Hemodynamic Refresher
LV Pressure Volume Loops

Diagram showing the LV Pressure Volume Loops with phases a, b, c, and d. Key points include:
- Aortic Valve Opening
- Aortic Valve Closing
- Mitral Valve Opening
- Mitral Valve Closing
- LVP (mmHg)
- LV Vol (ml)
- Time

Graph on the right shows:
- ESPVR
- EDPVR
- SV (Stroke Volume)
- ESF (End-Systolic Volume)
- EDH (End-Diastolic Volume)
Effect of Acute Changes in Preload

Increasing preload

Decreasing preload
Effect of Acute Changes in Afterload

Increasing afterload

Decreasing afterload
Assessment of LV Contractility: LV $E_{\text{max}}$
Effects of Chronic Increases in Preload or Afterload on LV Hypertrophy Pattern

Primary Stimulus

Pressure Overload → ↑ Peak Systolic

Volume Overload → ↑ End Diastolic

Parallel Replication Of Sarcomeres → Wall Thickening

Series Replication Of Sarcomeres → Chamber Enlargement

CONCENTRIC LVH

ECCENTRIC LVH

Carabello et al 1992, Am J Physiol
Collagen Skeleton of the Heart
Diastolic Dysfunction

DCM-Systolic Heart Failure

Normal

POH-Diastolic Heart Failure
Transition to Heart Failure

Colucci WS: Heart Failure: Cardiac Function and Dysfunction, 1995
Calcium Homeostasis in Cardiomyocyte

Bers *Circ Res* 87:275, 2000
Patient with Isolated MR
Ejection Dynamics in Chronic MR: Decreased LV $E_{\text{max}}$ Despite Normal LVEF
Pathologic vs Physiologic LVH

Normal  Marathon Runner  Chronic Mitral Regurgitation
Magnetic Resonance Imaging After 4 Months of MR

Dell’Italia, AJP 269:H2065, 1995
LV Remodeling of Cardiomyocyte and Extracellular Matrix in Canine MR

Dell’Italia, AJP 273:H961, 1997
Asymptomatic Isolated MR

Event-free Survival (%)

Years

Pts. at risk:

<table>
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<tr>
<th></th>
<th>OP</th>
<th>CONV</th>
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<tr>
<td>0</td>
<td>127</td>
<td>127</td>
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<tr>
<td>1</td>
<td>125</td>
<td>125</td>
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<tr>
<td>2</td>
<td>106</td>
<td>105</td>
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<tr>
<td>3</td>
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<td>78</td>
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<td>4</td>
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P = 0.001

7-yr event-free survival 99 ± 1%

7-yr event-free survival 85 ± 4%
Increased Oxidative Stress and Cardiomyocyte Myofibrillar Degeneration in Patients With Chronic Isolated Mitral Regurgitation and Ejection Fraction >60%

Mustafa I. Ahmed, MD,* James D. Gladden, BS,* Silvio H. Litovsky, MD,* Steven G. Lloyd, MD, PhD,* Himanshu Gupta, MD,* Seidu Inusah, MS,* Thomas Denney Jr, PhD,‡ Pamela Powell, MS,* David C. McGiffin, MD,* Louis J. Dell'Italia, MD†

Birmingham and Auburn, Alabama
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n = 39)</th>
<th>Pre-MV Repair (n = 23)</th>
<th>6 Months post op (n = 23)</th>
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</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>51 ± 1</td>
<td>62 ± 1*</td>
<td>55 ± 2#</td>
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<tr>
<td>LVESD</td>
<td>33 ± 1</td>
<td>38 ± 2*</td>
<td>37 ± 2</td>
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<tr>
<td>LV Mass (g)</td>
<td>96 ± 4</td>
<td>145 ± 9*</td>
<td>113 ± 6#</td>
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<tr>
<td>LVEDV (ml/m²)</td>
<td>68 ± 2</td>
<td>116 ± 5*</td>
<td>79 ± 5#</td>
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<tr>
<td>LVESV (ml/m²)</td>
<td>24 ± 2</td>
<td>43 ± 3*</td>
<td>38 ± 4*</td>
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<tr>
<td>LV SV (ml)</td>
<td>82 ± 3</td>
<td>136 ± 10</td>
<td>81 ± 4*</td>
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<tr>
<td>LV EF (%)</td>
<td>65 ± 1</td>
<td>65 ± 2</td>
<td>54 ± 2*</td>
</tr>
<tr>
<td>LVEDV / Mass</td>
<td>1.39 ± 0.06</td>
<td>1.58 ± 0.11*</td>
<td>1.35 ± 0.09*#</td>
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</tbody>
</table>
Normal Human Cardiomyocyte
Myofibrillar Degeneration in Human MR
Lipofuscin in Normal Human Cardiomyocyte
Lipofuscin in Human MR
Lipofuscin in Human MR by TEM
Lipofuscin in Human MR by TEM
Lipofuscin

• Nondegradable material primarily composed of oxidatively modified protein and lipid degradation residues

• Accumulation is usually seen in the aging heart and is considered to be the end product of excessive oxidative stress and overwhelmed protective mechanisms of the proteosome

• Deleterious effects on cellular function include triggering of mitochondrial pro-apoptotic pathways in cardiomyocytes and fibroblasts

• Oxidative stress enhances lipofuscin formation while administration of antioxidants decreases its formation
Why is XO Important?

- \( \cdot O_2^{-} \)
- \( \cdot O \)
- \( \cdot OH \)
- \( \text{OONO}^- \)
- \( \text{NO} \)
- \( \text{SOD} \)
- \( \text{H}_2\text{O}_2 \)

Reactions:
- Protein Oxidation
- DNA Damage
- Lipid peroxidation
Xanthine Oxidase

- Xanthine oxidase is widely distributed: liver, gut, lung, kidney, heart, brain, and plasma
- XO is capable of producing superoxide and hydrogen peroxide
- XO may have profound effects on the myocardium
  - XO depresses myofilament sensitivity to calcium
  - co-localises with nitric oxide synthase in SR and can cause oxidative myofilament damage
XO in Normal Human Cardiomyocyte
XO in Cardiomyocytes with Myofibrillar Degeneration in Human MR LV
Increased Nitrotyrosine Staining in Areas of Lipofuscin Accumulation (a) with Corresponding Image With Immunoabsorbed Antibody (b) in MR LV
Increased Xanthine Oxidase in Human MR Left Ventricle

Ahmed and Gladden JACC, In Press, Feb 16, 2010
The Vicious Cycle of XO-Mediated Oxidative Stress in VO

Increased catabolism of ATP/ADP

HX

↓ATP/ADP Ratio

Xanthine Oxidase

Oxygen Radical

O$_2^\cdot$
Mitochondria as Targets and Sources of Oxidative Stress In Cardiovascular Disease
Future Directions in VO

• Determine the connection
  – Increased oxidative stress
  – Mitochondrial dysfunction and reserve capacity
  – LV contractility
Translational Research