Heart Failure with Preserved Ejection Fraction: Mechanisms and Management

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Heart Failure

- A clinical syndrome resulting from cardiac dysfunction superimposed on a structural abnormality of the left ventricle
Cardiovascular Abnormalities

Functional

Structural
Effect of Impedance Reduction on Left Ventricular Performance

SV

Impedance

Normal

Vasodilators

Heart Failure
Role of Ventricular Compliance in CHF

![Graph showing the relationship between end-diastolic ventricular volume, pressure, and CHF.

- **Normal Heart**
- **CHF (Decreased Compliance)**
- **Threshold for Congestive Symptoms**

End-Diastolic Ventricular Volume vs. Pressure

End-Diastolic Ventricular Filling vs. Pressure

Threshold for Congestive Symptoms
LV Remodeling

↑ WT
↑ Mass
↑ LVDD
↑ Mass
LV Performance

↑ Impedance

Function
- Vasoconstrictor Neurohormone Activation
- Symptoms
  - Pump Failure
  - Easily Reversible

Structure
- Growth Neurohormone Activation
- Progression
  - Mortality
  - Slowly Reversible

LV Remodeling
Fig. 4. A: external view of heart 12 wk after shock demonstrating necrotic area extending from apex to base of left ventricle. B: transverse myocardial slice of heart in A showing thinned area on anterior left ventricle free wall.
Fig. 1. Change in global end diastolic volume (EDV), end systolic volume (ESV), and ejection fraction (EF) with phenylephrine challenge in the control group at baseline and 4 weeks (delta Vol and delta EF represent change in these parameters from data obtained during resting conditions and those obtained at a peak systolic pressure of 200 mmHg). Solid bar, baseline; hatched bar, 4-week study. *P < .05 with baseline.
Figure 2. Line plots show individual left ventricular mass (L.V.M.) and volume (L.V.V.) measurements from the control group.
Figure 2. Absolute change from baseline in left ventricular mass (LVM) and volume (LVV) at 1 and 16 weeks after myocardial damage in control and nitrate-treated groups. Values represent mean value ± 1 SD.
Fig 1. Bar graphs show relative antiremodeling effects of terazosin (black bars) and zofenopril (gray bars) compared with the control group (open bars) expressed as absolute changes in left ventricular mass (L.V.M.) in the top panel and left ventricular volume (L.V.V.) in the bottom panel. *Statistically different from control group ($P < .025$); †Statistical difference between zofenopril and terazosin groups ($P < .025$).
Left Ventricular Remodeling

SV 100
EF 60

SV 100
EF 40

SV 100
EF 25
Structural Basis for Heart Failure

Ventricular Remodeling and Its Pharmacological Inhibition

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The syndrome of heart failure has traditionally been viewed as a functional disorder precipitated by impaired left ventricular pump performance. The classification into systolic and diastolic dysfunction has emphasized the functional distinction between abnormalities in contraction and relaxation. Recently, however, attention has been directed toward fraction in the absence of peripheral demand for a high stroke volume. Therefore, it is perhaps appropriate to reexamine our approach to classifying heart failure as systolic or diastolic dysfunction on the basis of the ejection fraction. Perhaps remodeling, not contractile dysfunction, is the key to the severity of depression of ejection fraction.
Normal  
Eccentric Hypertrophy  
(in series)  
Concentric Hypertrophy  
(in parallel)
Classifications of Heart Failure

- Ejection Fraction (HFrEF, HFpEF, HFrecEF)
- End-diastolic chamber size
- Systolic vs. Diastolic
- Myocyte dimension
- Collagen content
- Symptoms (NYHA I-IV, QOL)
- Etiology (ischemic vs. non-ischemic)
Cardiac and Vascular Interaction
Large and Small Artery Elasticity Measurements

Capacitive Function (large artery elasticity)

Oscillatory/Reflective Function (small artery elasticity)

Systemic Vascular Resistance
• **Arterial Remodeling**

A structural process in which vascular smooth muscle hypertrophy, hyperplasia or realignment results in an alteration in configuration of the wall and/or lumen and contributes to altered arterial resistance, compliance and distensibility. It is linked to dysfunction of the endothelium and involves the large conduit arteries, the smaller distributive arteries and the arterioles. Prevention and reversibility are likely in response to appropriate interventions.
Femoral Artery
Impaired NO Release

- Platelet aggregation
- Increased vascular tone (decreased compliance)
- VSM hypertrophy / hyperplasia
- Atherosclerosis
Growth

Remodeling

From Mulvany: *Curr Opin Nephrol Hyperten* 1993;2:78
Small Artery Compliance

P

NO Deficiency

V
Large Artery Compliance

P

V

AGING
Causes of endothelial dysfunction

- Genetic
- Diabetes
- Smoking
- Obesity
- Inactivity
- Hypertension
- Elevated LDL cholesterol
- Reduced HDL cholesterol
Natural History of Heart Failure

Age (Years)

CV Disease

Endothelial Dysfunction

Vascular Remodeling

Neurohormone Activation

LV Remodeling

? Hypertension

? M.I.

Heart Failure
Influences on Cardiovascular Aging

- Smoking
- Obesity
- Inactivity

- ACE I/ARB’s
- Statins
- Beta Blockers
- Antioxidants
- Exercise

CV Disease

Genomic Determinants

Age (Years)
Goals of Therapy

• Make patient feel better
  – Symptom relief
  – Improve Q of L
  – Prevent hospitalization

• Make patient live longer
  – Survival assessment
  – ? Slow LV structural disease progression
Interventions that Inhibit LV Remodeling

- ACE Inhibitors
- Beta blockers
- Angiotensin Receptor Blockers
- Isosorbide dinitrate + hydralazine
- Sacubitril/valsartan
- Aldosterone Antagonists
- Resynchronization therapy
- Sinus node slowing (ivabradine)
- Left ventricular assist devices
Interventions that Relieve Symptoms in Heart Failure

- Diuretics
- Ultrafiltration
- Drugs that relax arteries
- Drugs that relax veins
- Counter-pulsation
- Positive Inotropic drugs
- Re-synchronization
Conclusions regarding Mechanisms and Management

• HFrEF and HFpEF are not distinct entities but have mechanistic overlap
• Benefit of therapy is mechanistic, not necessarily based on EF
• HFpEF is more common in the elderly with CV aging and reduced life expectancy
• Symptom relief and improved QOL are dependent on hemodynamic benefit
• Life prolongation is dependent on structural benefit
Conclusion regarding HFpEF

Prevention by delaying the process is more effective than treatment.