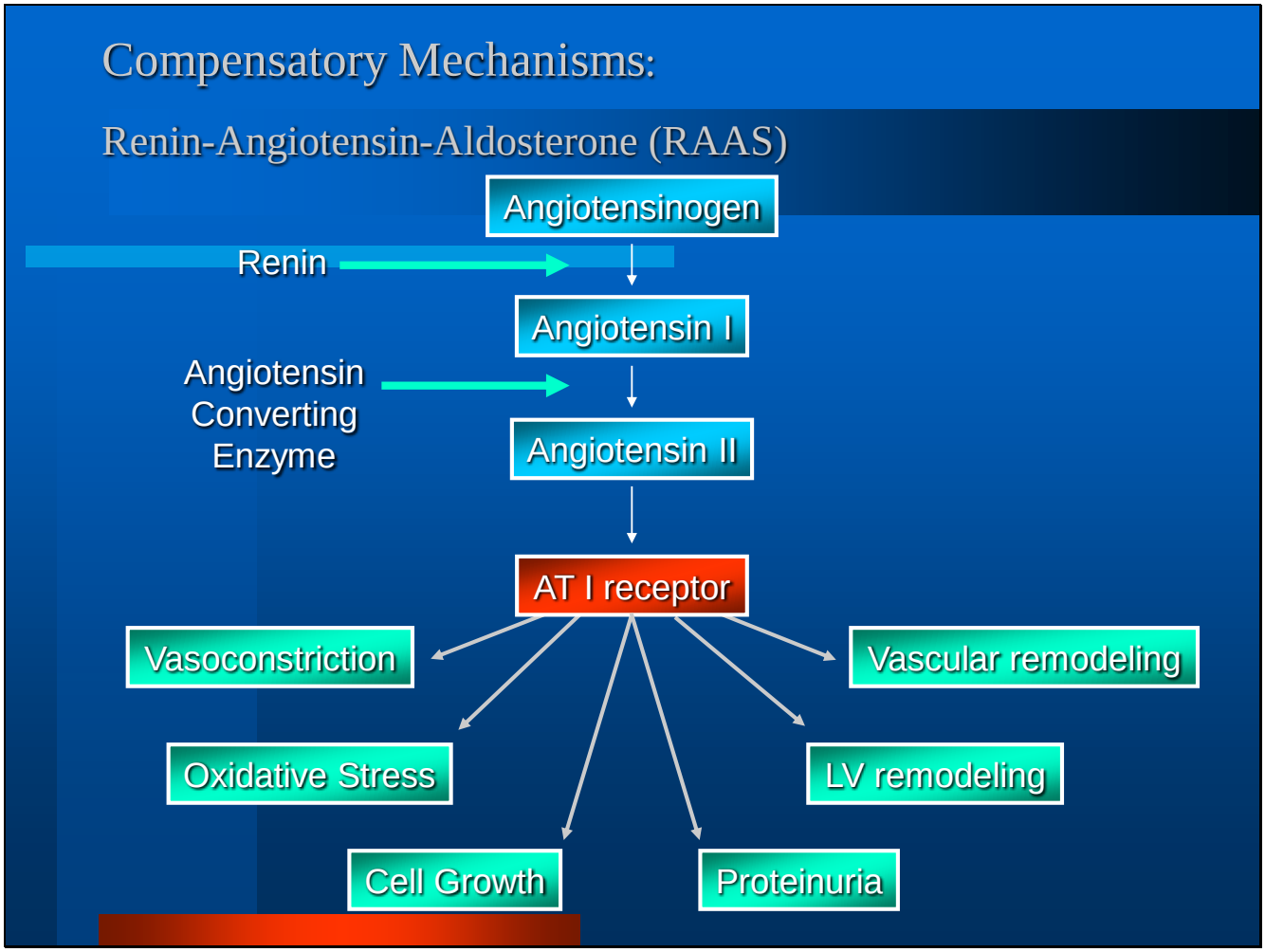
Slide 18



The sympathetic nervous system's goal is to increase cardiac sympathetic activity. This response is mediated through three receptors: Beta 1, Beta 2, and Alpha 1. In normal situations the Beta 1 receptor increases cardiac sympathetic activity.
In heart failure patients, the Beta 1 and Beta 2 receptors are activated. Alpha receptors and their role is yet to be fully delineated.
Beta 1, Beta 2, and Alpha 1 receptors lead to myocardial toxicity in the ventricles. Myocardial toxicity leads to decreased ejection fraction, arrhythmias, and tachyarrhythmias caused by sympathetic activation.
Increase in sympathetic activity also affects the kidneys and peripheral vasculature through the Beta 1 and Alpha 1 receptors. This mediates activation of the renin-angiotensin system (discussed on the next slide), which causes vasoconstriction, sodium retention, and thirst. All of these responses causes the disease to progress.

Prolonged neurohormone release also has direct adverse effects on the heart tissue itself. Norepinephrine, for example, is known to be directly cardiotoxic. In fact, studies have established that in patients with heart failure, the probability of survival is markedly worse for those whose plasma norepinephrine levels are >400 pg/ml than for those whose levels are <400 pg/ml.

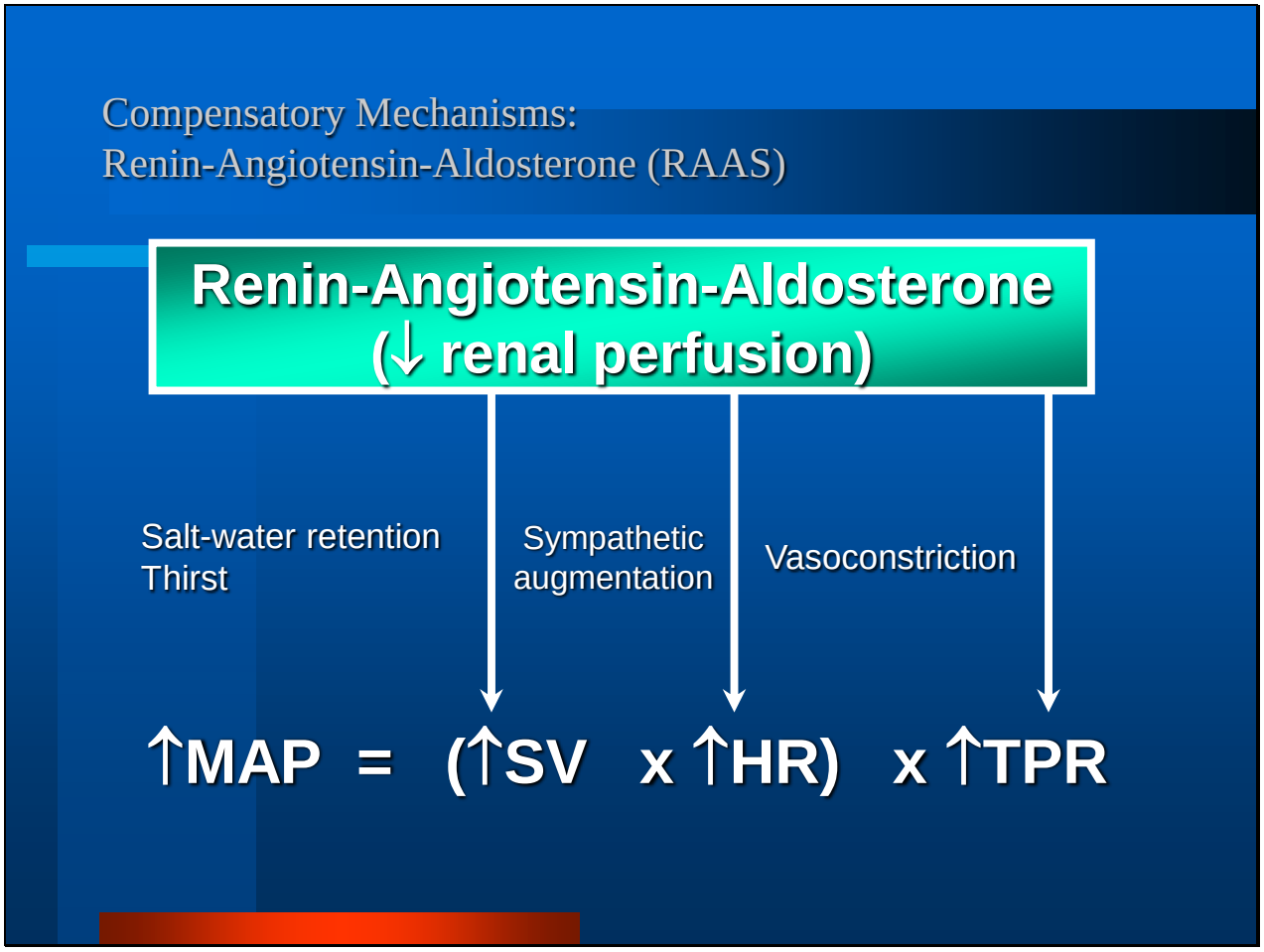
Slide 19



The other mechanism in the neurohumoral response to heart failure is the renin-angiotensin-aldosterone system (RAAS). In the RAAS, Renin (secreted by the kidney) acts on Angiotensinogen (secreted by the liver) to make Angiotensin I.
The Angiotensin converting enzyme (secreted by the lungs) acts on Angiotensin I to make Angiotensin II. Angiotensin II in turn causes vasoconstriction, an increase in aldosterone, facilitates the release of norepinephrine from the SNS, causes sodium reabsorption, stimulates vasopressin secretion from the brain (discussed later), and increases contractility. Subsequently, remodeling of the heart occurs.
In a heart failure patient, the effects of Angiotensin II are not beneficial. Why not think about using a medication to block the conversion of Angiotensin I to II? Or, an agent

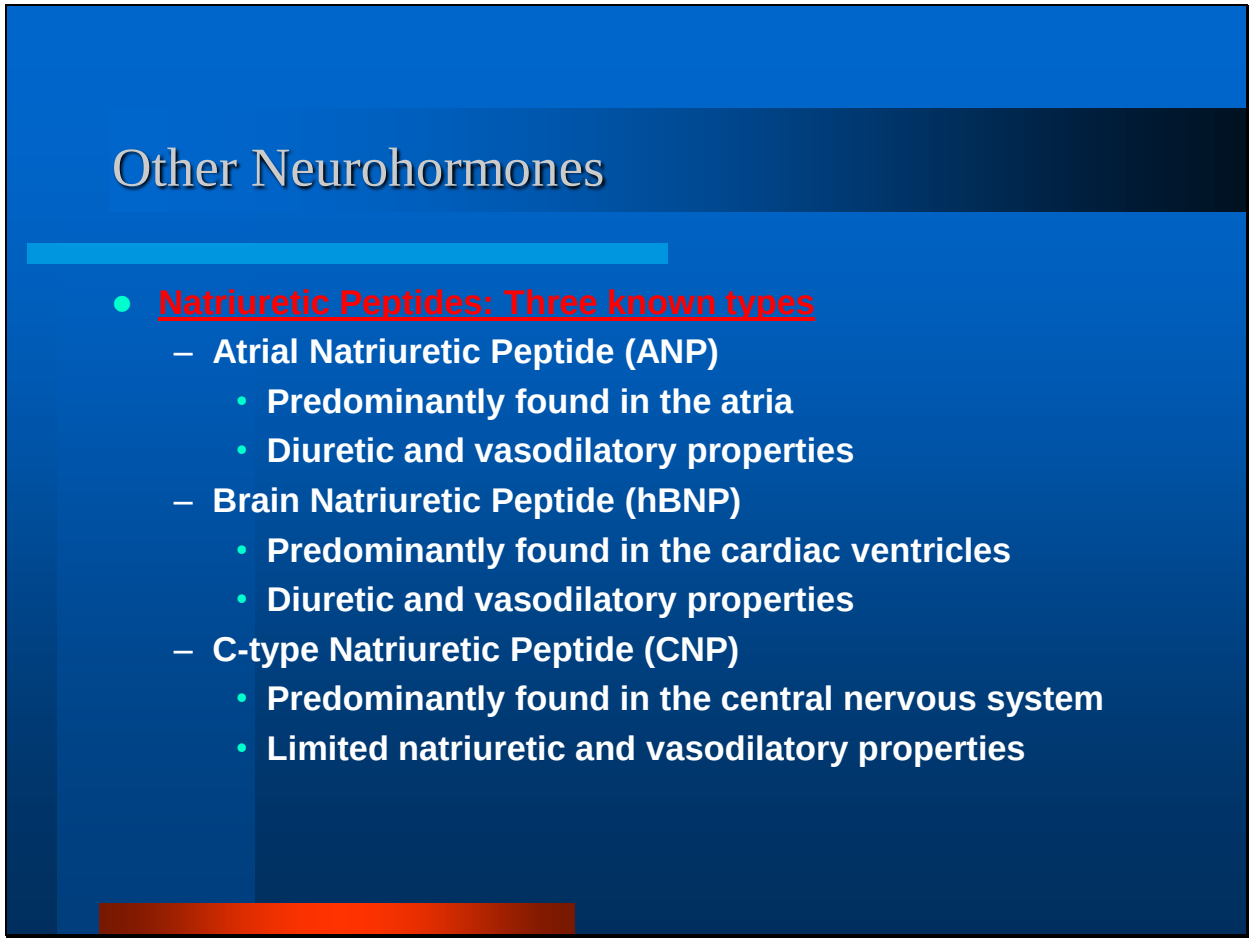
that blocks the Angiotensin I receptor? These blocking agents will be discussed later when we talk about the treatment of heart failure.

Slide 20



So, when there is a decrease in the mean arterial pressure, there is decreased renal perfusion. Hence, the RAAS is stimulated, and the MAP is increased.

Slide 21



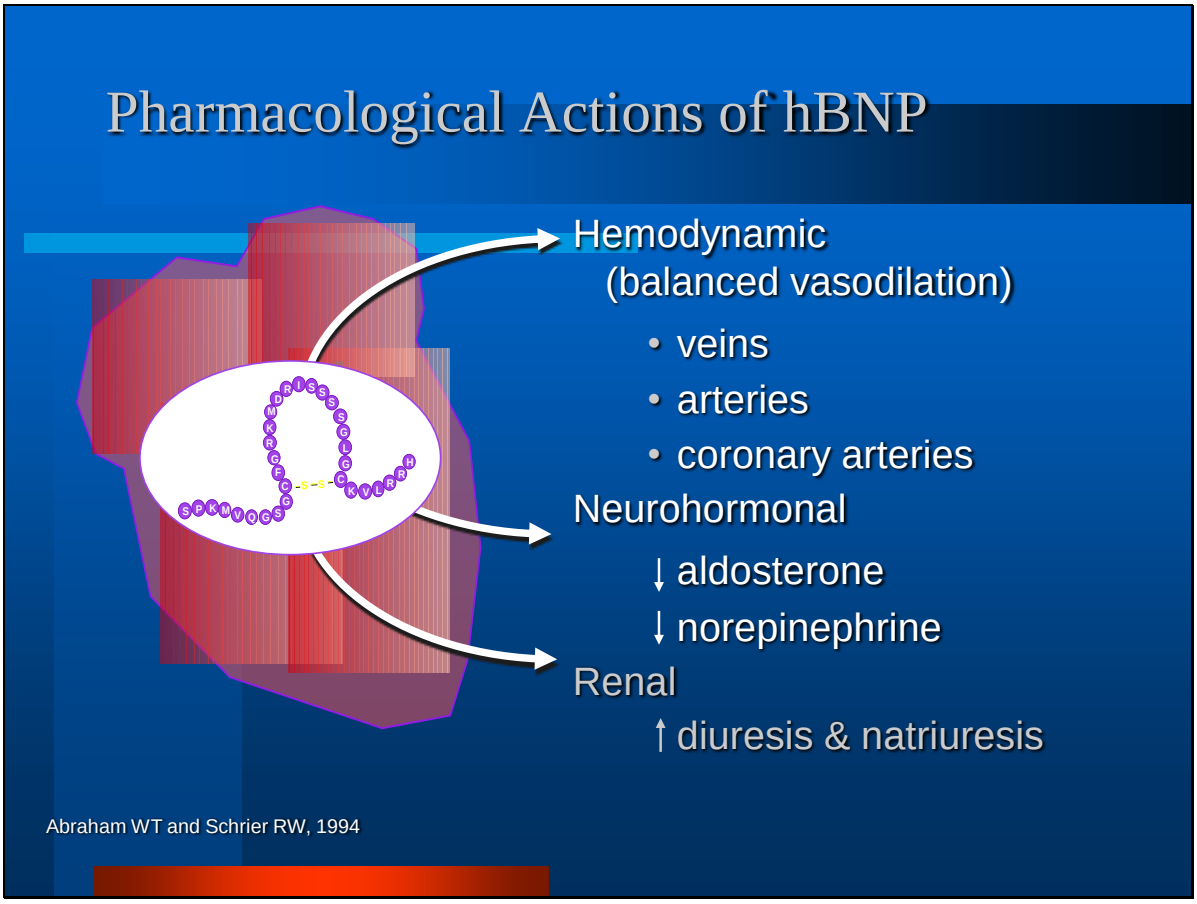
Natriuretic Peptides

The third neurohormone system on our list includes the natriuretic peptides. The natriuretic peptides—ANP, BNP, and CNP-- are vasodilating neurohormones. As such, they play an important role in counter-regulating the vasoconstricting effects of other neurohormones.

These peptides are made and stored in specialized cells in the atria and ventricles, and are released when the atria are stretched (e.g., in volume overload, which distends the atria) or when the ventricles are dilated.

The natriuretic peptides act directly on blood vessels to cause vasodilatation. They also have natriuretic (salt excreting) and diuretic (water excreting) effects because of their ability to inhibit the secretion of renin, aldosterone, and vasopressin.

Slide 22

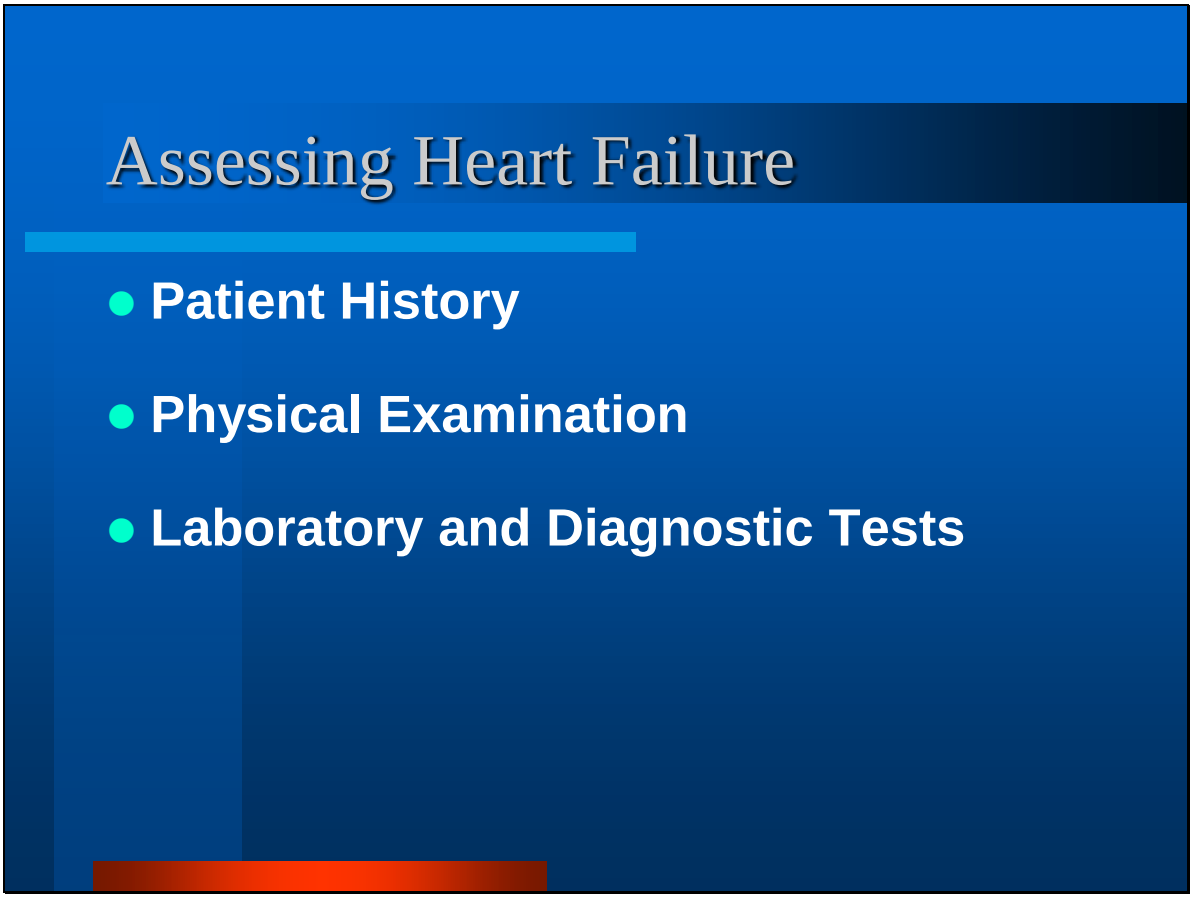


Human brain natriuretic peptide (hBNP) is found mainly in the cardiac ventricles which suggests that this particular natriuretic peptide may be more sensitive to ventricular disorders. Its level seems to correlate with the amount of shortness of breath and left ventricular volume and pressure. For this reason, the level of BNP may be the first "white count" for heart failure. For example, a low BNP level may mean that heart failure is unlikely in a patient. It also may be a way of following the progression of disease.
Natriuretic peptide levels, like norepinephrine, are also directly related to mortality.

Slide 23

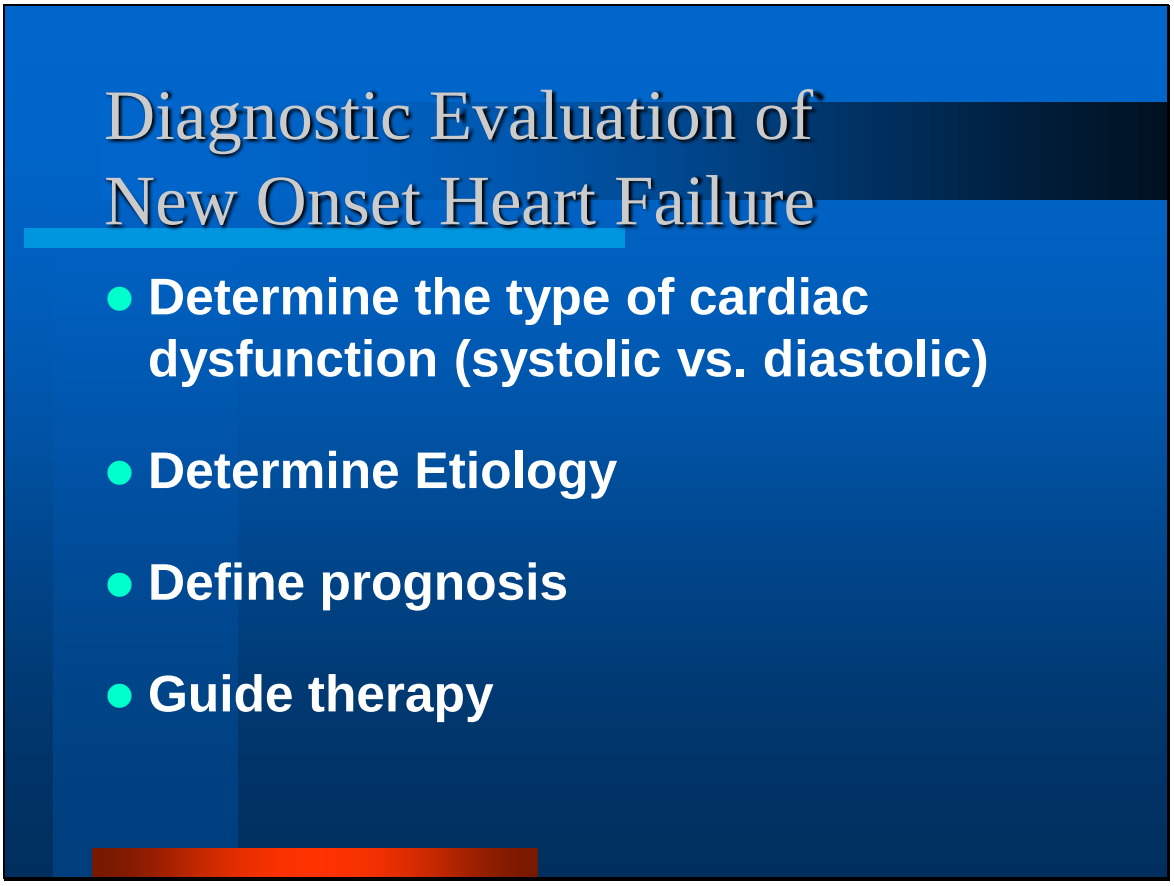
Part II:
Assessing Heart Failure

Slide 24



Evaluating patients with heart failure requires gathering information to document the history of the patient's heart failure, completing a physical examination, and obtaining laboratory and other diagnostic tests to gauge the severity of the disease. With this information, a prognosis and appropriate treatment plan can be made for the patient.

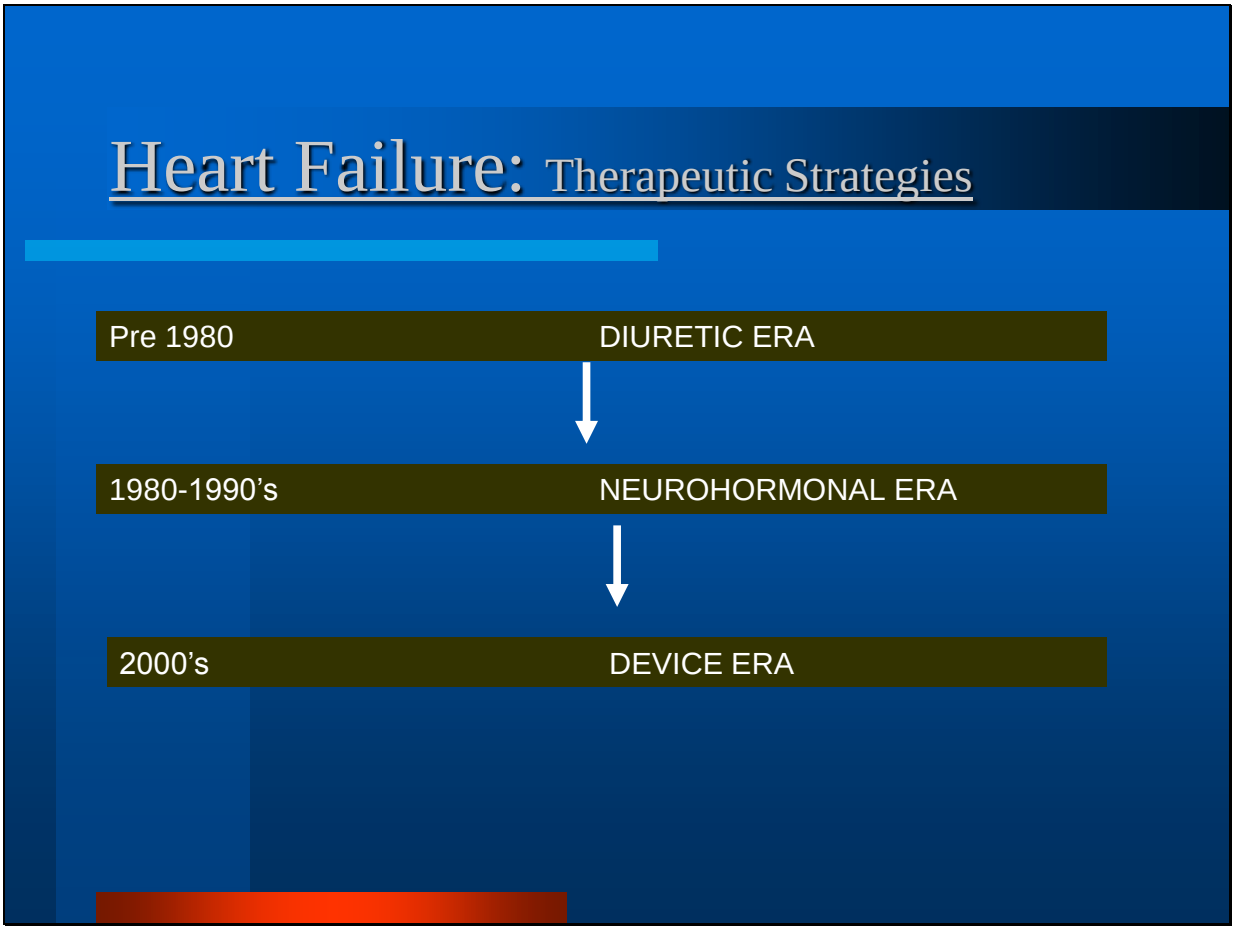
This section reviews the typical historical and physical findings typically seen in a patient with heart failure. Useful laboratory and diagnostic tests will also be reviewed.



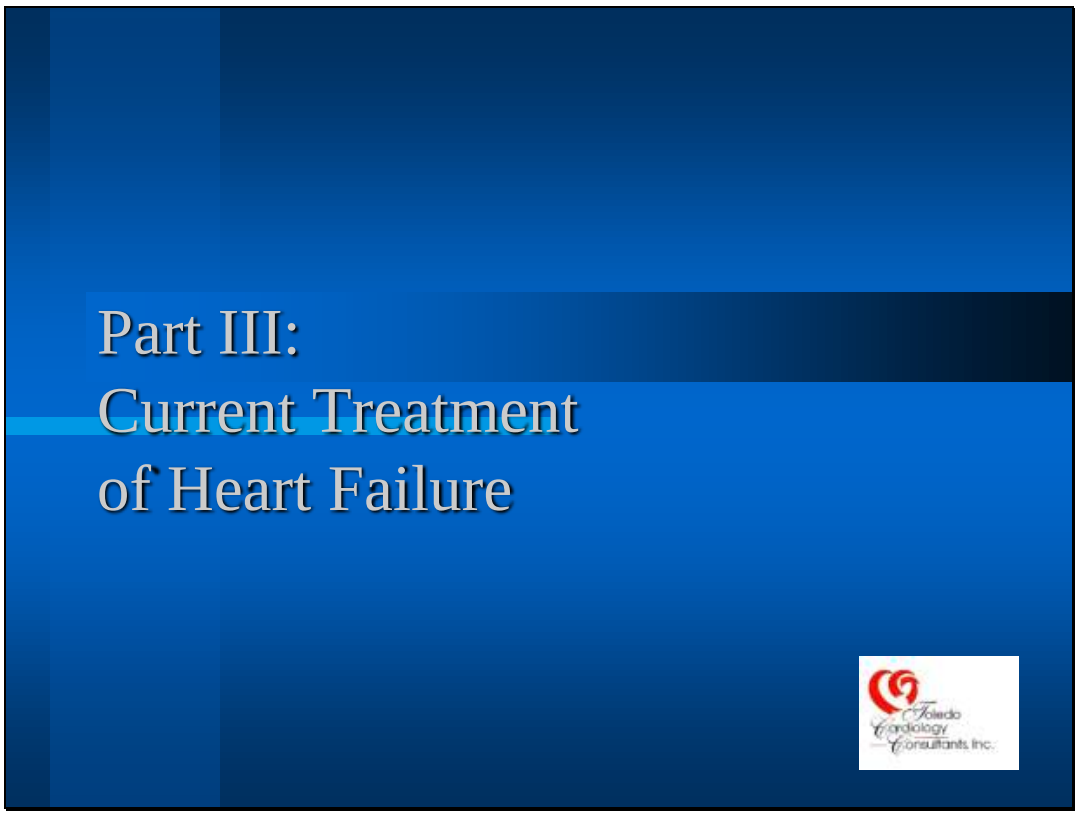
All patients presenting with heart failure should undergo diagnostic evaluation that:

- Determines the type of cardiac dysfunction (systolic vs. diastolic)
- Uncovers the etiology and if it is reversible
- Defines the prognosis, and
- Guides therapy

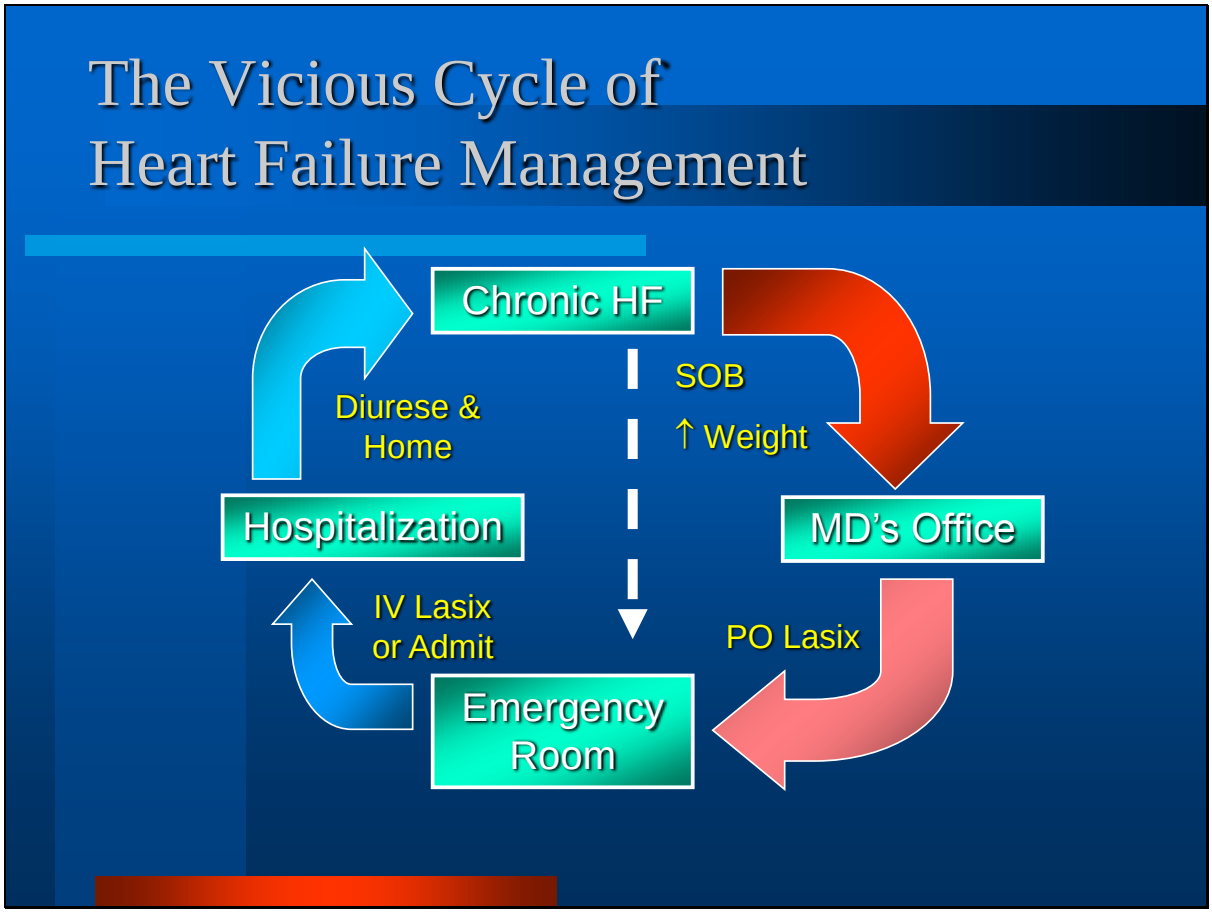
Slide 26


Heart Failure: Therapeutic Strategies
Pre 1980
DIURETIC ERA
1980-1990's
NEUROHORMONAL ERA
2000's
DEVICE ERA

Slide 27

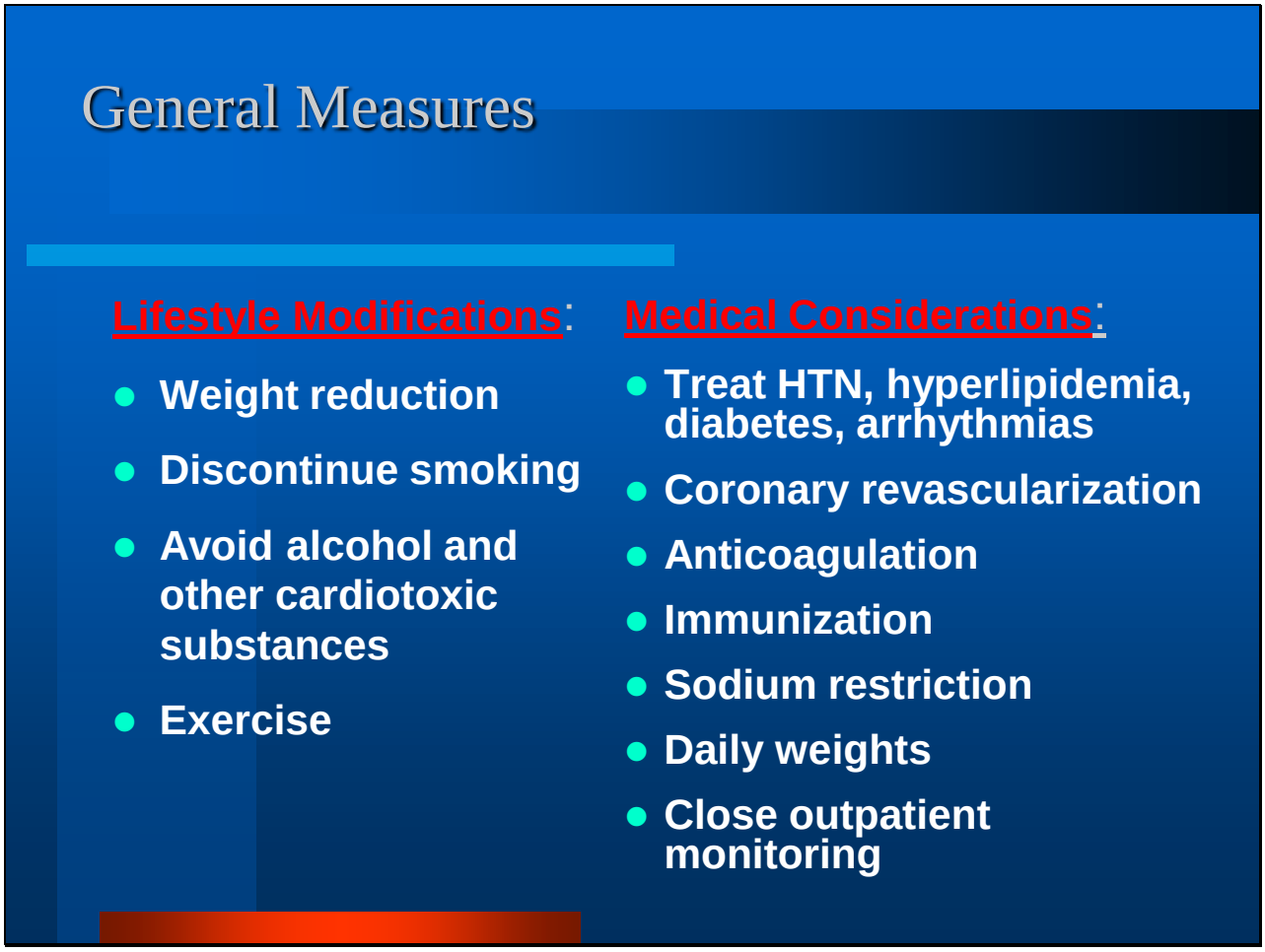

Part III:
Current Treatment
of Heart Failure
Toledo
Cardiology
Consultants, Inc.

Slide 28



As you can see from this diagram, heart failure is difficult to manage chronically. When a heart failure patient moves from a compensated state to a decompensated state, their symptoms increase. Subsequently, their medications are adjusted, and often hospitalization is required. After diuresis, the patient typically moves back to a compensated state until something occurs, such as eating too much salt, etc., which pushes them back to a decompensated state.

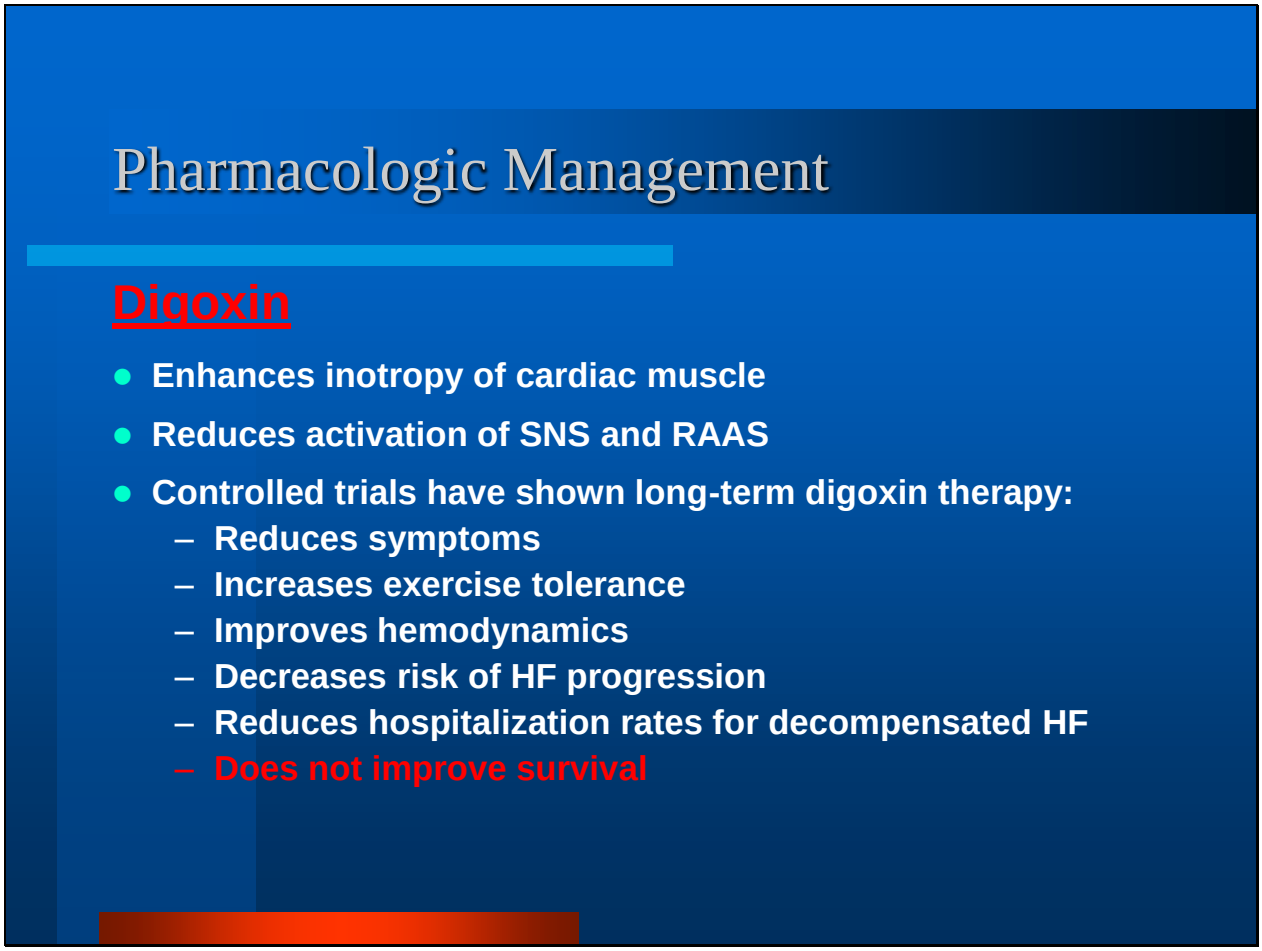
Slide 29



The treatment of heart failure has changed considerably over the past decade, primarily because we now understand the importance of neurohormonal activation in the progression of this disease. In this section we will learn about the treatment of heart failure; however, the focus will be on the ever-expanding armamentarium the pharmacologic agents used to treat this disease.
[Note: The material discussed in this section is based on the ACC/AHA Practice Guidelines 2001, *Circulation* December 2001.]
General Measures:
An important part of heart failure management is identifying and treating factors that are known to encourage heart failure and its progression. This often requires encouraging patients to adopt lifestyle changes to address these factors.
Lifestyle Modifications:

Weight Reduction—Obese patients should lose weight
Smoking—Smokers should stop smoking
Alcohol—Excessive alcohol use, and the use of other cardiotoxic substances, should be avoided
Exercise—Improve physical conditioning where appropriate

Slide 30



Digoxin

Digoxin has been used in the management of heart failure for more than 200 years, yet it wasn't formally approved by the FDA for this indication until 1997.

Digoxin enhances inotropy (contractility) of cardiac muscle and, at the same time, reduces activation of the SNS and RAAS. These neurohormonal effects are sustained during prolonged treatment with digoxin. Randomized, double-blind, placebo-controlled trials such as PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin) and RADIANCE (Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme) have shown that long-term therapy with digoxin reduces symptoms and increases exercise tolerance[1]. These two trials demonstrated that "patients with mild to moderate chronic heart failure due to left ventricular systolic dysfunction, who are clinically stable on either maintenance therapy of Digoxin and diuretics (PROVED), or with additional background therapy with ACE Inhibitors (RADIANCE), are at considerable risk for clinical deterioration if Digoxin is withdrawn."[2] Unfortunately, the Digoxin Investigation Group (DIG) Trial demonstrated that digoxin had no effect on mortality; however, digoxin *did* reduce the hospitalization rate for decompensated heart failure[3].

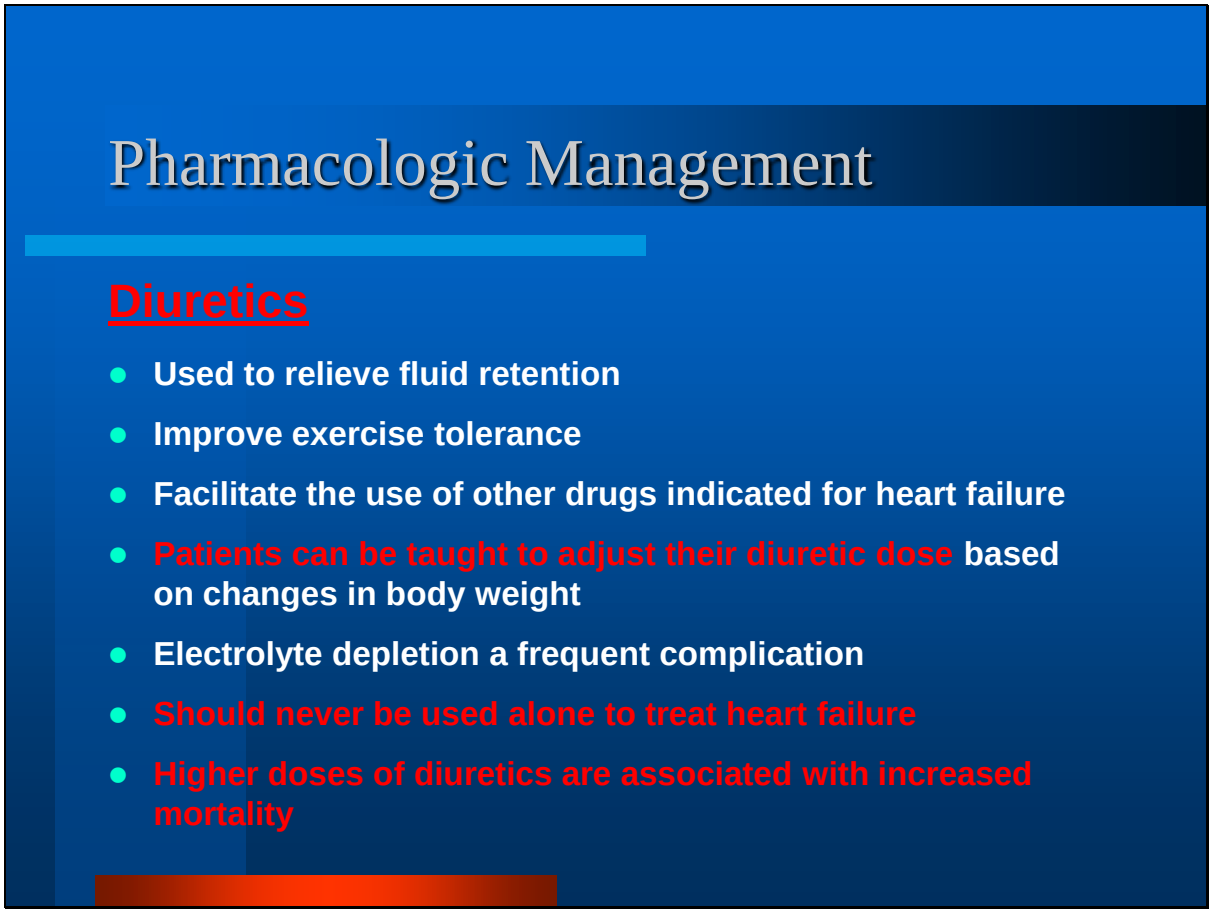
The ACC/AHA Guidelines support the use of digoxin in conjunction with diuretics, an ACE inhibitor, and a beta-blocker in patients with LV systolic dysfunction who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker, and in those in whom heart failure is accompanied by rapid atrial fibrillation.The usual digoxin dose is 0.125-0.25 mg per day, and should be adjusted for age, renal function, and body mass. The Guidelines note that although the adverse effects of digoxin, such as cardiac arrhythmias and gastrointestinal and neurologic complaints, occur primarily at high doses, these higher doses are usually not necessary to achieve clinical benefits in patients with heart failure.

1 Young, J. Clinical Management of Heart Failure. Professional Communications, Inc. 2001. p 97.

2 McMurray, J and Cleland, J. Heart Failure in Clinical Practice. Second Edition. Martin Dunitz Ltd. p 232.

3 Young, J., p. 111

Slide 31



Most patients with heart failure require a diuretic to relieve fluid retention. In addition to rapidly decreasing symptoms such as pulmonary congestion and peripheral edema, diuretics improve exercise tolerance and facilitate the use of other drugs indicated for heart failure.

Treatment with a diuretic is generally started at a low dose and then gradually tapered upward until a threshold dose is established. Some patients with heart failure can be taught to adjust their diuretic dose themselves based on changes in body weight, which should be monitored daily. After fluid retention has resolved, diuretic therapy is continued to prevent its recurrence.

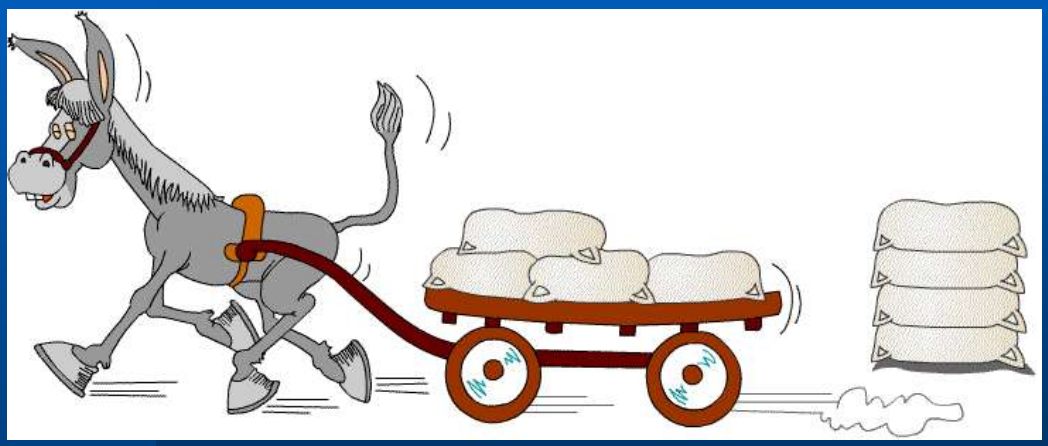
Electrolyte depletion is a frequent complication of long-term diuretic therapy; therefore, electrolyte levels need to be monitored frequently during initial stages of therapy and after increases in diuretic dose.

Diuretics are usually used along with ACE inhibitors and beta-blockers in heart failure, and should never be used alone. Increased doses of diuretics have been associated with increased mortality.

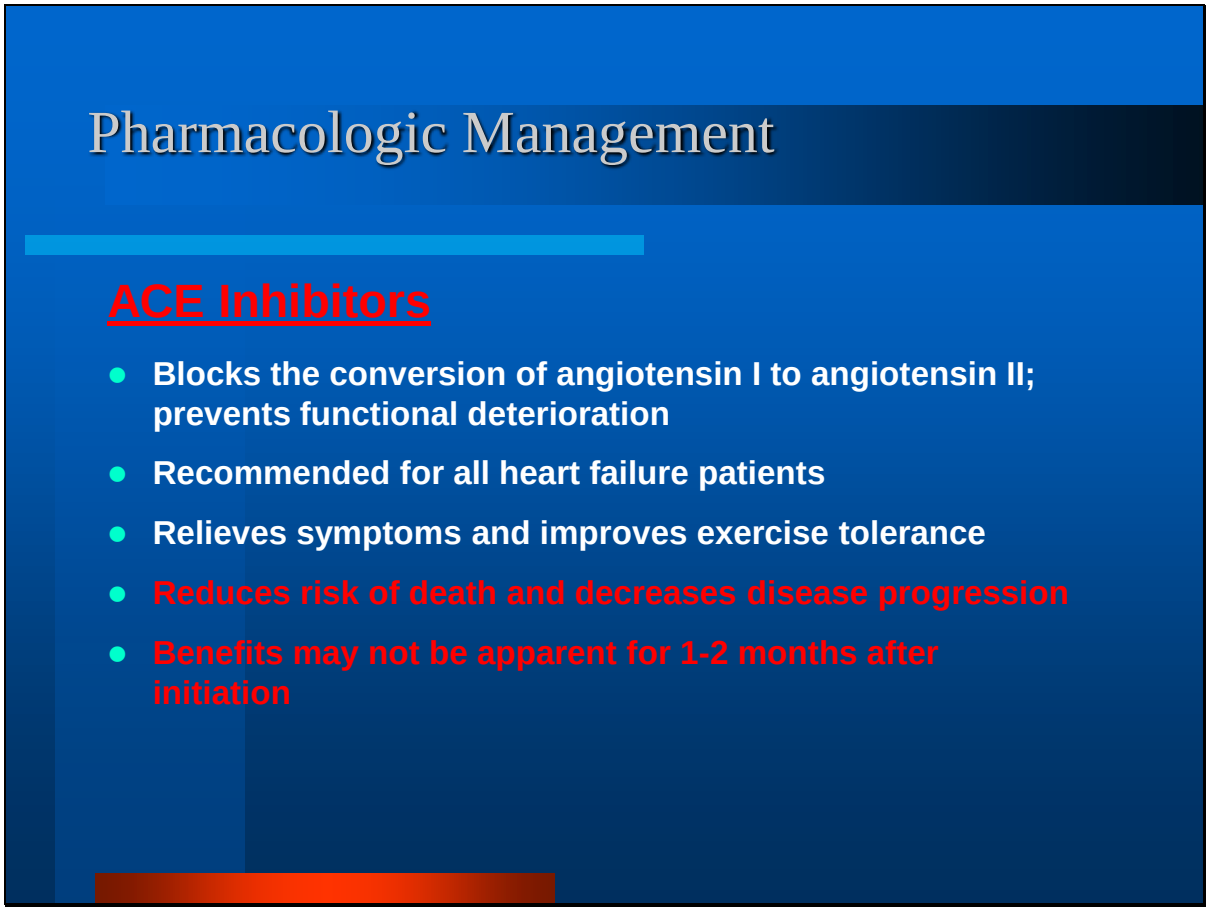
Slide 32

Diuretics, ACE Inhibitors

Reduce the number of sacks on the wagon



Slide 33



Angiotensin Converting Enzyme (ACE) inhibitors are recommended for all heart failure patients, whether they are symptomatic or not. Use of ACE inhibitors relieves symptoms and improves exercise tolerance in patients with chronic heart failure. Data from placebo-controlled trials show that ACE inhibitors can also reduce the risk of death and disease progression in heart failure patients.

The benefits of ACE inhibitor therapy may not become apparent for 1-2 months after initiation of treatment. But even in the absence of symptomatic improvement, continued long-term ACE inhibitor therapy is recommended to reduce the risk of death or hospitalization.

Most patients with heart failure tolerate long-term ACE inhibitor therapy. Potential side effects include a decrease in blood pressure, transient worsening of kidney function, hyperkalemia, and chronic cough. Angioedema, a disorder characterized by the development of large, edematous areas of the skin, mucous membranes, and organs, is

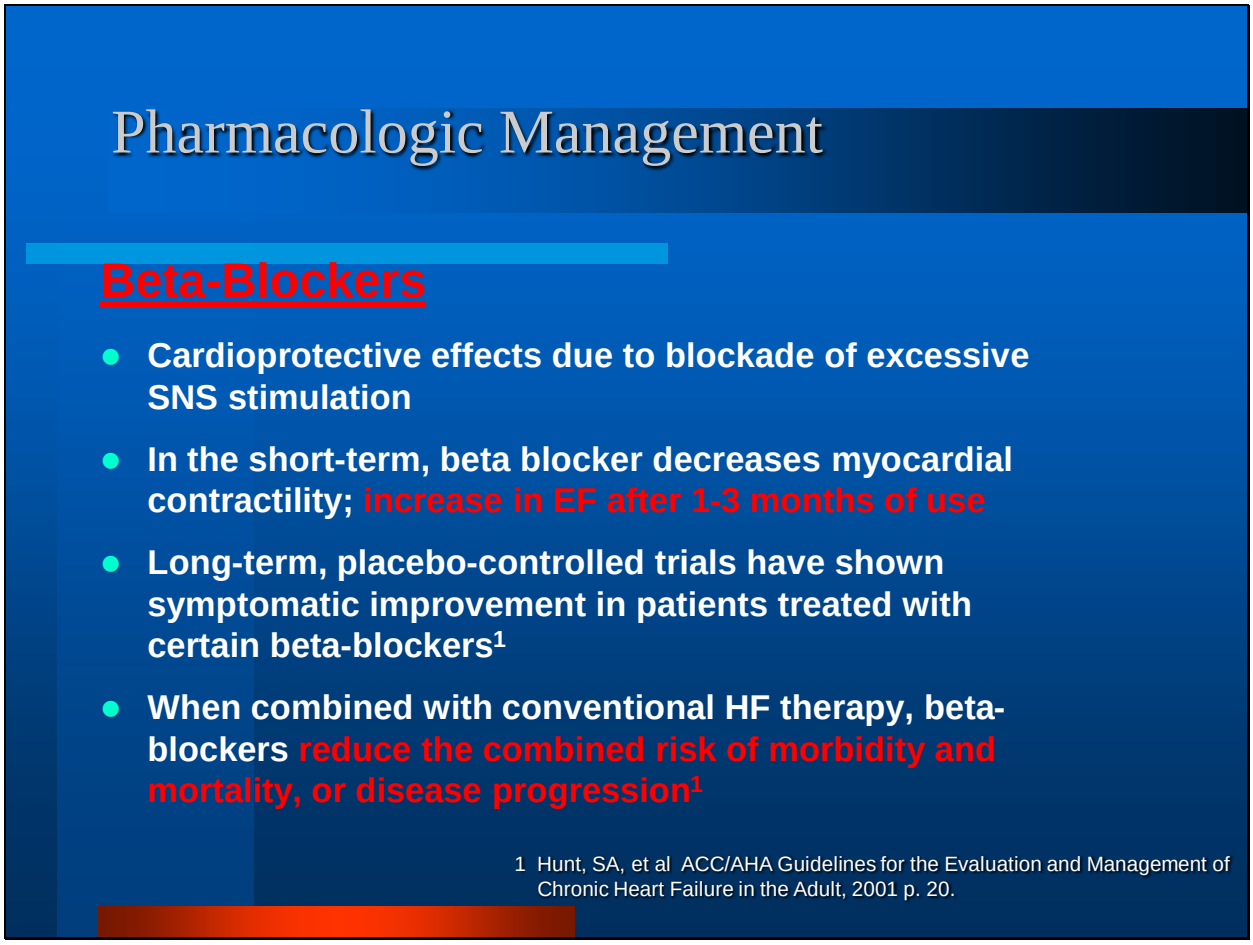
an infrequent, but life-threatening complication of ACE inhibition, and obviously, ACE inhibitors should not be used in patients with a history of this condition.
Enalapril (Vasotec) and Captopril (Capoten), have been shown to decrease mortality in large heart failure clinical trials. For this reason, these two are typically the drugs of choice.

Slide 34

ß-Blockers

Limit the donkey's speed, thus saving energy

Slide 35



Beta-Blockers

Beta-blockers exert their cardioprotective effects through blockade of excessive sympathetic stimulation of the myocardium, peripheral vasculature, and kidneys. While a short-term fall in myocardial contractility is to be expected, it is usually followed by a rise in ejection fraction over the next 1-3 months of use.

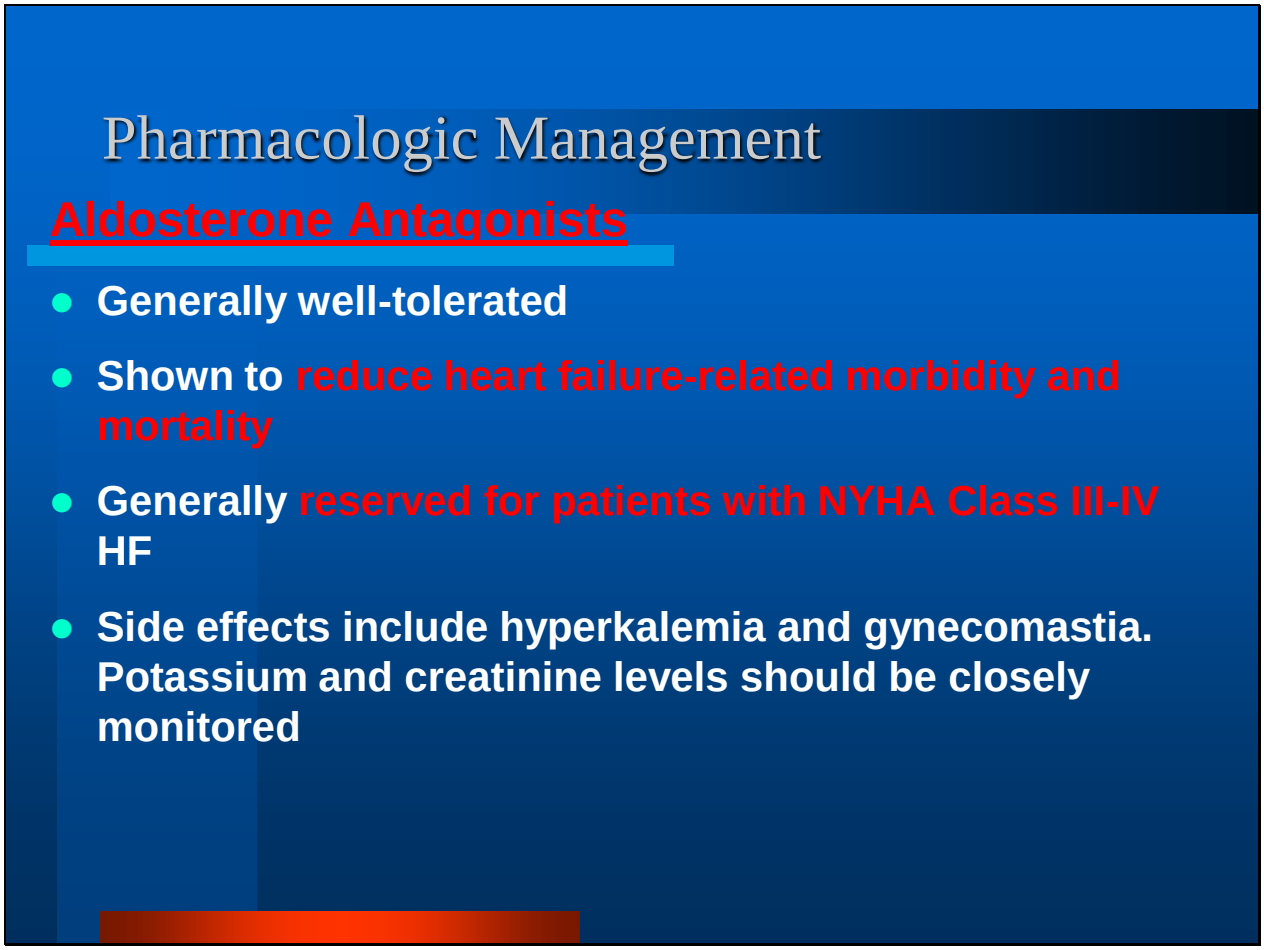
In the past, beta-blockers were believed to be contraindicated in patients with heart failure because of the LV depression that occurs with short-term use. More recently, the favorable long-term effects of beta-blockade on the heart have been recognized, and the ACC/AHA guidelines support the use of beta-blockers for patients with stable NYHA Class I, II or III heart failure related to LV systolic dysfunction.

Beta-blockers are generally well-tolerated. Hypotension associated with dizziness, light-headedness, or blurred vision may occur within the first few days of treatment, but tends to subside with continued drug administration. Decreases in heart rate and alterations in cardiac conduction produced by beta-blockers may also lead to to bradycardia or heart block. These

changes can be severe, causing symptomatic hypotension, especially when high doses are used. In these cases, the dose must be reduced or discontinued if the condition persists. Carvedilol (COPERNICUS Trial), bisoprolol (CIBIS-II Trial), and metoprolol CR/XL (MERIT-HF Trial) have all shown to decrease mortality in patients with mild to severe HF[1]. Currently, carvedilol and metoprolol-CR/XL are the only FDA approved beta-blockers for HF patients.

1 Young, J. Clinical Management of Heart Failure. Professional Communications, Inc. 2001. pp 96, 100, 178.

Slide 36



Aldosterone Antagonists

Spironolactone, long known for its potassium-sparing diuretic effects, is an aldosterone antagonist, and the only aldosterone antagonist available for clinical use in the US. The RALES study (Randomized Aldactone Evaluation Study), a multi-center mortality trial examined the effect of adding low-dose spironolactone to standard diuretic/ACE inhibitor therapy in HF (NYHA Class III and IV patients) has shown to reduce mortality in heart failure patients[1].

ACC/AHA Guidelines recommends the use of spironolactone in patients with severe HF. The role of spironolactone in patients with mild to moderate HF has not been defined, and use of the drug cannot be recommended in such individuals [2].

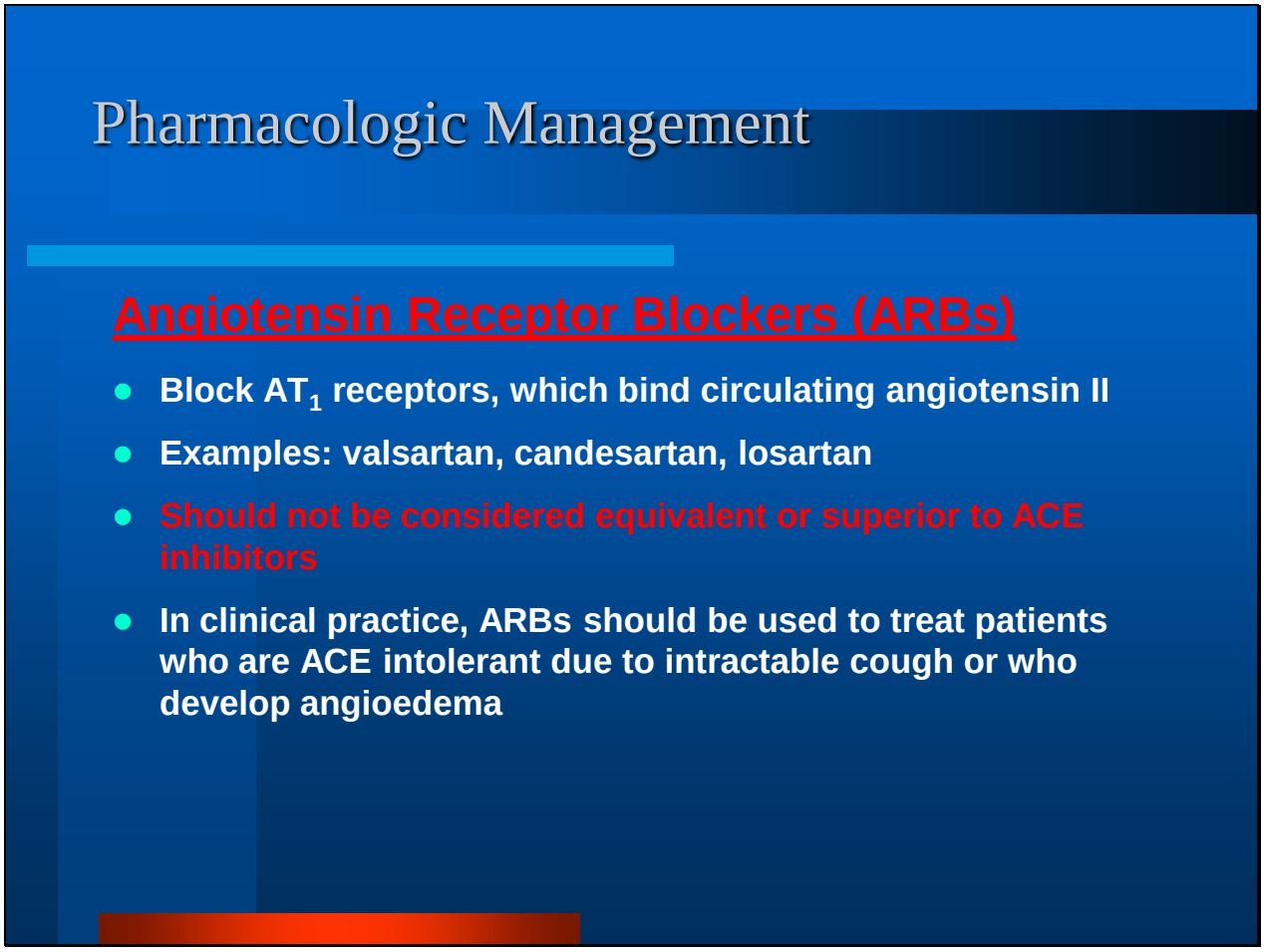
Hyperkalemia is a concern. Serum potassium and creatinine should be closely monitored, and patients with a potassium level >5 or creatinine >2.5 should not be treated with spironolactone.

While therapy with spironolactone is generally well-tolerated, about 9% of patients in the Randomized Aldactone Evaluation Study experienced gynecomastia (swelling of the mammary glands in the male).

1 McMurray, J and Cleland, J. Heart Failure in Clinical Practice. Second Edition. Martin Dunitz Ltd. p 101.

2 Hunt, SA, et al ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2001 pp 23-24

Slide 37



Angiotensin Receptor Blockers

Angiotensin receptor blockers, or "ARBs," are the newest class of drugs to be promoted as a potential treatment for patients with heart failure. ARBs are most often given when a patient cannot tolerate an ACEI. To understand how these unique drugs work, we must first take a closer look at angiotensin II and and the receptors that bind it. Angiotensin II, as we learned previously in this program, is produced from angiotensin I by the action of angiotensin converting enzyme (ACE). As we now know, angiotensin II has a number of potentially adverse effects that contribute to the development and progression of HF, including vasoconstriction, salt and water retention, and activation of the SNS. In addition, angiotensin II is associated with collagen deposition, fibrosis, and myocardial and vascular hypertrophy, which contribute to cardiac remodeling.

The effects of angiotensin II throughout the body are mediated via two receptor subtypes, designated AT_1 and AT_2, which bind angiotensin II. The AT_1 receptor has been extensively studied, and has been shown to be widely distributed in the vasculature, heart, kidneys, adrenal glands, and brain. The AT_1 receptor subtype is responsible for most of the physiologic effects of angiotensin II on blood pressure, salt and water balance, and cell growth, and therefore plays a central role in the pathogenesis of heart failure.

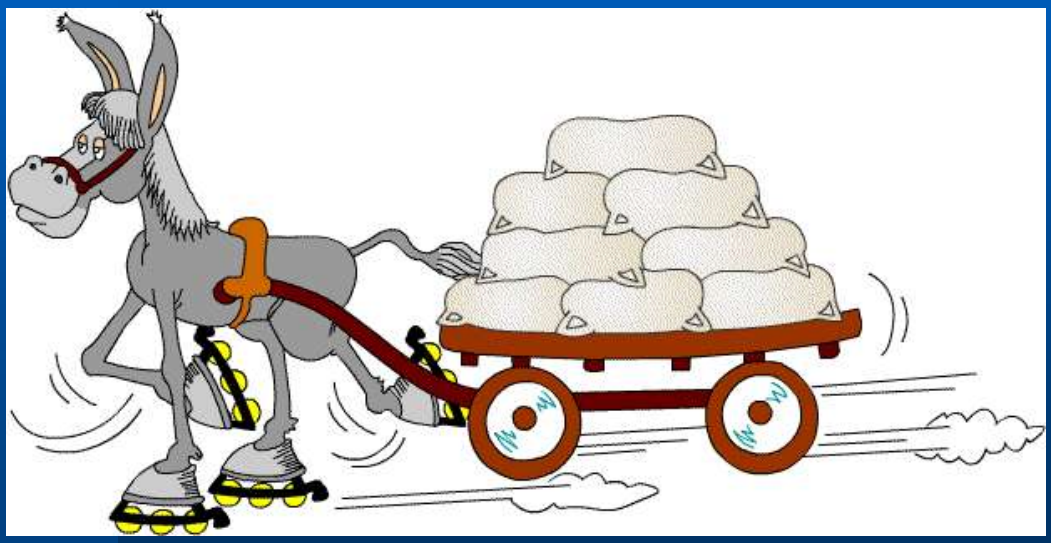
Slide 38

Part IV: Assessment and Treatment of the Heart Failure Patient

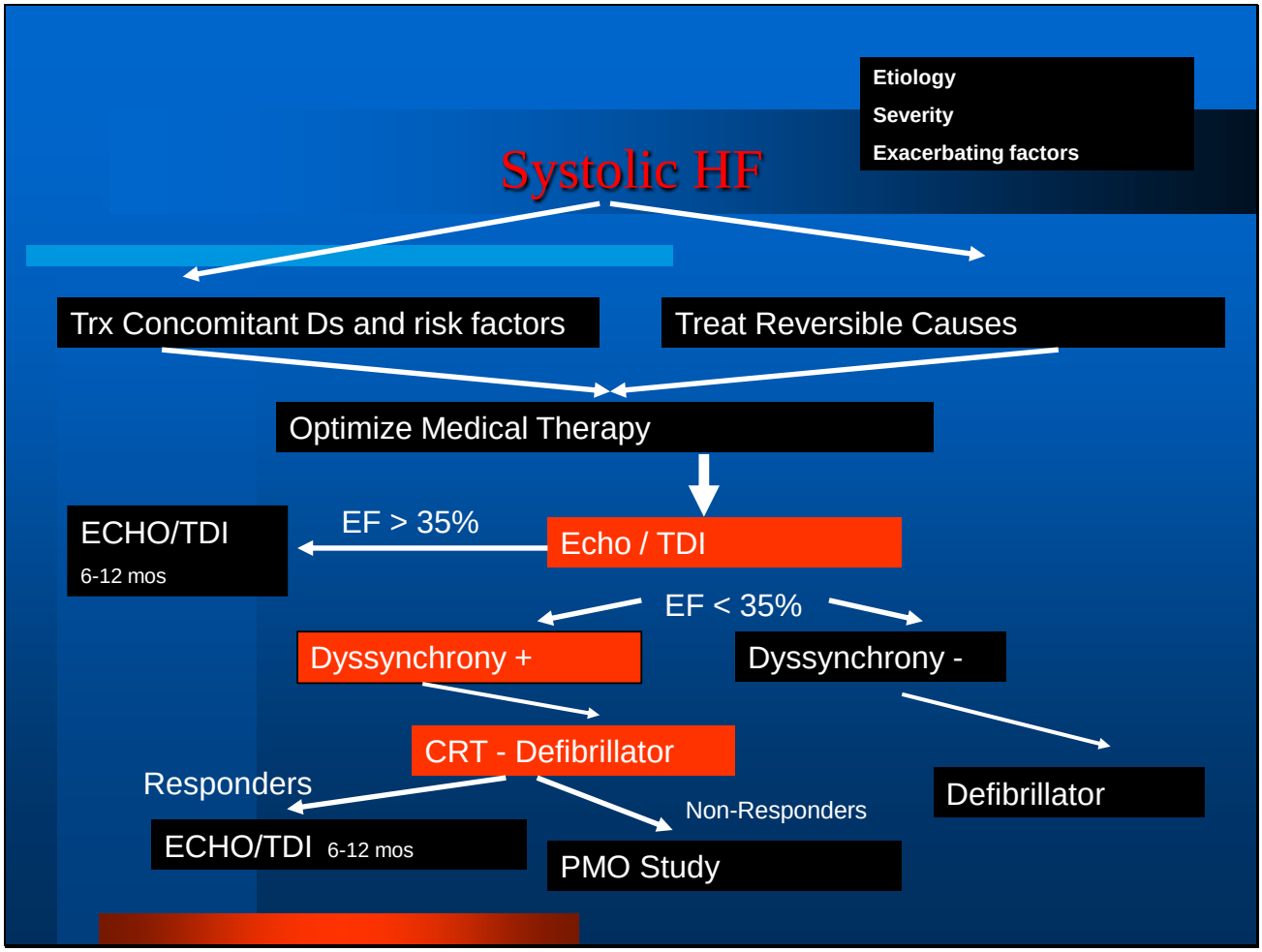
Slide 39

Cardiac Resynchronization Therapy

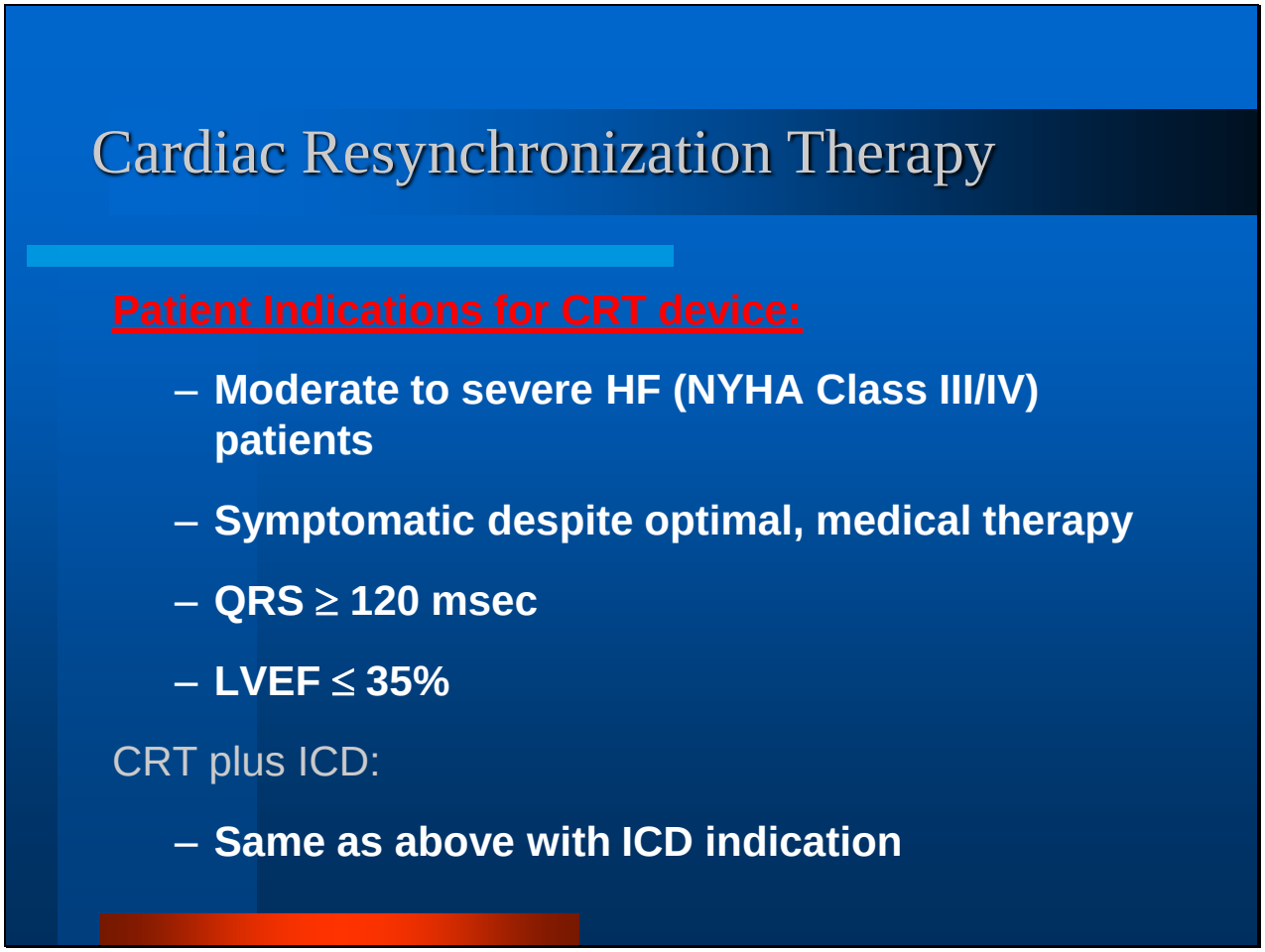
Increase the donkey's (heart) efficiency



Slide 40

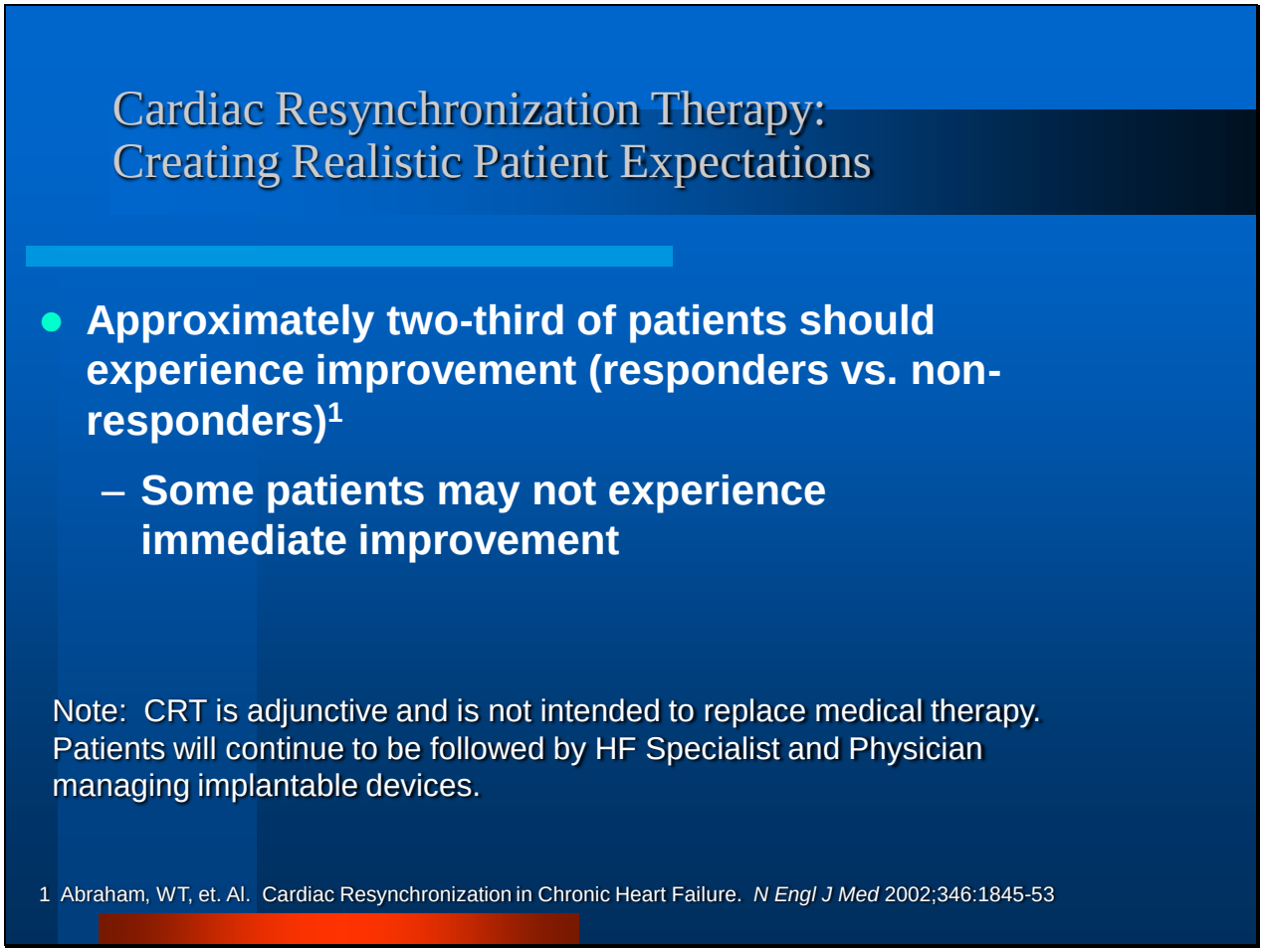

Etiology
Severity
Exacerbating factors
Systolic HF
Trx Concomitant Ds and risk factors
Treat Reversible Causes
Optimize Medical Therapy
ECHO/TDI
6-12 mos
EF > 35%
Echo / TDI
EF < 35%
Dyssynchrony +
Dyssynchrony -
CRT - Defibrillator
Responders
Non-Responders
Defibrillator
ECHO/TDI 6-12 mos
PMO Study

Slide 41



Cardiac resynchronization is a new, proven therapy which improves the ventricular pumping efficiency in moderate to severe heart failure patients with ventricular dysynchrony by simultaneously pacing both right and left ventricles.

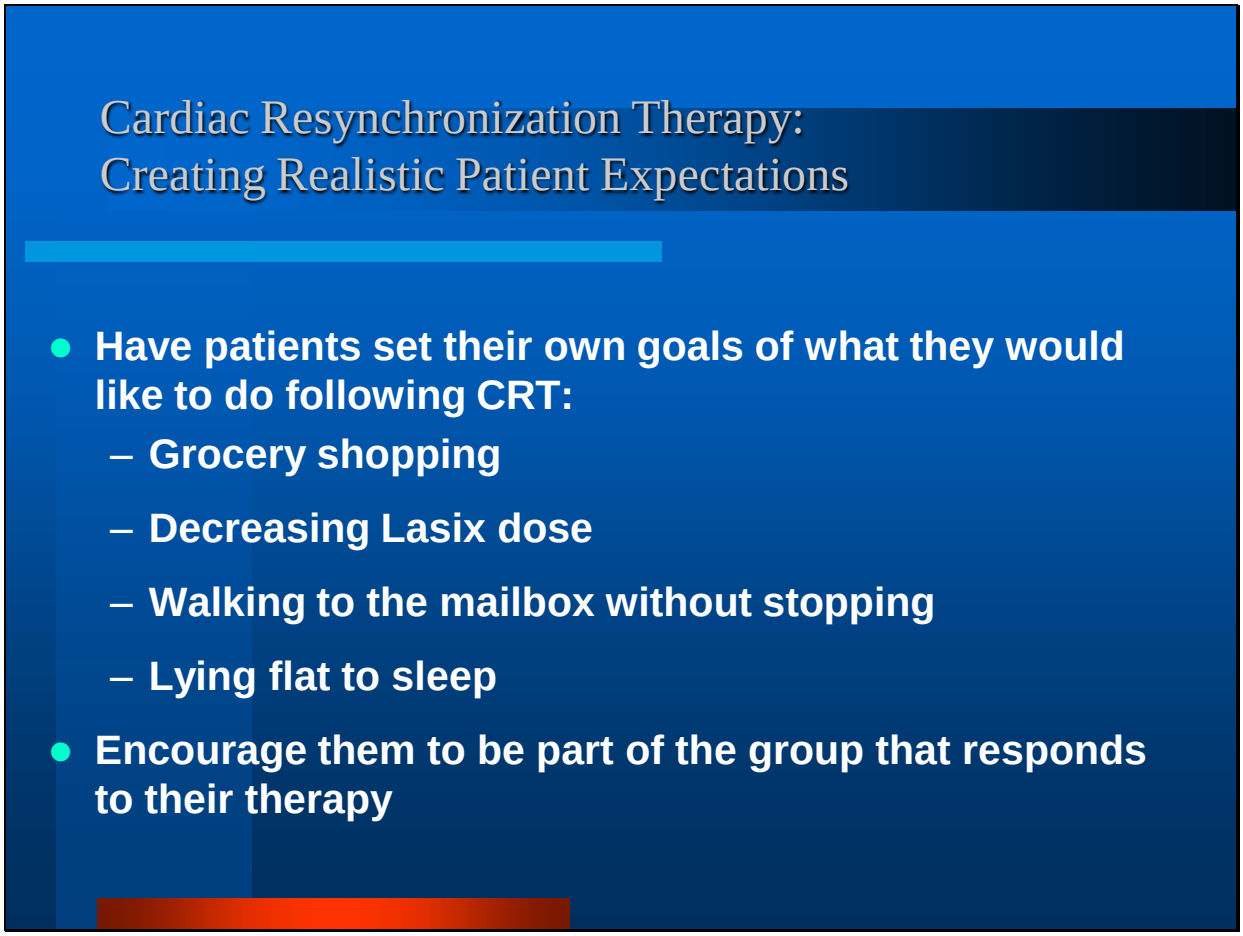
Slide 42



Some of the most frequently asked questions by patients:

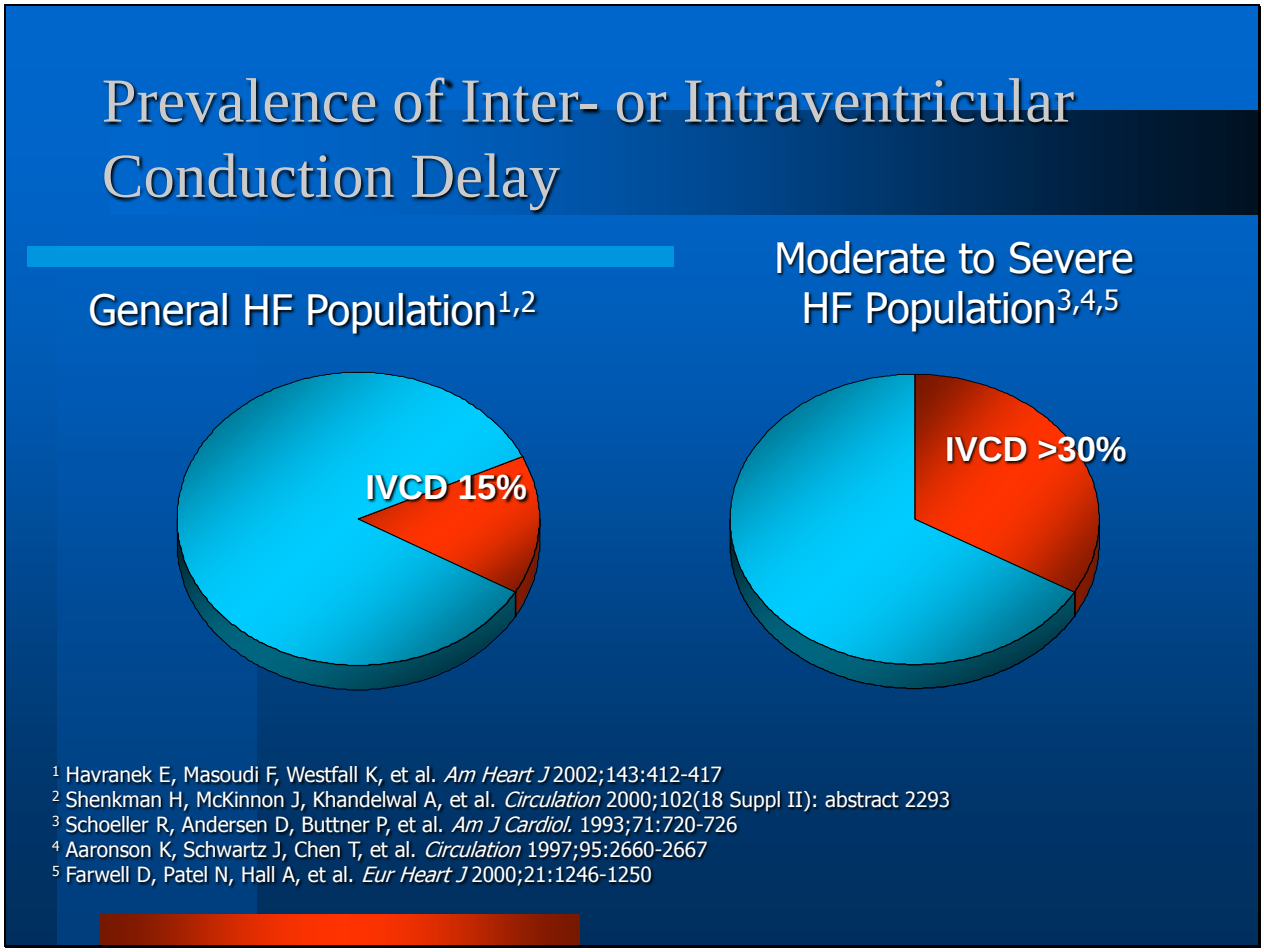
- What are the chances that this procedure will be successful and make me feel better?
- How soon after the procedure can I expect to see improvement in the way I feel?
- Will I still have to see my HF specialist?
- Will I still have to take medicine?
- Will the device be noticeable?
- How long will the procedure take?

Slide 43



It is very important that a patient set his/her own goals to therapy that are realistic.

Slide 44

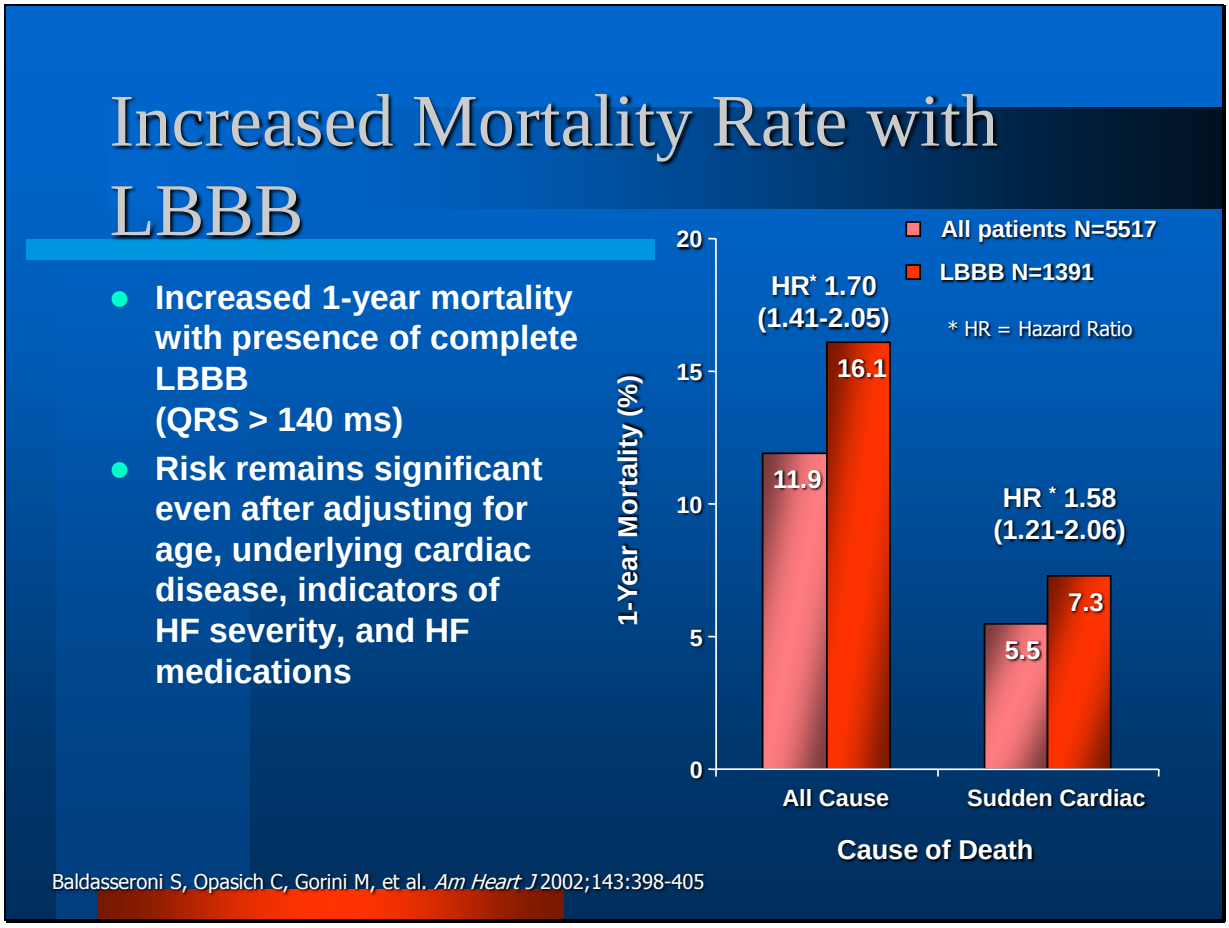


Approximately 15% of all heart failure patients have an inter- or intraventricular conduction delay (QRS > 120 msec)[1-2].
Over 30% of moderate to severe heart failure patients have a prolonged QRS. The prevalence of conduction defects increases with severity of heart failure.[3-5]
Shenkman and colleagues 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**

Slide 45



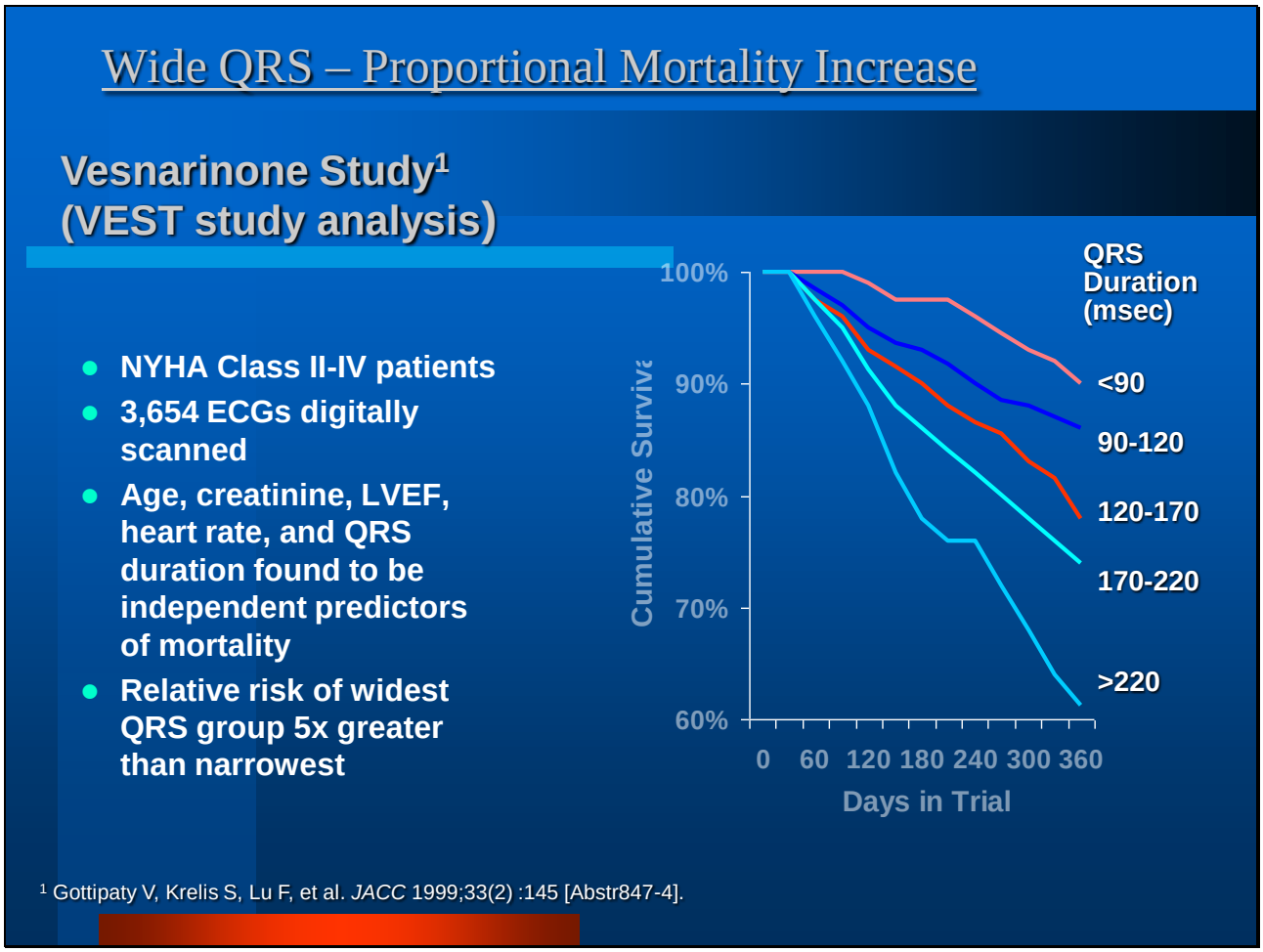
This slide was developed using data from Italian Network on CHF Registry, established in 1995 in 150 cardiology centers distributed throughout Italy. The group defined complete LBBB as a QRS duration greater than 140 ms.

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

Slide 46



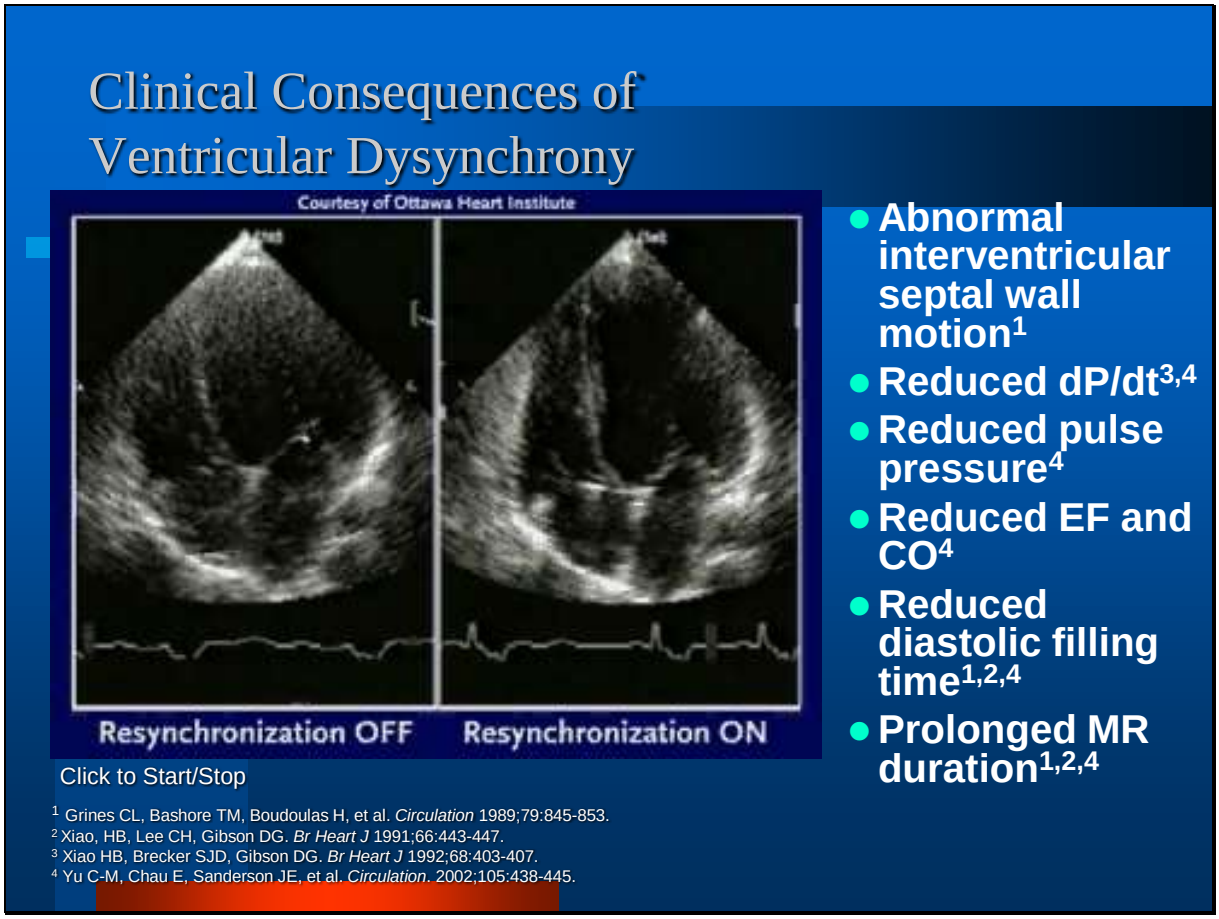
The VEST Study demonstrated QRS duration was found to be an independent predictor of mortality.
Patients with wider QRS (> 200 ms) had five times greater mortality risk than those with the narrowest (< 90 ms).
Resting ECG is a powerful yet accessible and inexpensive marker of prognosis in patients with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

Slide 47



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.

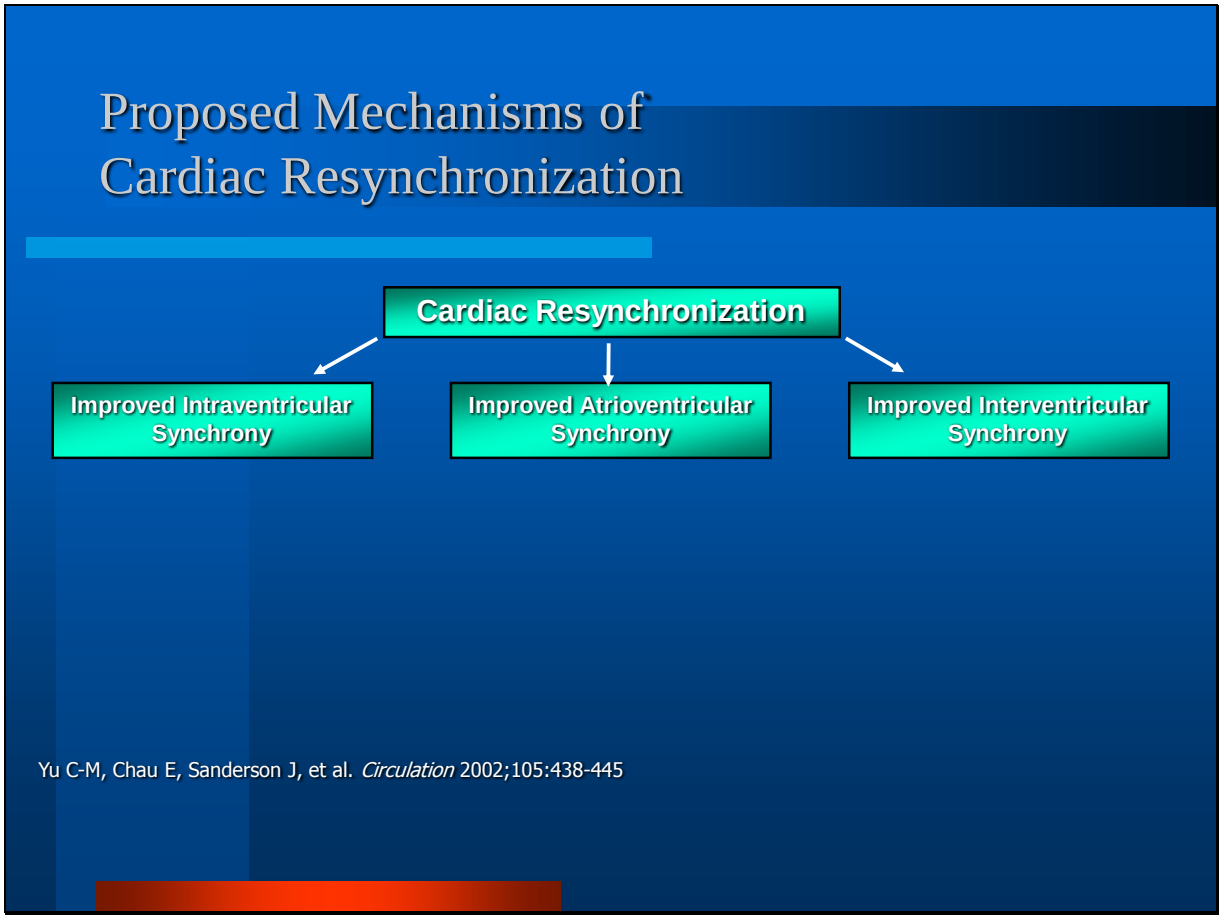
Xiao Lee C, Gibson D. effect of left bundle branch block on diastolic function in dilated cardiomyopathy. *Br Heart J* 1991;66:443-447.

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.

Slide 48



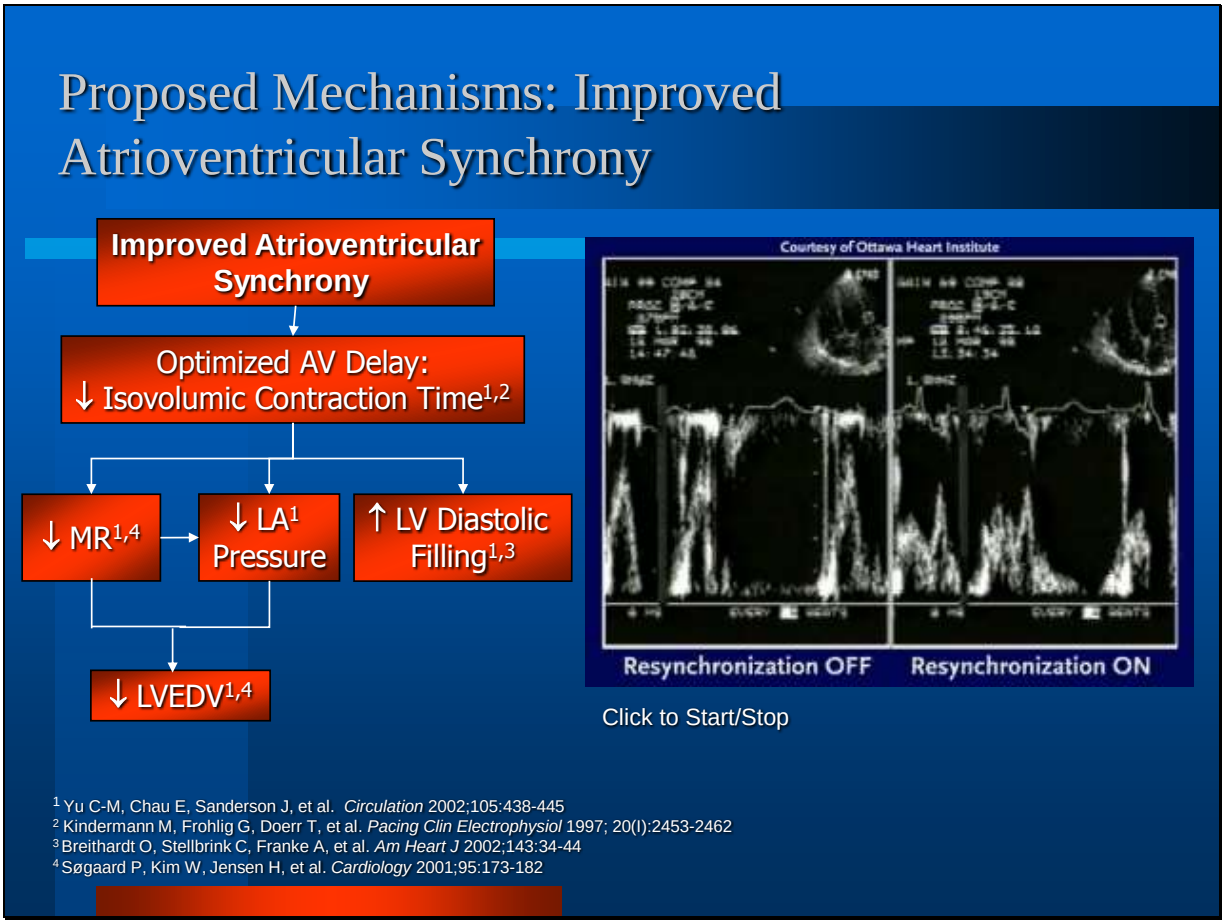
Heart failure patients have problems with ventricular remodeling (progressive LV dilitation and loss of contractile function). The goal in treating these patients is to prevent remodeling or reverse it, if possible. This slide reflects the three proposed mechanisms of benefit attributed to cardiac resynchronization 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.

Slide 49



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(I):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.

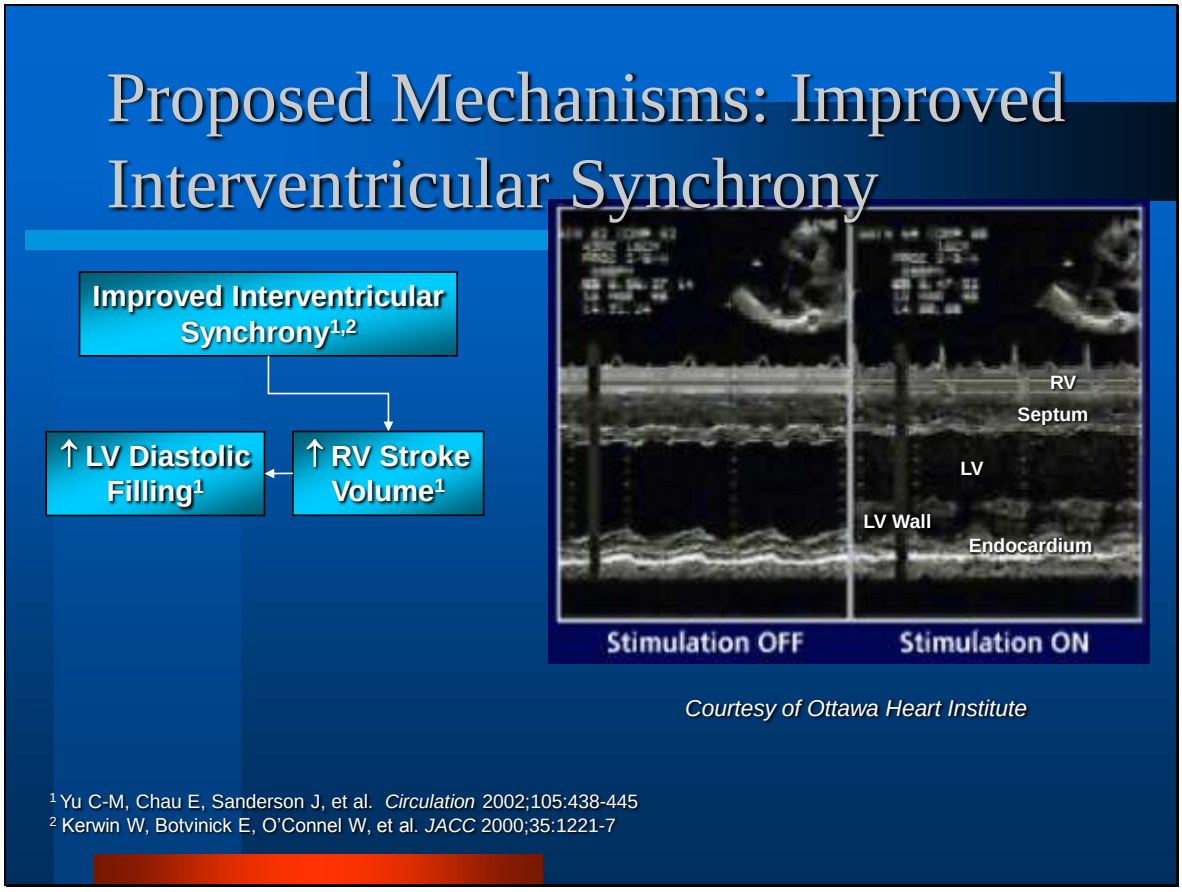
Sogaard P, Kim W, Jensen Henrik, Mortensen P, Pedersen A, Kristensen B, Egeblad H. Impact of acute biventricular pacing on left ventricular performance and volumes in patients with severe heart failure. *J Am Coll Cardiol* 2001;38:1957–1965.

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 resynchronization On, note less fusion of the E and A-waves and improved diastolic filling time.

Slide 50



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).

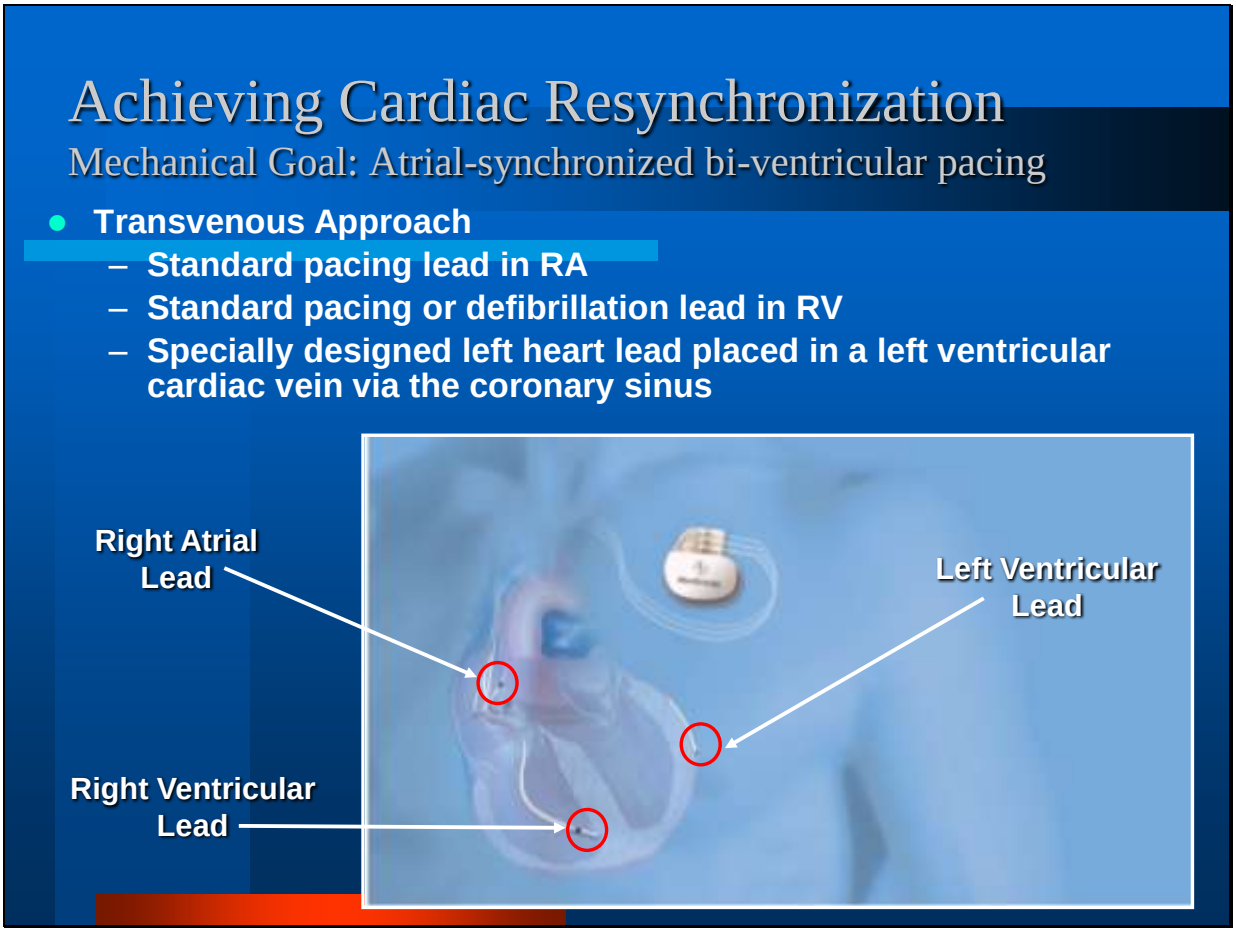
The still images of the M-mode echos above illustrate how the LV freewall contracts toward a stable septum with cardiac resynchronization On versus away from the septum with cardiac resynchronization Off.

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.

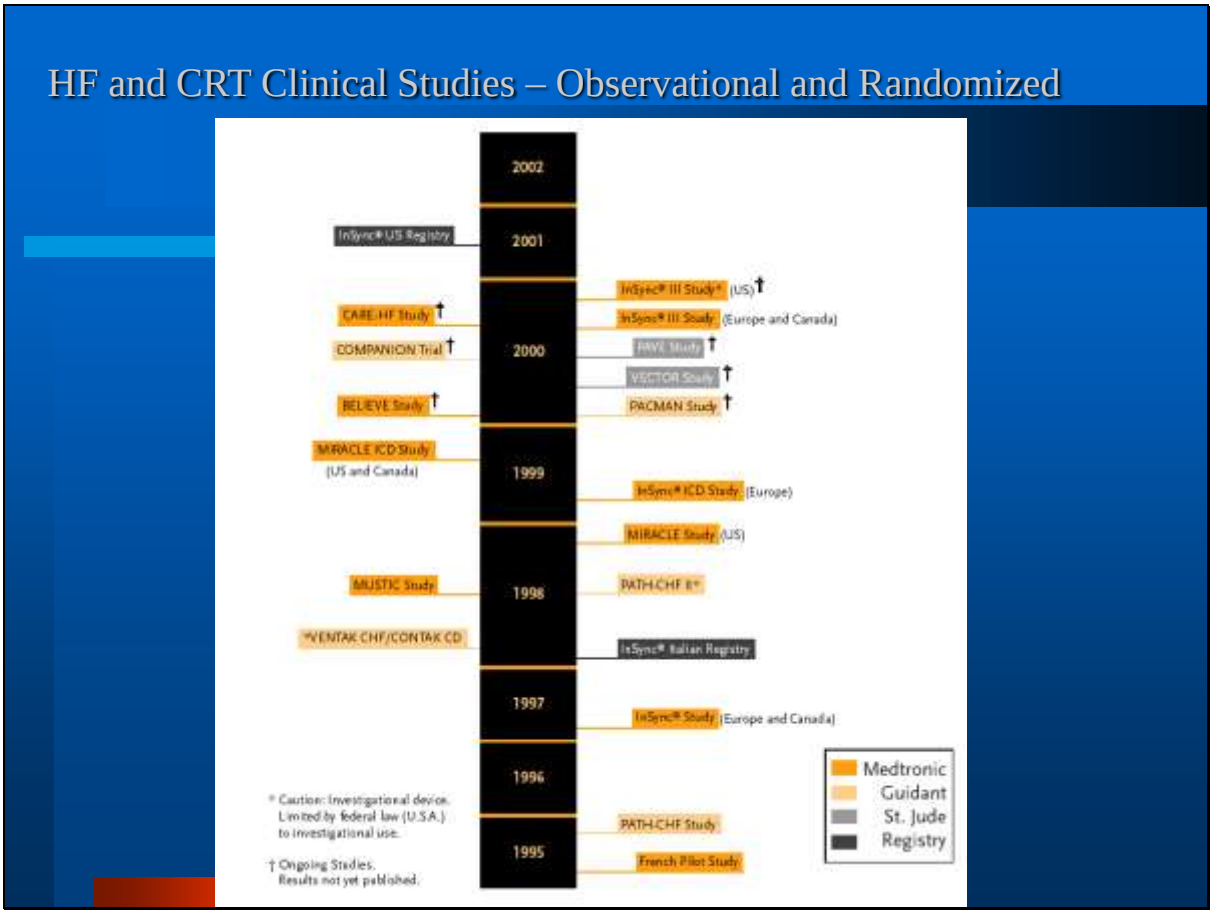
In this still echo picture, note with resynchronization OFF, the LV wall moves away from the interventricular septum during systole. With resynchronization ON, the LV wall moves toward the interventricular septum.

Slide 51



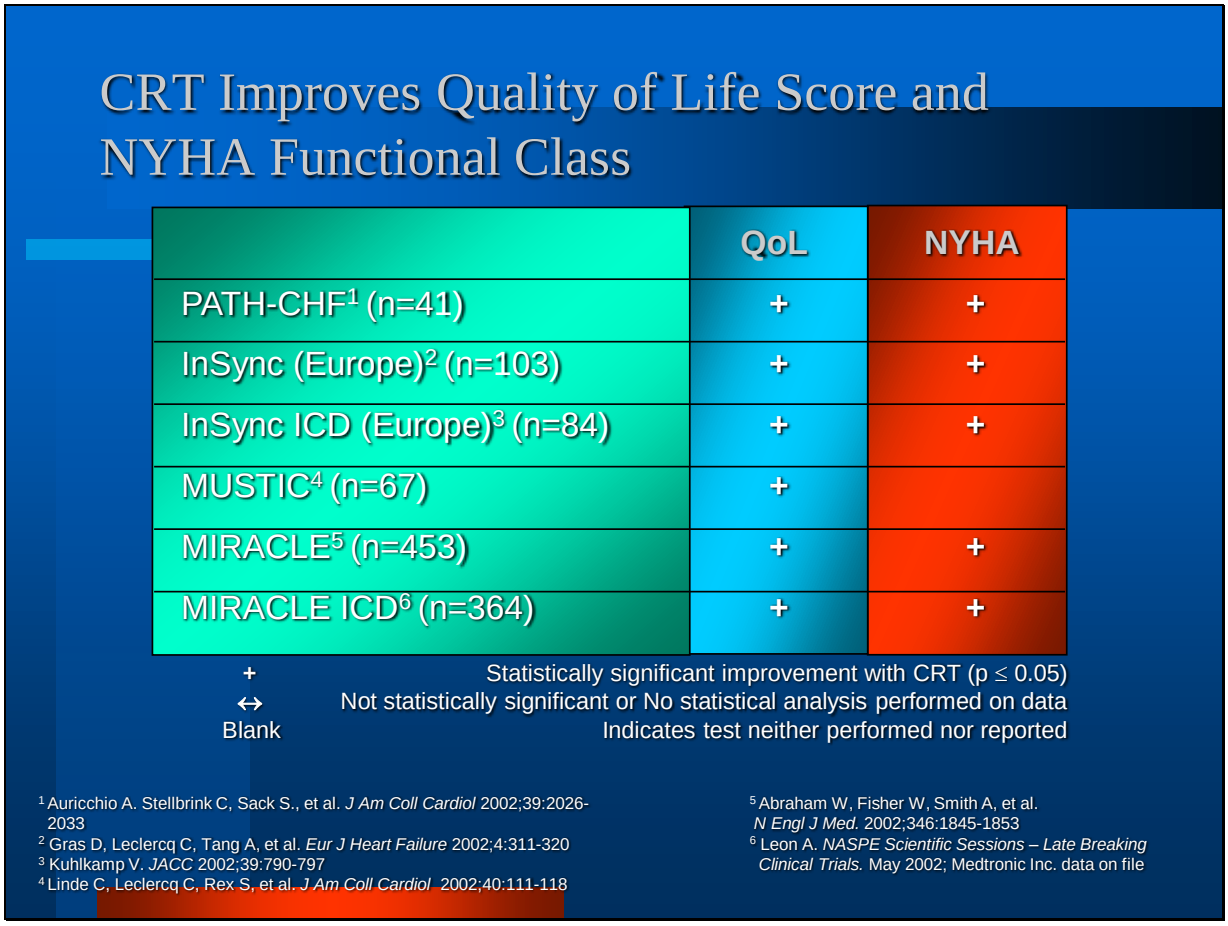
A specially designed pacing lead is passed through the coronary sinus into a cardiac vein on the left lateral freewall.
A standard pacing lead is placed in the right atrium. If the patient is indicated for an ICD and receives a device that combines both VT/VF therapies with cardiac resynchronization,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

Slide 52



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

Slide 53



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 echocardiographic parameters.

Slide 54

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.

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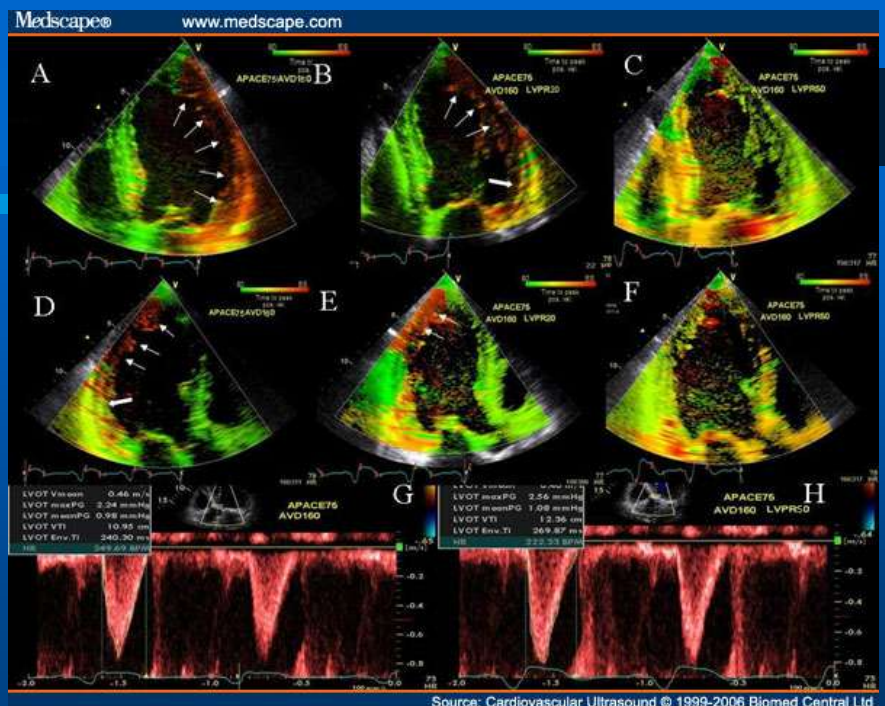
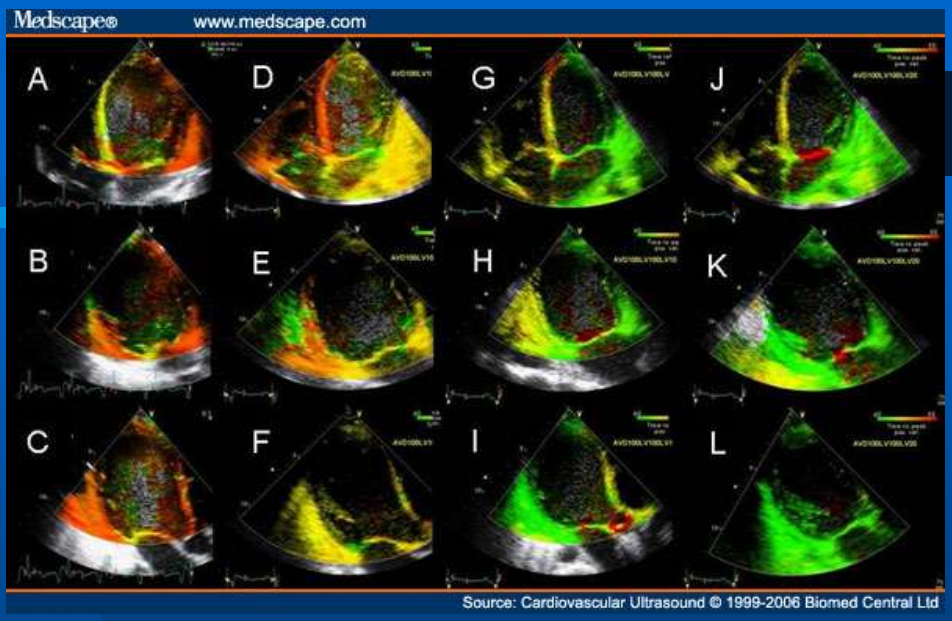
TSI



Source: Cardiovascular Ultrasound © 1999-2006 Biomed Central Ltd

Color bar at the top right of each panel denotes severity of delay in peak contraction during ejection phase. In TSI, normal myocardium is coded in green. Presence of delay is coded in progressive sequence of green, yellow, orange, and red. Figure shows severe lateral wall (white arrows, A) and posterior wall delay (white arrows, D) which decreased at LV pre-excitation of 20 ms (white arrows, B and E) and was abolished (C and F) at LV pre-excitation of 50 ms is shown

Slide 56



Significant mechanical dyssynchrony was identified on TSI in the apical 4 (A), 2 (B) and 3 chamber (C) views (red color in the myocardium). Panels D-F are same views post CRT at AVD of 100 and VV delay of 0 ms. LV pre-excitation by 10 ms is shown in panels G-I and by 20 ms in panels J, K and L respectively

Slide 57

TVI

Tissue velocity maps obtained at baseline (A and C), during LV pre-excitation of 20 ms (B and D) and during LV pre-excitation of 40 ms (C and E) in apical 4 and 3 chamber views

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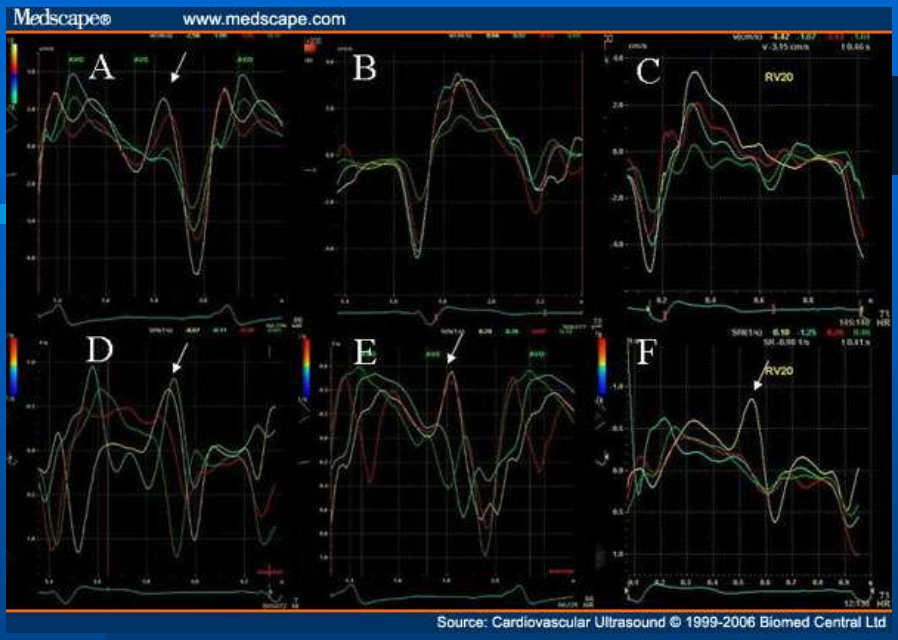
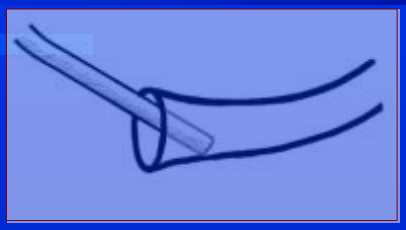


Tissue velocity (A, B and C) and strain rate (D, E and F) maps in the apical 2 chamber view at baseline pre cardiac resynchronization treatment (A and D), post cardiac resynchronization treatment with LV pre-excitation of 20 ms (B and E) and post optimization with RV pre-excitation of 20 ms (C and F

Slide 59

Step 1: Cannulate CS
Attain LDS Model 6216A

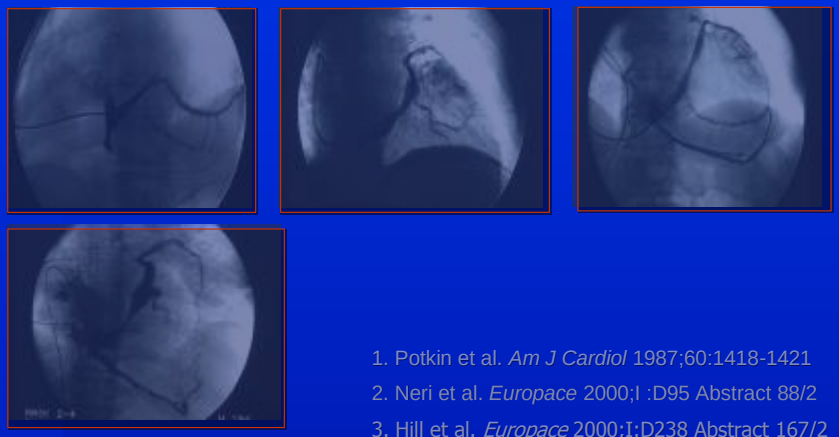


- Use extreme care when passing the guide catheter through vessels
- Due to the relative stiffness of the catheter, damage to the walls of the vessels may include dissections or perforations

Slide 60

Step 2: Perform Venograms

Varying Patient Anatomy [1,2,3]



1. Potkin et al. *Am J Cardiol* 1987;60:1418-1421
2. Neri et al. *Europace* 2000;I :D95 Abstract 88/2
3. Hill et al. *Europace* 2000;I:D238 Abstract 167/2

Photos Courtesy of Dr. Daniel Gras

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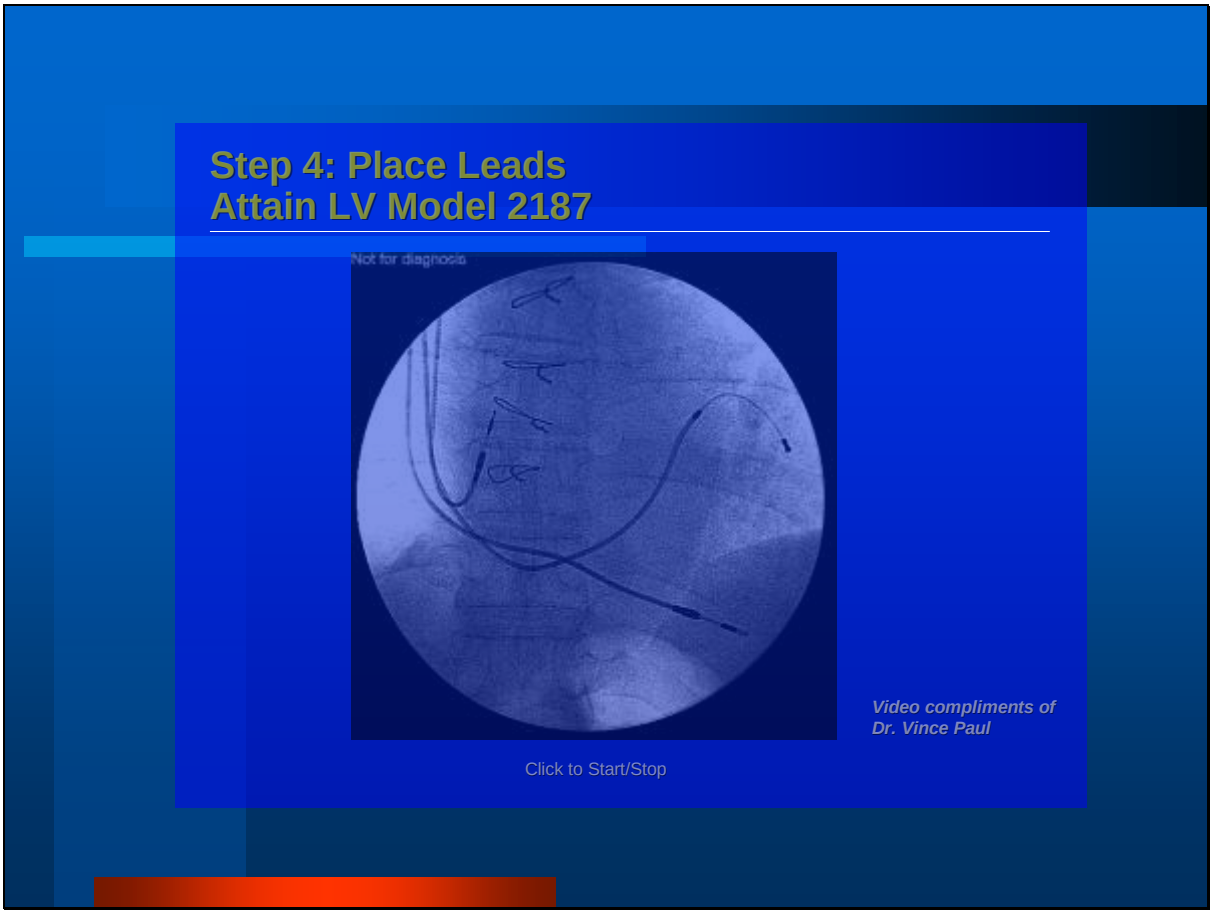
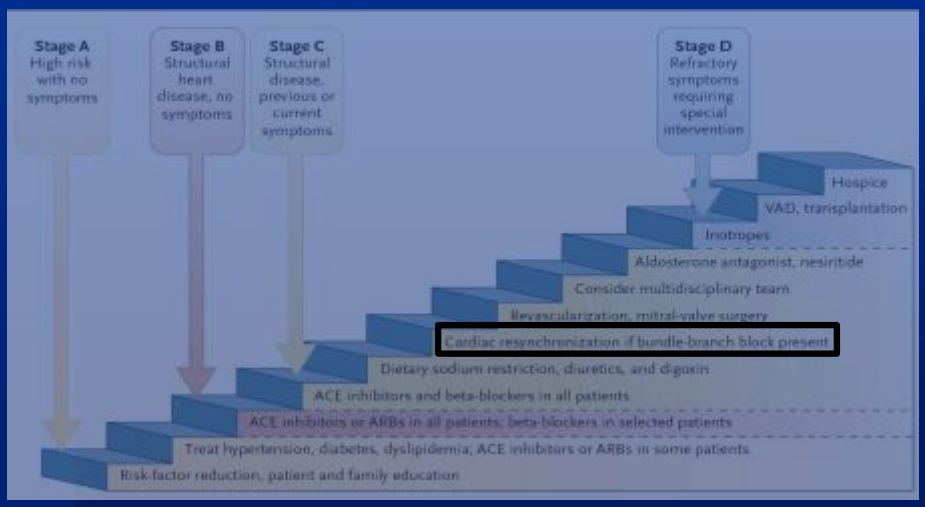

Step 4: Place Leads
Attain LV Model 2187
Not for diagnosis
Video compliments of
Dr. Vince Paul
Click to Start/Stop

Slide 62

Stages of Therapy



Jessup M. N Engl J Med. 2003:348;.2007-2018

Slide 63


Synchrony:
It's important thing to improve CHF patients quality of life?

Slide 64

Slide 65