Heart failure from coronary heart disease. Present and future challenges.

I. KANONIDIS
Heart failure, a worldwide burden

26 million

Number of heart failure patients worldwide.¹

1-2%

Health care expenditure attributed to heart failure in Europe and North America.²

74%

Heart failure patients suffering from at least 1 comorbidity: more likely to worsen the patient’s overall health status.³
Prevalence of HF

North America
- Canada: 1.5%
- USA: 1.9%

Europe
- France: 2.2%
- UK: 1.3%
- ~1–2%

Asia
- China: 1.3%
- Japan: ~1%
- Malaysia: 6.7%
- Singapore: 4.5%

Middle East
- Oman: 0.5%

Australasia
- Australia: 1.3%
### Incidence - Framingham

<table>
<thead>
<tr>
<th>age (years)</th>
<th>men</th>
<th>women</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54</td>
<td>2</td>
<td>1</td>
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<tr>
<td>55–64</td>
<td>4</td>
<td>3</td>
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<td>65–74</td>
<td>8</td>
<td>5</td>
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<td>75–84</td>
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<td>85–94</td>
<td>54</td>
<td>85</td>
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<td>35–64</td>
<td>3</td>
<td>2</td>
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<tr>
<td>65–94</td>
<td>10</td>
<td>8</td>
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</tbody>
</table>

**Graph:**
- **X-axis:** Age (years)
- **Y-axis:** Annual rate per 1000
- **Legend:**
  - **Solid line:** women
  - **Dashed line:** men
Fig. 2.3  Aetiology of incident cases of heart failure in the Hillingdon Study: not otherwise specified causes are included.

- CAD (Coronary Artery Disease): 36%
- Hypertension: 13%
- Valvular: 7%
- Not known: 32%
- AF alone: 6%
- Others: 7%
- Alcohol: 4
- Cor pulmonale: 4
- Other arrhythmia: 5
- Hypertrophic CM: 1
- Restrictive CM: 1

These figures represent the distribution of causes for heart failure cases.
From AMI to HEART FAILURE
VENTRICULAR REMODELING

- Changes in ventricular architecture following acute myocardial infarction

Local changes          Early changes
Remote changes          Late changes
Remodeling

- Genetic changes
- Biochemical changes
- Molecular changes
- Cellular changes
- Structural changes
INFARCT EXPANSION

• Acute dilatation and thinning of the area of infarction not explained by additional myocardial necrosis.

(Hutchins and Bulkley 1978)
EXPANSION versus EXTENSION
MYOCARDIAL EXPANSION

Myocyte Necrosis
Oedema Inflammation
Degradation of the intermyocyte collagen struts
Resorption of necrotic tissue
Fibroblast proliferations
Collagen deposition
Scar formation

Hutchins and Bulkley (1978)
Factors influencing cardiac expansion

Infarct size

Transmurality of infarct

Infarct position (anterior – posterior)

Curvature of the infarct region (anterior – apical segment)

Coronary artery patency
\[ x = \text{endocardial length of asynergy-containing segment} \]
\[ y = \text{endocardial length of segment without asynergy} \]
\[ a = \text{average thickness of asynergic zone} \]
\[ b = \text{average thickness of non-asynergic zone} \]

**Expansion Index** = \( \frac{x}{y} \)

**Thinning Ratio** = \( \frac{a}{b} \)
Relation between infarct size and LV Volume in the acute and chronic phases post MI
Relation between infarct size and ejection fraction post MI (> 2 weeks)
Effect of TNT in myocardial expansion
Pressure - Volume relationship after experimental infarction in rats

Effect of Captopril
Ventricular expansion and open artery

![Graph showing LV volume (ml) at different times with patent and occluded conditions.]

- LV VOLUME (ml)
  - 280
  - 260
  - 240
  - 220
  - 200
  - 0

- Time:
  - 3wks 1yr
  - 3wks 1yr

- Conditions:
  - PATENT
  - OCCLUDED

* †
Early remote changes

- Hypertrophy
INFARCTED

BASAL - Posterolateral

Wall thickness (mm)

0 2 4 6 8 10 12 14 16 18 20

Time after the R-wave (msec)

11 Days

3 Months

NON-INFARCTED

MID - Anterior

Wall thickness (mm)

0 2 4 6 8 10 12 14 16 18 20

Time after the R-wave (msec)

11 Days

3 Months

Wall thinning and loss of contractility

Maintenance of wall thickness with compensatory wall thickening
Late changes

• Cardiac chamber dilatation
• Change of ventricular size from ellipsoid to spherical
• Increase of interstitial volume
Arrhythmias
(VT - VF)

Ion channel changes

Inactivation of sodium channels
Changes in calcium and potassium channels
Alteration of Ca/Na exchanger function
Ventricular remodeling after acute infarction

- Initial infarct
- Expansion of infarct (hours to days)
- Global remodeling (days to months)
LV Remodeling Post Anteroseptal MI

1 week

EDV 137ml ESV 80ml EF 41%

3 months

EDV 189ml ESV 146ml EF 23%
<table>
<thead>
<tr>
<th><strong>Cellular changes during remodeling</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocytes</strong></td>
</tr>
<tr>
<td>Hypertrophy, cell lengthening</td>
</tr>
<tr>
<td>Re-expression of fetal gene program</td>
</tr>
<tr>
<td>Altered excitation–contraction coupling</td>
</tr>
<tr>
<td>Altered energy metabolism</td>
</tr>
<tr>
<td>Altered myofibrillar content and function</td>
</tr>
<tr>
<td>Apoptosis</td>
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<tr>
<td>Necrosis</td>
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<tr>
<td><strong>Vasculature</strong></td>
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<tr>
<td>Endothelial dysfunction</td>
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<tr>
<td>Intima thickening</td>
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<tr>
<td>Smooth muscle hyperplasia</td>
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<tr>
<td>Rarefication of capillaries</td>
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<tr>
<td><strong>Interstitium</strong></td>
</tr>
<tr>
<td>Induction of matrix metalloproteases</td>
</tr>
<tr>
<td>Myocyte slipping</td>
</tr>
<tr>
<td>Increased collagen synthesis, fibrosis</td>
</tr>
<tr>
<td>Collagen isoform shift</td>
</tr>
</tbody>
</table>
Major mechanisms

Inflammation

• Inflitratrion of inflammatory cells (monocytes – macrophages)
• Release of cytokines

Fibrosis

• Collagen matrix accumulation
• Reparative or replacement fibrosis
• Reactive fibrosis

Cell death

• Necrosis  - Apoptosis  - Autophage
Mechanisms and Potential Relationships Among Autophagy, Apoptotic, and Necrotic Pathways

Mitochondria

**Mild**
- Bcl2
- Bnip3

**Moderate**
- Bnip3
- Bcl2
- Bax, Bak
- Nix
- BID
- PUMA

**Severe**
- Ca\(^{2+}\) overload

Autophagolysosome

(Apoptotic extrinsic pathway)
- Apaf-1
- Cyt c
- dATP
- Casp 9
- Casp 8
- DNA
- Apoptosome
- AIF
- EndoG
- DNA frag (50000 bp)

**Autophagy**
- Beclin-1, Atg
- LC3

**Apoptosis**
- Casp 3
- Casp 8
- DNA (200 bp)

**Necrosis**
- Cyp-D
- MPTP
- \(\Delta \Psi_{m}\)
- ROS
- ATP

\(\Delta \Psi_{m}\): membrane potential
Myocardial injury

Infiltration by inflammatory cells

Neutrophils
- ↑ Pro-oxidant cytokines (i.e., TNF-α) and
- ↓ Anti-oxidant cytokines (i.e., IL-10)

- Oxidative stress
  - Activation of apoptosis
  - Degradation of collagen scaffold

Monocytes/macrophages
- ↑ Pro-fibrotic cytokines (i.e., TGF-β)
- Stimulation of fibroblasts

- Myocardial fibrosis
Schematic of Extracellular Steps

1. Mechanical stimuli, Metabolic stimuli, Humoral stimuli → DNA
2. DNA → Preprocollagen type I
3. Preprocollagen type I → Procollagen type I
4. Procollagen type I secreted into the interstitial space
5. Procollagen type I proteolysis by proteases
6. Mature collagen type I
7. Lysyl oxidase mediates assembly and cross-linking
8. Collagen type I fiber deposition
9. Deposition leads to:
   - Physiologic scaffold
   - Pathologic fibrosis
# Emerging Targets and Potential Therapeutic Agents to Treat Structural Myocardial Remodeling

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Target</th>
<th>Therapeutic Agent</th>
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</thead>
<tbody>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
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<tr>
<td></td>
<td>TNF-α</td>
<td>Pentoxifylline, pentaclin 3, IL-10</td>
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<td></td>
<td>IL-1β</td>
<td>Pentraxin 3</td>
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<tr>
<td></td>
<td>PI3Kγ/δ</td>
<td>TG100-115</td>
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<tr>
<td></td>
<td>IL-6 gp130/STAT3</td>
<td>Cobra venom factor derivatives?</td>
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<tr>
<td></td>
<td>TLR4</td>
<td>Molecules targeting TLR4 (e.g., statins, vitamin D3)</td>
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<tr>
<td></td>
<td>NF-κB</td>
<td>Inhibitors (e.g., lactacystin)</td>
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<tr>
<td><strong>Alterations of collagen matrix</strong></td>
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<tr>
<td></td>
<td>Renin-angiotensin system</td>
<td>ACEIs or ARBs</td>
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<tr>
<td></td>
<td>Aldosterone</td>
<td>Spironolactone or eplerenone</td>
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<td>TGF-β₁</td>
<td>Receptor antagonists</td>
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<tr>
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<td>PCP/PCPE</td>
<td>Torasemide</td>
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<td></td>
<td>LOX</td>
<td>Torasemide</td>
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<tr>
<td></td>
<td>miR-21</td>
<td>AntagomiR-21</td>
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<tr>
<td></td>
<td>MMPs</td>
<td>Several inhibitors</td>
</tr>
<tr>
<td></td>
<td>Several</td>
<td>Thrombospondin-2</td>
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<td><strong>Cardiomyocyte death</strong></td>
<td>Mitochondrial Omi/HtrA2</td>
<td>UCF-101</td>
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<tr>
<td></td>
<td>Nogo-A protein</td>
<td>Several inhibitors</td>
</tr>
<tr>
<td></td>
<td>miR-320</td>
<td>AntagomiR-320</td>
</tr>
<tr>
<td></td>
<td>Akt protein</td>
<td>Stimulants (e.g., IGF-1)</td>
</tr>
</tbody>
</table>
Reverse Remodeling
Reverse Remodeling

- With surgery
  - Batista operation
  - Aneurysmatectomie
  - Heterotopic transplatation

- With cardiac assist divises
  - LVAD
  - CRT

- With pharmacological therapy
  - ACE inhibitors
  - b-blockers
Reverse remodeling in heart failure

**Enalapril**

- EDV (ml)
  - Placebo (n=130)
  - Enalapril (n=128)
  - p=0.025

- ESV (ml)
  - Placebo (n=130)
  - Enalapril (n=127)
  - p=0.019

- LV Mass (g)
  - Placebo (n=100)
  - Enalapril (n=107)
  - p=0.001

**Carvedilol**

- EDVI [mL/m²]
  - Placebo
  - Carvedilol
  - 2P=0.0042

- ESVI [mL/m²]
  - Placebo
  - Carvedilol
  - 2P=0.0002

- EF%
  - Placebo
  - Carvedilol
  - 2P=0.0017

Baseline 4 mo 12 mo
Reversal Remodeling in CRT

- Left ventricular volume (mL)
- Ejection fraction (%)
- dp/dt (mmHg/s)
- Mitral regurgitation (%)

Graphs show changes over time from baseline to 1 week, 1 month, 3 months, off-imed, off-1 week, off-4 weeks.
Reverce Remodeling with LVAD
## Examples for reverse remodeling with therapy

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>6 months</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td><strong>Training</strong></td>
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<tr>
<td>LVEDVI (mL/m²)</td>
<td>142 ± 26</td>
<td>135 ± 26*</td>
<td>(Giannuzzi et al., 2003; n = 45)</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>107 ± 24</td>
<td>97 ± 24*</td>
<td>(Giannuzzi et al., 2003; n = 45)</td>
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<tr>
<td>EF (%)</td>
<td>25 ± 4</td>
<td>29 ± 4*</td>
<td>(Giannuzzi et al., 2003; n = 45)</td>
</tr>
<tr>
<td><strong>CPAP in OSA or CSA</strong></td>
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<td></td>
<td></td>
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<tr>
<td>LVEDD (mm)</td>
<td>64.3 ± 1.8</td>
<td>63.4 ± 1.8</td>
<td>(Kaneko, 2003; n = 12)</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>54.5 ± 1.8</td>
<td>51.7 ± 1.2*</td>
<td>(Kaneko, 2003; n = 12)</td>
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<tr>
<td>EF (%)</td>
<td>25 ± 3</td>
<td>34 ± 3*</td>
<td>(Kaneko, 2003; n = 12)</td>
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<tr>
<td></td>
<td>37.6 ± 2.5</td>
<td>42.6 ± 0.3*</td>
<td>(Mansfield, 1997; n = 19)</td>
</tr>
<tr>
<td></td>
<td>20.6 ± 11.3</td>
<td>28*#</td>
<td>(SIn, 2000; n = 14; # = estimated)</td>
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<tr>
<td><strong>Beta-blockers</strong></td>
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<tr>
<td>LVEDVI (mL/m²)</td>
<td>100.2 ± 4.6</td>
<td>95.6 ± 4.9</td>
<td>(Doughty, 1997; n = 81; p n.a.)</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>72.9 ± 4.1</td>
<td>65.5 ± 4.5</td>
<td>(Doughty, 1997; n = 81; p n.a.)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>28.6 ± 0.9</td>
<td>34.1 ± 1.5</td>
<td>(Doughty, 1997; n = 81; p n.a.)</td>
</tr>
<tr>
<td><strong>Cardiac resynchronization therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>72.7 ± 9.2</td>
<td>71.6 ± 9.1</td>
<td>(Gras et al., 2002; n = 43)</td>
</tr>
<tr>
<td></td>
<td>70 ± 10</td>
<td>−3.5*</td>
<td>(Abraham, 2002; n = 90)</td>
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<td>74 ± 10</td>
<td>67 ± 12</td>
<td>(Linde, 2002; n = 40)</td>
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<tr>
<td>LVESD (mm)</td>
<td>63 ± 10</td>
<td>58 ± 12</td>
<td>(Linde, 2002; n = 40)</td>
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<tr>
<td>LVESVI (mL/m²)</td>
<td>100 ± 36</td>
<td>92 ± 40*</td>
<td>(Saxon, 2002; n = 53)</td>
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<tr>
<td></td>
<td>116 ± 43</td>
<td>85 ± 29*</td>
<td>(Pitzalis, 2002; n = 20)</td>
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<tr>
<td>LVEDVI (mL/m²)</td>
<td>129 ± 37</td>
<td>121 ± 45</td>
<td>(Saxon, 2002; n = 53)</td>
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<tr>
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<td>150 ± 53</td>
<td>119 ± 37*</td>
<td>(Pitzalis, 2002; n = 20)</td>
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<tr>
<td>EF (%)</td>
<td>21.7 ± 6.4</td>
<td>26.1 ± 9.0*</td>
<td>(Gras et al., 2002; n = 33)</td>
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<tr>
<td></td>
<td>21.8 ± 6.3</td>
<td>+4.6*</td>
<td>(Abraham, 2002; n = 155)</td>
</tr>
<tr>
<td></td>
<td>24.5 ± 7.8</td>
<td>30.0 ± 12.1</td>
<td>(Linde, 2002; n = 26)</td>
</tr>
<tr>
<td></td>
<td>24 ± 5</td>
<td>29 ± 6*</td>
<td>(Pitzalis, 2002; n = 20)</td>
</tr>
</tbody>
</table>
HEART FAILURE

The degree and time of development of heart failure depends on:

• The extension of necrosis (AMI size).
• The repetition of necrosis (AMI).
From ISCHEMIA to HEART FAILURE
Acute ischemia

- Metabolic acidosis
  - Loss of contractility
  - ECG changes
  - Clinical manifestation (angina)

Chronic ischemia ?
Myocardial Hibernation

• Term **hibernation** is borrowed from zoology

• Diamond et al. in 1978 first used the word hibernation in ischemic dog myocardium.

• Its importance was recognized by Rahimtoola in early 1980s.
• Term **hibernation** implies an adaptive reduction of energy expenditure through reduced activity in situation of reduced energy supply.

• In CAD myocardial hibernation refers to adaptive reduction of myocardial contractile function in response to reduction of myocardial blood flow.
Mechanisms of hibernation

- **Smart heart** hypothesis:
  Myocardial metabolism and function are reduced to match concomitant reduction in coronary blood flow which prevents necrosis.

- **Repetitive stunning** hypothesis:
  Repetitive episodes of ischemia results in sustained depression of contractile function.
• Genomics of Survival

Maintained viability in hibernation suggests possibility of genomic adaptation.

Major survival genes (antiapoptotic, cytoprotective & growth-promoting genes) and their corresponding proteins are up regulated in hibernating myocardium.
Chronic coronary artery disease

Coronary stenosis

- Decreased blood flow at rest
  - Decreased metabolism
    - Decreased function
      - Chronically depressed contractile function
        - CABG, angioplasty
          - Recovery of function

- Maintained blood flow at rest
  - Demand ischemia
    - Recovery from ischemia
      - Chronic stunning
        - Chronically depressed contractile function
          - CABG, angioplasty
            - Recovery of function

Genomic trigger for cell survival
- Proteins of survival
  - Protection against apoptosis
    - Activation of autophagy
      - CABG, angioplasty
        - Recovery of function

“Smart heart” hypothesis

“Repetitive stunning” hypothesis

“Survival” hypothesis
Natural history of hibernation

Coronary Artery Disease
- Critical stenosis
- progressive CVR

Stenosis > 80%
- Exhaustion of CVR
  (myocardial ischemia and stunning for minimal changes in MVO₂)

Repetitive Ischemia and Stunning are cumulative
  (occur with daily life activities and often asymptomatic)

Functional Hibernation

Revascularization
- Early functional recovery
  (days/weeks)

Delayed Revascularization
- Tissue degeneration

Revascularization
- Late Functional Recovery
  (6-12 months)

Structural Hibernation

Cell Death
Histological Features

• Myolysis
• Glycogen accumulation
• Increased interstitial fibrosis
Clinical Relevance

• 20 to 50% of pts with chronic ischemic LV dysfunction have significant amount of viable hibernating myocardium.

• They improve with revascularization.
MYOCARDIAL VIABILITY

NORMAL + Ischemia

CONTRACTILE DYSFUNCTION

SCAR

STUNNED

HBERNATING
ASSESSMENT OF MYOCARDIAL VIABILITY

• ECG: gives little information.
• Dobutamine stress echocardiography.
• SPECT with thallium-201 or technetium-99 m.
• PET
• MRI
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Main changes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell death</strong></td>
<td>↑ apoptosis, ↑ necrosis, ↓ autophagy</td>
</tr>
<tr>
<td></td>
<td>Progressive myocyte loss</td>
</tr>
<tr>
<td><strong>Energy metabolism</strong></td>
<td>β oxidation, Triglyceride accumulation, ↑ glycolysis, Mitochondrial dysfunction, Mitochondrial atrophy</td>
</tr>
<tr>
<td></td>
<td>Lipotoxicity, ↓ energy, ↑ oxidative stress</td>
</tr>
<tr>
<td><strong>Oxidative stress</strong></td>
<td>↑ NADPH oxidase, ↑ catecholamine degradation, ↑ xanthine oxidase, Mitochondrial dysfunction, ↓ antioxidant systems</td>
</tr>
<tr>
<td></td>
<td>Lipid peroxidation, Protein oxidation, DNA damage, Cell dysfunction, Fibroblast proliferation, Metalloproteinase activation, ↑ apoptosis, ↑ signaling pathways to hypertrophy</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>innate response, Adaptive response dysfunction</td>
</tr>
<tr>
<td></td>
<td>↑ inflammatory cytokines, Macrophage, T cell and B cell dysfunction</td>
</tr>
<tr>
<td><strong>Collagen</strong></td>
<td>Fibroblast proliferation, ↑ metalloproteinases</td>
</tr>
<tr>
<td></td>
<td>Degradation of normal collagen, Fibrosis</td>
</tr>
<tr>
<td><strong>Contractile proteins</strong></td>
<td>β- myosin, ↓ α- myosin, ↑ troponin T type 2, ↓ troponin I phosphorylation</td>
</tr>
<tr>
<td></td>
<td>↓ contractility</td>
</tr>
<tr>
<td><strong>Calcium transport</strong></td>
<td>↓ L-type calcium channels, ↓ryanodine, ↓ calsequestrin, ↓ calmodulin, ↓ Phospholamban phosphorylation, ↓ SERCA 2a</td>
</tr>
<tr>
<td></td>
<td>↓ Calcium in systole, ↑ Calcium in diastole</td>
</tr>
<tr>
<td><strong>Geometry</strong></td>
<td>LV cavity, ↓ wall thickness, Elliptical shape → spherical shape</td>
</tr>
<tr>
<td></td>
<td>↑ pial wall stress of the LV</td>
</tr>
<tr>
<td><strong>Neurohormonal activation</strong></td>
<td>↑ renin-angiotensin-aldosterone system, ↑ Sympathetic</td>
</tr>
<tr>
<td></td>
<td>↑ cell death, ↑ oxidative stress, ↑ inflammation, ↑ metalloproteinases and fibroblasts, hypertrophy, vasoconstriction</td>
</tr>
</tbody>
</table>
Pharmacological treatment of cardiac remodeling. ACE: Angiotensin-converting-enzyme; ARBs: Angiotensin receptor blockers.

**Pharmacological treatment**

- **Consolidated**
  - ACE inhibitor
  - ARBs
  - Beta blockers

- **Promising**
  - LCZ696

- **Potential**
  - Neuregulin, Galectin-3
  - Cyclosporine A, Torsemide
  - Necrostatin-1, Metformin
Thank you