Epidemiology, Pathophysiology, and Management Guidelines of Aortic Insufficiency

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Associate Professor of Medicine, Harvard Medical School
Presenter Disclosure Information

- No relationships to disclose
## Prevalence of AI by Age and Gender: Framingham Offspring Study

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>20-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-83</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>1.4%</td>
<td>3.7%</td>
<td>12.1%</td>
<td>12.2%</td>
</tr>
<tr>
<td>≥ Moderate</td>
<td>0</td>
<td>0.3%</td>
<td>0.5%</td>
<td>0.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>0.7%</td>
<td>1.9%</td>
<td>6.0%</td>
<td>14.6%</td>
</tr>
<tr>
<td>≥ Moderate</td>
<td>0</td>
<td>0</td>
<td>0.2%</td>
<td>0.8%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Etiology of Chronic Aortic Insufficiency

- Bicuspid aortic valve
- Aortic aneurysm
  - Aortic root
    - Marfan syndrome
  - Ascending aorta
- Calcific changes
  - Mixed AS/Al
- Infectious endocarditis
- Marantic endocarditis
- Rheumatic valve disease
- Aortitis
  - Takayasu, GCA, Behcet’s
  - Syphilis
- Subvalvular membrane
- Supracristal (subvalvular) VSD
  - Aortic cusp prolapse
- Anorectic drugs
- Prosthetic valve dysfunction
  - Bioprosthetic leaflet failure
  - Mechanical valve thrombosis
  - Paravalvular leaks
- TAVR paravalvular leaks
- LVAD – especially continuous flow devices
## Most Common Etiologies of Chronic AI

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicuspid aortic valve</td>
<td>13-28</td>
</tr>
<tr>
<td>Dilated root or ascending aorta</td>
<td>19-26</td>
</tr>
<tr>
<td>Degenerative</td>
<td>7-40</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>6-12</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3-10</td>
</tr>
<tr>
<td>Other/Uncertain</td>
<td>4-35</td>
</tr>
</tbody>
</table>
Pathophysiology of Chronic Severe AI: Early to Mid → Compensated

- Volume of regurgitation increases gradually
  - LV cavity progressively dilates
  - LV hypertrophy
    - Increased volume → eccentric LVH = addition of new sarcomeres (preload at sarcomere level relatively unchanged)
    - Increased afterload → concentric LVH
  - LV end-diastolic volume increases
  - Stroke volume increases
    - Net cardiac output maintained
- Pattern progresses slowly
  - Patients can tolerate even severe AI for years.
Pathophysiology of Chronic Severe AI: Late → Decompensated

• After significant dilatation, myocardial dysfunction follows
  – Ejection fraction falls
    • Cardiac output falls
  – LA pressure rises
    • Patient develops heart failure
• Myocardial oxygen demand rises, supply falls
  – Mismatch leads to ischemia, angina, ventricular arrhythmias.
Survival of Patients with Chronic Severe AI: by LV End-Systolic Diameter (LVESD)

Survival of Patients with Chronic Severe AI: by Symptoms (NYHA class)

Evaluation
Grading of AI by Echocardiography

- Primary goal is to distinguish severe from moderate
  - Jet height / LVOT diameter > 0.6
    - May not be true if the jet is eccentric
  - Pressure half-time < 250 msec
  - Regurgitant volume > 60 ml
  - Regurgitant fraction > 55%
  - Early termination of the mitral inflow (due to increase in LV pressure due to the AI)
  - Holodiastolic flow reversal in the descending aorta.
Grading of AI Severity by TTE in a Sample of 20 Cases by 20 Expert Readers

Quantification of AR with direct measurement of the vena contracta area using 3D TTE

Comparison between 2D and 3D TTE for AR quantification, using 3D 3-directional velocity-encoded MRI (VE-MRI) as reference method

Ewe SH, et al. Am J Cardiol 2013;112:560-566
MRI: Advantages

- Unlimited imaging planes
- Comprehensive and quantitative
- Integrated quantitative flow assessment
  - Accurate measure of regurgitant fraction
Survival without surgery for conventional indications vs. MRI regurgitant fraction ≥ 37%

Echo remains the modality most often used
Management
Medical Management

• Vasodilators have long been used in cases when AI is moderate or severe
  – Nifedipine
  – ACE inhibitors

• 2 key studies, conflicting data
  – Scognamiglio et al. in 1994
  – Evangelista et al. in 2005

Probability of AVR in Patients with Severe AI Treated with Nifedipine (20 mg bid) vs. Digoxin

N.B.: there was no placebo control group

Vasodilator Therapy

- The 1998 ACC/AHA guidelines gave a class I recommendation for the use of long-term vasodilator therapy in patients with chronic, severe AI
Probability of AVR in Patients with Severe AI Treated with Nifedipine, Enalapril, or Placebo

P = 0.29 at 7 years

Efficacy of Vasodilators in Severe AI: A Controlled Animal Model

- Eric Plante and colleagues, Université Laval, Quebec
- 60 rats had severe AR (confirmed by echo) induced by retrograde puncture of the AV leaflets
- Randomly divided into 5 groups:
  - Normal sham-operated animals
  - AR untreated
  - AR treated with nifedipine
  - AR treated with captopril
  - AR treated with losartan
- Drug treatments were started 2 weeks after surgical procedure and continued thereafter for 6 months
- Echos at 6 months.

### Echo Data After 6 Months of Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham (n=11)</th>
<th>Placebo (n=11)</th>
<th>Captopril (n=10)</th>
<th>Losartan (n=10)</th>
<th>Nifedipine (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR, %</td>
<td>NA</td>
<td>63 ± 4</td>
<td>64 ± 4</td>
<td>61 ± 3</td>
<td>60 ± 4</td>
</tr>
<tr>
<td>EDD, mm</td>
<td>8.5 ± 0.2*</td>
<td>11.6 ± 0.3</td>
<td>10.8 ± 0.3</td>
<td>10.9 ± 0.2</td>
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<tr>
<td>ESD, mm</td>
<td>4.3 ± 0.3*</td>
<td>7.7 ± 0.3</td>
<td>6.5 ± 0.4†</td>
<td>6.5 ± 0.2†</td>
<td>8.1 ± 0.4</td>
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<tr>
<td>EF, %</td>
<td>74 ± 2*</td>
<td>55 ± 2</td>
<td>63 ± 3†</td>
<td>64 ± 2†</td>
<td>53 ± 3</td>
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* = p < 0.01 compared with placebo; † = p < 0.05 compared with placebo

Efficacy of captopril in rat model of pure AI: Showed for the first time a survival benefit

Retrospective Analysis of 2266 Pts with Mod or Severe AI: Benefits of ACEI/ARB use

Freedom from CV events (CV hospitalization or death)

Treatment of hypertension (SBP >140 mmHg) is recommended in patients with chronic AR, preferably with dihydropyridine Ca++ channel blockers or ACEIs/ARBs.

I see no good reason to choose nifedipine if patient can tolerate ACEIs or ARBs.
Use of Beta-blockers in Severe AI?
Effect of Beta-Blockers on Survival in Patients with Severe AR: A Cohort of 756

The Timing of Surgery
Surgical Indications Are Based on Symptoms and on LV Size and Function
<table>
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Nishimura RA, et al. JACC 2014.02.536
## Indications for Surgery in AI: 2014 ACC/AHA guidelines

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|       | • Asymptomatic pt with severe AI and LV EF < 50% at rest  
|       | • Asymptomatic pt with severe AI undergoing cardiac surgery for other indications |

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| IIA   | • Asymptomatic pt with severe AI and normal LV function but severe LV dilatation (LVESD > 50 mm or > 25 mm/m²) |

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| IIa   |  • Asymptomatic pt with severe AI and normal LV function but severe LV dilatation (LVESD > 50 mm or > 25 mm/m²) |
| IIa   |  • Asymptomatic pt with moderate AI undergoing ascending aortic surgery, mitral valve surgery, or CABG |

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| IIa   | • Asymptomatic pt with severe AI and normal LV function but severe LV dilatation (LVESD > 50 mm or > 25 mm/m²) |
| IIa   | • Asymptomatic pt with moderate AI undergoing ascending aortic surgery, mitral valve surgery, or CABG |
| IIb   | • Asymptomatic pt with severe AI and normal LV function (LV EF ≥ 50%) but with progressive severe LV dilatation (LVEDD > 65 mm) if surgical risk is low |

Nishimura RA, et al. JACC 2014.02.536
Refining Risk Stratification: Biomarkers
BNP to Risk Stratify Patients with Asymptomatic Severe AI and Normal LV Function

Pizarro R, et al. JACC 2011;58:1705-14
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