Hypertensive heart disease: overview, aetiology and epidemiology

Franco Veglio
NO CONFLICTS OF INTEREST
The lifecourse approach to management of elevated blood pressure

Holsen, Lancet 2016
The spectrum of risk conferred by HHD on cardiovascular morbidity and mortality

Stanton, Med Clin N Am, 2017
The maladaptive feedback of Hypertensive Heart Disease

- Arterial stiffness
- Myocardial Ischemia
- LV hypertrophy
- Diastolic dysfunction
- Endothelial dysfunction
- Myocardial fibrosis
- Cardiomyocyte growth
- Apoptosis

Stanton, Med Clin N Am, 2017
Factors in hypertensive heart disease resulting in ischemia

- Ventricular fibrosis with associated extraventricular ischemia
- Coronary arteriolar constriction due to fibrosis.
- Endothelial dysfunction of coronary resistance vessels
- Reduced coronary luminal area in relation to increased LV mass
- Increased LV wall tension
- Altered subendocardial-subepicardial blood flow ratio
- Impairment of diastolic coronary artery blood flow
- Decreased subendocardial capillary density
- Inflammatory responses

Stanton, Med Clin N Am, 2017
Pathophysiological pathways of hypertensive heart disease

Shenasa, Intern J Cardiol 2017
Changes of gene expression during cardiomyocyte hypertrophy

**Genes whose expression is reactivated**
- β-Myosin heavy chain
- Embryonic myosin light chain in ventricles
- IVS3A form of calcium channel
- α3-Subunit of Na\(^+\), K\(^+\)-ATPase
- Switch from fatty acid oxidation to glycolysis genes
- Lactate dehydrogenase M subunits
- B subunit of creatine kinase
- Ventricular expression of atrial natriuretic factor
- Genes directing cardiomyocyte lengthening

**Genes whose expression is blunted**
- Calcium ATPase of sarcoplasmic reticulum (SERCA2)
- β\(_1\)-Adrenergic receptors
- M\(_2\)-Muscarinic receptors
- Early transient K\(^+\) current, \(I_{to}\)
- Myoglobin
- N2BA titin isoform
Mosaic of the histologic alterations in myocardium

Cardiomyocyte hypertrophy

Cardiomyocyte apoptosis

Interstitial fibrosis

Perivascular fibrosis

Arteriolar wall alterations

Capillary rarefaction

Altered contraction, relaxation, perfusion, and electrical activity

Moreno, Med Clin N Am, 2017
Role of nuclear unphosphorylated STAT3 in angiotensin II type 1 receptor-induced cardiac hypertrophy

Yue, Cardiovascular Res Ad, 2009
Left ventricular (LV) structure in normal, renovascular hypertension (RVH)

Zhang, Hypertension, 2014
Aldosterone and Heart

KIDNEY
- ↑Na⁺ and water retention
- ↓K⁺ and Mg²⁺ excretion
- ↑Microalbuminuria
- ↑Fibrosis
- ↑Extracellular volume
- Edema
- ROS generation

HEART
- ↑Hypertrophy/Fibrosis
- Cardiac Remodeling
- ↑Inflammation
- Vascular damage
- ↑Cardiac arrhythmias
- ↑Ischemic events
- Thrombosis
- ROS generation

VESSELS/BLOOD
- Vasoconstriction
- Endothelial dysfunction
- ↑Arterial stiffness
- ↑Vascular inflammation
- Cytokine activation
- ↑PAI-1
- ↑Platelet activation
- ROS generation

NERVOUS SYSTEM
- ↓Baroreceptor sensitivity
- ↑Sympathetic tone
- ↓HR variability
- ↓Myocardial NE uptake
- ↓Sudden cardiac death

Hypertension, heart failure, ischemic events, CKD, sudden cardiac death

Increased Mortality

Tamargo, Sem Nephrol 2014
Staging of Hypertensive Heart Disease

Degree I
- LV diastolic dysfunction
- No LV hypertrophy

Degree II
- LV diastolic dysfunction and
- LV hypertrophy

Degree III
- Clinical heart failure with
- Preserved LV ejection fraction

Degree IV
- Eccentric LV hypertrophy
- Reduced LV ejection fraction

Messerli, JACC 2017
Hypertension is a major risk factor for LVH

# Prevalence of LVH

<table>
<thead>
<tr>
<th>Author</th>
<th>ECG LVH criteria</th>
<th>ECHO LVH criteria</th>
<th>Prevalence of LVH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verdecchia [13]</td>
<td>Wilson</td>
<td>LVMI &gt;125 g/m²</td>
<td>ECG 0.6 ECHO 27.2</td>
</tr>
<tr>
<td></td>
<td>LV strain</td>
<td>LVMI &gt;51 gm².&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Rønnhilt-Estes</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Gubner Ungerleider</td>
<td></td>
<td>7.1</td>
</tr>
<tr>
<td>Sokolow-Lyon</td>
<td></td>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>Cornell voltage</td>
<td></td>
<td>11.9</td>
</tr>
<tr>
<td>Perugia score</td>
<td></td>
<td></td>
<td>18.4</td>
</tr>
<tr>
<td>Salles [17]</td>
<td>Sokolow-Lyon, or Cornell voltage</td>
<td>LVMI &gt;294 g (M); &gt;198 g (F)</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Perugia score</td>
<td>LVMI &gt;49.2 gm².&lt;sup&gt;2&lt;/sup&gt; (M); &gt;46.7 gm².&lt;sup&gt;2&lt;/sup&gt; (F)</td>
<td>17.1</td>
</tr>
<tr>
<td>Martinez [19]</td>
<td>Cornell voltage</td>
<td>LVMI &gt;134 gm² (M); &gt;110 gm² (F)</td>
<td>9.0</td>
</tr>
<tr>
<td>Schneider [21]</td>
<td>Cornell voltage-duration product</td>
<td>LVMI &gt;134 gm² (M); &gt;110 gm² (F)</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Cornell voltage-duration product</td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>Cuspidi [29]</td>
<td>Sokolow-Lyon</td>
<td>LVMI &gt;125 gm² (M); &gt;110 gm² (F)</td>
<td>10.4</td>
</tr>
<tr>
<td>Radulescu [32]</td>
<td>Sokolow-Lyon or Cornell voltage-duration product</td>
<td>LVMI &gt;125 gm²</td>
<td>40.0</td>
</tr>
<tr>
<td>Salles [38]</td>
<td>Sokolow-Lyon</td>
<td>LVMI &gt;125 gm² (M)</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>Cornell voltage-duration product</td>
<td>&gt;110 gm² i(f)</td>
<td>21.9</td>
</tr>
</tbody>
</table>

F, females; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; M, males.

**EKG: 18 % ECHO 32%**

Cuspidi, J of Hypertens, 2012
Prevalence of left ventricular hypertrophy (LVH)

A

Prevalence of LVH, %

<120 120-139 ≥140

Office SBP, mm Hg

P<0.001

B

Prevalence of DD, %

<120 120-139 ≥140

Office SBP, mm Hg

P=0.003

Nakanishi, J Am Heart Assoc 2017
The prognostic legacy of left ventricular hypertrophy: cumulative evidence after the MAVI study

LVM measured at baseline and 2 years after the initial assessment in 374 patients. FU after 2nd vis 3.2 yrs.

![Graph showing probability of event-free survival over follow-up (years)]

- **(A) Never LVH**
- **(B) Regression**
- **(C) Persistence/new**

<table>
<thead>
<tr>
<th>Group</th>
<th>Log-rank $X^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>7.208</td>
<td>0.027</td>
</tr>
<tr>
<td>(A) vs (B)</td>
<td>3.824</td>
<td>0.144</td>
</tr>
<tr>
<td>(A) vs (C)</td>
<td>7.207</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Angeli, Journal of Hypertension 2015
Cox multivariable free-time events curves in relation to target-organ damage (TOD) groups.
## Risk Reduction After Regression of Echocardiographic Left Ventricular Hypertrophy

(3,149 patients)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Hazard ratio and 95% CI</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verdecchia 1998</td>
<td>0.180</td>
<td>0.049</td>
<td>0.664</td>
<td>-2.575</td>
<td>0.010</td>
<td></td>
<td></td>
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<tr>
<td>Deverex 2004</td>
<td>0.580</td>
<td>0.386</td>
<td>0.873</td>
<td>-2.614</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muiesan 2007</td>
<td>0.550</td>
<td>0.322</td>
<td>0.938</td>
<td>-2.195</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pierdomenico 2008</td>
<td>0.360</td>
<td>0.190</td>
<td>0.681</td>
<td>-3.141</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yasuno 2009</td>
<td>1.210</td>
<td>0.620</td>
<td>2.361</td>
<td>0.559</td>
<td>0.576</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.542</td>
<td>0.348</td>
<td>-2.710</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing hazard ratio and 95% CI for each study, with shaded area indicating significant results.](image)

Favors LVH regression/persistent NLVM

Favors LVH persistence/LVH development

Pierdomenico, Am J Hyperten 2010
Methods of assessing hypertensive cardiomiopathy

<table>
<thead>
<tr>
<th></th>
<th>ECG</th>
<th>M-mode echocardiography</th>
<th>2D echocardiography</th>
<th>3D echocardiography</th>
<th>Cardiac MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Specificity</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cost</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Availability</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Complexity</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Interpatient reproducibility</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
### Markers of LVM regression

<table>
<thead>
<tr>
<th>Marker of organ damage</th>
<th>Sensitivity for changes</th>
<th>Time to change</th>
<th>Prognostic value of changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH/ECG</td>
<td>Low</td>
<td>Moderate (&gt;6 months)</td>
<td>Yes</td>
</tr>
<tr>
<td>LVH/echo</td>
<td>Moderate</td>
<td>Moderate (&gt;6 months)</td>
<td>Yes</td>
</tr>
<tr>
<td>LVH/cardiac magnetic resonance</td>
<td>High</td>
<td>Moderate (&gt;6 months)</td>
<td>No data</td>
</tr>
</tbody>
</table>

ESH/ESC 2013 Guidelines
Metanalysis of echocardiographic studies on LVH regression

38 studies, 4227 patients

Muiesan, ESH 2010
LVH and RAS inhibitors

Zang, J H Hyperten 2013

-17.85 g m⁻²
Eplerenone enhances cardioprotective effects of standard heart failure therapy through matricellular proteins in hypertensive heart failure

Munoz-Pacheco, J Hypertension 2013
β1-Adrenergic blockers exert antioxidant effects, reduce matrix metalloproteinase activity, and LVH.
Increasing by age

A virulent, but indolent process

Elefteriades *JACC* 2010

Coady et al. *Circulation* June 2010
Prognosis

- Average Yearly Rate
- Outcome
  - Rupture
  - Dissection
  - Rupture or Dissection
  - Death
  - Rupture, Dissection or Death

- Prognosis rates for different aortic conditions
  - Aortic Dissection
  - Penetrating Ulcer
  - Intramural Hematoma

Elefteriades JACC 2010
Prevalence

9.1 %

12% males

4% females

Echocardiographic aortic root dilatation in hypertensive patients: a systematic review and meta-analysis

Michele Covella\textsuperscript{a,\,*}, Alberto Milan\textsuperscript{a,\,*}, Silvia Totaro\textsuperscript{a}, Cesare Cuspidi\textsuperscript{b}, Annalisa Re\textsuperscript{b}, Franco Rabbia\textsuperscript{a}, and Franco Veglio\textsuperscript{a}

\textit{J of Hypertens} 2014
Prognosis of LVH and ARD

Aortic root diameter and risk of cardiovascular events in a general population: data from the PAMELA study

Cuspidi et al J of Hypertens 2014
<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic organ damage</td>
<td></td>
</tr>
<tr>
<td>LVH</td>
<td>ACE inhibitor, calcium antagonist, ARB</td>
</tr>
<tr>
<td>Asymptomatic atherosclerosis</td>
<td>Calcium antagonist, ACE inhibitor</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Clinical CV event</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>Any agent effectively lowering BP</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>BB, ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>BB, calcium antagonist</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>BB</td>
</tr>
<tr>
<td>Atrial fibrillation, prevention</td>
<td>Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td>Atrial fibrillation, ventricular rate control</td>
<td>BB, non-dihydropyridine calcium antagonist</td>
</tr>
<tr>
<td>ESRD/proteinuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>ACE inhibitor, calcium antagonist</td>
</tr>
</tbody>
</table>
## Effects of Antihypertensive Agents in Hypertensive Heart Disease

<table>
<thead>
<tr>
<th>Pharmacologic Class</th>
<th>Decrease of Blood Pressure</th>
<th>Reduction of LV Mass</th>
<th>Repair of Remodeling Lesions$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Yes</td>
<td>Mild</td>
<td>Proven for torasemide$^{44}$</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Yes</td>
<td>Mild to moderate</td>
<td>Apparently not</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>Yes</td>
<td>Mild</td>
<td>Unknown</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Yes</td>
<td>Moderate</td>
<td>Apparently not</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Yes</td>
<td>Marked</td>
<td>Proven for lisinopril$^{46}$</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>Yes</td>
<td>Marked</td>
<td>Proven for losartan$^{47}$</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Yes</td>
<td>Mild-moderate</td>
<td>Proven for spironolactone$^{48}$</td>
</tr>
<tr>
<td>Direct renin inhibitors</td>
<td>Yes</td>
<td>Marked</td>
<td>Unknown</td>
</tr>
<tr>
<td>Angiotensin receptor blocker and neprolysin inhibitor</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Moreno, Med Clin N Am, 2017
Antihypertensive Strategy in Heart Failure Patients With Hypertension

Presumptive HF therapy: ACEi/ARB + Beta-blocker + loop diuretic

Switch from ACEi/ARB to valsartan/sacubitril, continue or add statin

Switch from traditional B-blocker to vasodilating β-Blocker

- add Ca-channel-Blocker
- add Spironolactone
- add Thiazide-like diuretic

- add Spironolactone
- add Thiazide-like diuretic
- add Doxazosin

Messerli, JACC 2017
Grazie