Stress Echocardiography—New Applications and Comparison with Other Stress Modalities

Robert T. Palac, MD
April 28, 2016
Disclosure

• No Conflicts Related to This Presentation
Overview

• Stress Testing—Basics

• Stress Echocardiography and Stress Nuclear Perfusion Imaging

• New Applications of Stress Echocardiography
## History of Stress Testing

<table>
<thead>
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<td>ST ↓</td>
<td>Masters</td>
<td>Stair</td>
<td>Stair</td>
<td>Max Ex vs</td>
<td>Treadmill</td>
<td>Bruce</td>
<td>Imaging</td>
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<td>Used</td>
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</table>

**NEWER**

**REGADENOSON MRI**

**CTA/FRACTIONAL FLOW RESERVE**
Conceptualizing Stress Testing

**Stressor**
- Exercise
  - Treadmill
  - Bicycle
- Pharmacologic
  - Regadenoson (Nuclear)
  - Dobutamine (Echo)

**Imaging**
- ECG
  - ST segment change
- Echocardiography
  - LV wall motion change
- MIBI/Thallium (radioisotope)
  - Regional perfusion defects
DYNAMIC EXERCISE

- Vagal tone ↓, Sympathetic tone ↑
- Energy demands of exercising muscle ↑
- Total-body oxygen uptake ↑
- Heart rate (HR) × stroke volume (SV) = cardiac output ↑
- Myocardial oxygen demand ↑
- Venous return ↑
- Vasodilation ↑, Extraction of oxygen ↑
- Coronary blood flow ↑

Braunwald, Heart Disease 9th Edition
Stress Testing Ischemic Sequence

↓ Perfusion (detected by nuclear stress imaging) → Metabolic changes (detected by positron emission tomography) → Diastolic dysfunction (detected by stress echocardiography*) → Systolic dysfunction (detected by single photon emission computed tomography and stress echocardiography) → ECG changes → Chest pain

↑ Mismatch between oxygen supply and demand

Magri CJ
British Journal of Hospital Medicine, June 2012, Vol 73, No 6
## Indications and Contraindications

### Indications

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Common indications for NCST</th>
</tr>
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<tbody>
<tr>
<td>Diagnosis of obstructive coronary heart disease (CHD)</td>
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<tr>
<td>Risk assessment and prognosis for individuals with known CHD</td>
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<tr>
<td>Prognostic assessment after acute coronary syndrome (ACS)</td>
<td></td>
</tr>
<tr>
<td>Cardiac surveillance after revascularization (percutaneous coronary intervention or coronary artery bypass graft)</td>
<td></td>
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<tr>
<td>Investigation of cardiac arrhythmias</td>
<td></td>
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<tr>
<td>Evaluation of clinical response to exercise in individuals with valvular heart disease</td>
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<tr>
<td>Preoperative cardiac risk evaluation</td>
<td></td>
</tr>
<tr>
<td>Evaluation in asymptomatic individuals with high risk for CHD</td>
<td></td>
</tr>
<tr>
<td>Assessment of individuals in high-risk occupations</td>
<td></td>
</tr>
<tr>
<td>Evaluation prior to initiation of vigorous exercise regimen</td>
<td></td>
</tr>
<tr>
<td>Determination of pacemaker responsiveness and function</td>
<td></td>
</tr>
</tbody>
</table>

### Contraindications

**Absolute Contraindications**
- Acute myocardial infarction (within 2 days)
- High-risk unstable angina
- Uncontrolled cardiac arrhythmia with hemodynamic compromise
- Active endocarditis
- Symptomatic severe aortic stenosis
- Decompensated heart failure
- Acute pulmonary embolism or pulmonary infarction
- Acute myocarditis or pericarditis
- Physical disability precluding safe and adequate testing

**Relative Contraindications**
- Known left main coronary artery stenosis
- Moderate aortic stenosis with uncertain relationship to symptoms
- Tachyarrhythmias with uncontrolled ventricular rates
- Acquired complete heart block
- Hypertrophic cardiomyopathy with a severe resting gradient
- Mental impairment with limited ability to cooperate

*KM Anderson et al.*

*Journal of the American Association of Nurse Practitioners 26 (2014) 59-69*

*Braunwald, Heart Disease 9th Edition*
<table>
<thead>
<tr>
<th>STAGE</th>
<th>TIME</th>
<th>SPEED (mph)</th>
<th>GRADE (%)</th>
<th>METs</th>
</tr>
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<tbody>
<tr>
<td>Rest</td>
<td>00:00</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>03:00</td>
<td>1.7</td>
<td>10.0</td>
<td>4.6</td>
</tr>
<tr>
<td>2</td>
<td>03:00</td>
<td>2.5</td>
<td>12.0</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>03:00</td>
<td>3.4</td>
<td>14.0</td>
<td>10.1</td>
</tr>
<tr>
<td>4</td>
<td>03:00</td>
<td>4.2</td>
<td>16.0</td>
<td>12.9</td>
</tr>
<tr>
<td>5</td>
<td>03:00</td>
<td>5.0</td>
<td>18.0</td>
<td>15.1</td>
</tr>
<tr>
<td>6</td>
<td>03:00</td>
<td>5.5</td>
<td>20.0</td>
<td>16.9</td>
</tr>
<tr>
<td>7</td>
<td>03:00</td>
<td>6.0</td>
<td>22.0</td>
<td>19.2</td>
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</tbody>
</table>

Braunwald, Heart Disease 9th Edition
Patient Response During Exercise Stress--Report

• Symptoms
  • Chest Pain (Typical vs Atypical vs Non Anginal)
  • Perceived exertion (Borg Scale)
  • Reason for termination

• Exercise Capacity
  • Time
  • METs (Metabolic Equivalent) Total Body O2 Consumption
  • 1 MET = resting O2 consumption; reported multiple of rest, varies by protocol

• Hemodynamic
  • Heart Rate
  • Max Blood Pressure

• ECG
  • ST change
  • Arrhythmia

Target HR = (220 - age) x 0.85
ECG Response—Stress Testing

Braunwald, Heart Disease 9th Edition
Major Indications for Imaging ETT (Echo or Nuclear)

- LVH by ECG
- LBBB (consider vasodilator)
- Digoxin Rx
- Abnormal ST-T on resting ECG
- Localization of region(s) of ischemia
- Increased sensitivity in selected populations
- Imaging always combined with pharmacologic stress in pts who cannot exercise

Hendel et.al. J Nucl Card, 13 (6); E152-E156;2006
Segmental Anatomy Imaging Planes LV--ASE

Segmental Anatomy Coronary Perfusion LV—Echocardiography

Echo Wall Motion Score

Criteria for Positive

- Worsening segmental wall motion by at least 1 grade

Braunwald, Heart Disease 9th Edition
Stress Echo Example
Stress Nuclear Tomography/Regional Perfusion

Braunwald, Heart Disease 9th Edition
Stress/Rest Abnormal
Gated Perfusion

Braunwald, Heart Disease 9th Edition
Stress Nuclear Quantitative

Braunwald, Heart Disease 9th Edition
## Pharmacologic Stressors

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Administration</th>
<th>Usual Duration</th>
<th>Common Transient Effects</th>
<th>Prior to Test Evaluation</th>
<th>Patient Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regadenoson (Lexiscan®)</td>
<td>0.4 mg IV</td>
<td>10 seconds infusion</td>
<td>Headache, Chest discomfort, Nausea, Flushing</td>
<td>Tachycardia, Hypotension, Methylxanthines, Weight limit of camera, Claustrophobia, Medications, Able to be supine 20-30 min BP</td>
<td>No caffeine for 48 h, No phosphodiesterase inhibitors, No food or fluids 4-8 h, Medication instructions Nitrates, beta-blockers, calcium channel blockers, insulin, pulmonary inhalers</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>10-40 to 50 mcg/kg/min IV, begin at 5-10 mcg/kg/min, then increase 10 mcg/kg/min every 3 min</td>
<td>Four to five stages, 3 min stage, 12-15 min total infusion</td>
<td>Headache, Chest pain, Palpitations, Nausea, Tremor, Hypertension or hypotension, Atrial or ventricular arrhythmias</td>
<td></td>
<td>No food or fluids 4-8 h, Medication instructions Nitrates, beta-blockers, calcium channel blockers, insulin, pulmonary inhalers</td>
</tr>
</tbody>
</table>
# Testing--Definitions

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive (TP)</td>
<td>Abnormal test result in an Individual with disease</td>
</tr>
<tr>
<td>False positive (FP)</td>
<td>Abnormal test result in an Individual without disease</td>
</tr>
<tr>
<td>True negative (TN)</td>
<td>Normal test result in an Individual without disease</td>
</tr>
<tr>
<td>False negative (FN)</td>
<td>Normal test result in an Individual with disease</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Percentage of patients with CAD who have an abnormal result = TP/(TP + FN)</td>
</tr>
<tr>
<td>Specificity</td>
<td>Percentage of patients without CAD who have a normal result = TN/(TN + FP)</td>
</tr>
<tr>
<td>Predictive value of a positive test</td>
<td>Percentage of patients with an abnormal result who have CAD = TP/(TP + FP)</td>
</tr>
<tr>
<td>Predictive value of a negative test</td>
<td>Percentage of patients with a normal result who do not have CAD = TN/(TN + FN)</td>
</tr>
<tr>
<td>Test accuracy</td>
<td>Percentage of true test results = (TP + TN)/total number of tests performed</td>
</tr>
</tbody>
</table>
Test Performance

Magri CJ
British Journal of Hospital Medicine, June 2012, Vol 73, No 6
Classic anginal features:

- Substernal chest tightness or pressure triggered by physical or emotional stress
- Is relieved by rest or SL NTG
- Lasts for 15-20 minutes each episode

2-3/3: typical angina
1/3: atypical angina
0/3: likely non-cardiac chest pain
Stress Testing: Who?

Adults with intermediate (10-90%) pre-test probability of CAD

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Typical</th>
<th>Atypical</th>
<th>Non-anginal</th>
<th>Asymp</th>
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<tr>
<td>30-39</td>
<td>Male</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Intermediate</td>
<td>Very Low</td>
<td>Very low</td>
<td>Very low</td>
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<tr>
<td>40-49</td>
<td>Male</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
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<tr>
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<td>Female</td>
<td>Intermediate</td>
<td>Low</td>
<td>Very low</td>
<td>Very low</td>
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<td>50-59</td>
<td>Male</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
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<tr>
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<td>Intermediate</td>
<td>Low</td>
<td>Very low</td>
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<tr>
<td>60-69</td>
<td>Male</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
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<tr>
<td></td>
<td>Female</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Low</td>
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</table>
Post-Test Probability of CAD Based on Pre-Test Symptoms - Men

Post-Test Probability of CAD Based on Pre-Test Symptoms - Women

Proposed Algorithm Women

Intermediate- to High-Likelihood Women with Atypical Chest Pain Symptoms

- Normal rest ECG and able to exercise
  - Exercise treadmill testing
    - Low post-ETT likelihood
    - Int-risk TM
      - Risk factor modification +/- or anti-ischemic Rx
  - Normal or mildly abnormal with normal LV function

- Diabetes, abnormal rest ECG, or questionable exercise capacity
  - Stress cardiac imaging
    - Able to exercise or h/o symptoms with low-level exercise
      - Exercise stress
    - Unable to exercise (orthopedic reasons, CVA, LBBB, etc.)
      - Pharmacologic stress
        - Moderately or severely abnormal or reduced EF
          - Cardiac catheterization

Braunwald, Heart Disease 9th Edition
Prognosis Stress Testing

**Other Parameters**
- Fall in BP >20 mm Hg below rest
- Heart rate recovery 12 beats 1 min with cool down, 18 beats with rest
- Ventricular Arr depends on population

**Duke Treadmill Score**

$$\text{Score} = \text{Duration (min Bruce protocol)} - (5\times \text{ST-seg deviation})(\text{mm}) - (4\times \text{angina index})(0, 1, 2)$$

**Annual CV mortality (%)**
- Low (≥5): 0.25%
- Intermediate (-10 to +4): 1.3%
- High (<-10): 5.0%

Prognosis Nuclear Stress

Reclassification of Duke Risk Score

Miller TD et al. Cardiol Clin 32 (2014) 387-404
Prognosis Stress Echo

High Risk
- Ext Rest WMA (4-5 segs)
- LVEF < 40%
- Ext Stress WMA (4-5 Segs)
- Ext Rest + Stress WMA
- Low Ischemic Threshold

Miller TD et al.
Cardiol Clin 32 (2014) 387-404
## Advantages/Disadvantages Stress Modality

<table>
<thead>
<tr>
<th></th>
<th>Exercise (ECG only)</th>
<th>Nuclear (Regadenoson)</th>
<th>Echo (Dobutamine)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Inexpensive</td>
<td>• More sensitive</td>
<td>• More sensitive</td>
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<tr>
<td></td>
<td>• No IV</td>
<td>• Can perform in pts with baseline ECG abnormalities</td>
<td>• No radiation</td>
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<tr>
<td></td>
<td>• Allows functional assessment</td>
<td>• Regadenoson well tolerated</td>
<td>• Visualize cardiac function and anatomy</td>
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<td></td>
<td>• Not affected by beta blockers</td>
<td>• Performed within one hour</td>
</tr>
<tr>
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<td></td>
<td>• Not arrhythmia provoking</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Lower sens and spec</td>
<td>• Radiation</td>
<td>• Dobutamine (hold beta blockers at least 24 hrs)</td>
</tr>
<tr>
<td></td>
<td>• Cannot perform in patients with baseline ECG abnormalities or certain drugs</td>
<td>• Nausea/vomiting, chest pain, flushing with regadenoson</td>
<td>• Tachyarrhythmias</td>
</tr>
<tr>
<td></td>
<td>• Cannot perform if patient cannot exercise</td>
<td>• Lengthy study</td>
<td>• Difficulty when resting wall motion abnormalities are present</td>
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<td></td>
<td></td>
<td>• No caffeine/chocolate 24 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Theo hold for 48 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Difficulty when resting wall motion abnormalities are present</td>
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</table>
Hemodynamic Stress Echo

Indication

Diagnostic and prognostic purposes?

Able to exercise?

Yes

No

Pharmacologic stress imaging

Normal findings on resting ECG (see text)
Patient not taking digoxin?

Yes

No

Standard treadmill exercise test

Localization of ischemia?

Able to exercise?

Yes

Able to exercise?

Yes

Cardiopulmonary exercise test

Direct measurement of $\dot{V}O_{2\text{max}}$, timing of cardiac transplantation, or selected patients with unexplained dyspnea?

Able to exercise?

Yes

Exercise imaging study
Local expertise with the technique
Primary question to be answered
Patient characteristics
Cost

Hemodynamic Stress Echo
Summary

• Pretest likelihood of disease has to be incorporated into the interpretation of stress testing
• The most important use of stress testing is determining prognosis
• Duke treadmill score works well for prognosis
  • Imaging can re-stratify in low and intermediate risk patients
• Exercise testing preferred if patients can adequately exercise
  • Pharmacologic stress for those who cannot exercise must be combined with imaging
• Imaging choice depends on local expertise and patient characteristics and clinical question
Hemodynamic Stress Echo

• Evaluation of patients with valvular disease
  • Mitral disease
  • Aortic stenosis

• Evaluation of patients with unexplained dyspnea on exertion
  • Diastolic stress test
Hemodynamic Stress Echo

• Technique and Measures
  • What stressor?
  • What measures?

• Application to Specific Patient Subsets
  • Mitral Regurgitation
  • Low Gradient Aortic Stenosis

• Interpretation of Stress Echo Results
  • What is an abnormal response?
  • What outcomes are predicted?
<table>
<thead>
<tr>
<th>Hemodynamic Stress Echo</th>
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<table>
<thead>
<tr>
<th>Stressor</th>
<th>MR</th>
<th>Measure</th>
<th>Low Grad AS</th>
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<tbody>
<tr>
<td>Exercise</td>
<td>CR</td>
<td>CR</td>
<td>Dobutamine</td>
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<tr>
<td></td>
<td>PASP</td>
<td>LVOT Vel</td>
<td></td>
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<tr>
<td></td>
<td>PVR</td>
<td>Mean Gradient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E/E’</td>
<td>DOI</td>
<td></td>
</tr>
<tr>
<td>MR severity</td>
<td>ER OA</td>
<td>AVA</td>
<td></td>
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<tr>
<td></td>
<td>O²Sat</td>
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</table>
Hemodynamic Stress Test – Determinants of Pulmonary Pressure

\[ \text{Pressure} = \text{Flow} \times \text{Resistance} \]

\[ \frac{\text{TRV}}{\text{Pul VTI}} = \text{Resistance} \]

\[ \frac{\text{TRV}}{\text{Pul VTI}} < 0.2 \]

\[ \times 10 = \text{Wood Units} \]

- **RV**: TR jet/Pul TVI
- **Lungs**: O² SAT
- **LV/LA**: E/E’ MR
Pulmonary Pressure and Resistance in Athletes vs Pts(COPD)

Bidart CM et al. JASE 2007;20:270-275
LV Pressure during Exer/Echo

Burgess MI et al. JACC 2006;47:1891-900
R  LVEF = 42%
S  LVEF = 34%
PVR = 2.29/15.7 = 0.15

PVR = 3.85/15.8 = 0.24
E/E' = 9.0

E/E' = 15.0
Role of ExEcho in Mitral Regurgitation

- Correlate pathology with patient’s symptoms
  - Assess PAP, PVR, change in MR severity
- Organic MV disease
  - Unmask latent LV dysfunction
- Functional MR
  - Prognosis
Hemodynamic Exercise Stress Echo in MR

• **Supine bike**
  • Some studies: pre/ post treadmill or upright bike

• **Measurements at each stage**
  • TR jet, RVOT TVI, E mitral, E annulus
  • MR (EROA)
  • LV function assessment
  • O² Sat

• **Normal response**
  • Pulmonary pressure < 50 mmHg (assumes normal resting pressure)
  • Need to integrate pulmonary resistance, level of conditioning, clinical indication
Importance of Contractile Reserve

- 74 patients
- Organic MR
- Subsequent MV repair
- Post op LVEF assessed at 8 +/- 14d

Leung D. et al. JACC. 1996;28:1198-205
Contractile Reserve and LVEF

- 71 pts, Org MR, NYHA I and II
- CR assessed
  - CR+ (19/45) MVrep
  - CR- (22/26) MVrep
- Follow up 3yrs
- EF, Functional Status, Outcome

Event Free Survival

Prognosis in Functional MR

82pts, Med Tx, FU 19mos, 11% mortality

323pts, Med Tx, FU 1.7 years, 43 endpoints
Severe Aortic Stenosis Review

### Grading AS with Normal LV Function

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Peak Velocity</td>
<td>&lt;3.0 m/s</td>
<td>3.0-4.0 m/s</td>
<td>&gt;4.0 m/s</td>
</tr>
<tr>
<td>Mean Grad</td>
<td>&lt;15 mmHg</td>
<td>15-40 mmHg</td>
<td>&gt;40 mmHg</td>
</tr>
<tr>
<td>Valve Area</td>
<td>&gt;1.5cm²</td>
<td>1.0-1.5cm²</td>
<td>&lt;1.0cm²</td>
</tr>
</tbody>
</table>

- **Dimensionless Obstructive Index (DOI):** Ratio LVOT peak velocity/transvalve peak velocity
- DOI \(\leq 0.25\) = severe    DOI \(> 0.30\) = not severe
- **2D/3D Assessment of AoV excursion**
Low Gradient /Low Flow/Low EF Aortic Stenosis

• **Definition**
  - Aortic valve area < 1.0 cm²
  - Mean trans aortic valve gradient < 30 mmHg
  - LVEF < 40%

• **Clinical Questions**
  - Is severity of aortic stenosis overestimated due to low flow state?
  - Is systolic dysfunction caused by aortic stenosis or primary myocardial disease?

• **Purpose of using Dobutamine**
  - Evaluation of trans-aortic valve gradients and aortic valve areas at different flow states
  - Evaluation of myocardial contractile reserve (ICR)
Low Flow/Low Gradient AS Method and Interpretation

INTERPRETATION

- Severe Aortic Stenosis:
  - Dobutamine -- mean trans-AoV gradient $> 30$ mmHg provided AoV area $< 1.2 \text{ cm}^2$

- Evidence of ICR:
  - $\uparrow$ LVEF $> 5$
  - $\uparrow$ TVI of LVOT/AoV $> 20$

DOSE($\mu g/kg/min$)  
0  5  10  15  20

IMAGE/ACQUIRE
+  +  +  +  +

INFUSION TIME 3 MIN

Ap4/2, Para LX/SX
Doppler LVOT/AoV
### Low Flow/Low Gradient AS--Interpretation

<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>LVOT = 2.2CM</th>
<th>FINAL</th>
<th>INTERPRET</th>
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<tbody>
<tr>
<td><strong>LVOT VELOCITY</strong></td>
<td><strong>JET VELOCITY</strong></td>
<td><strong>MX/Mean GRAD</strong></td>
<td><strong>LVOT VELOCITY</strong></td>
<td><strong>JET VELOCITY</strong></td>
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<tr>
<td>0.6</td>
<td>3.0</td>
<td>36/23</td>
<td>1.0</td>
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<tr>
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<td>DOI = 0.22</td>
<td>AVA = 0.84cm²</td>
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<td>DOI = 0.29</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>DOI = 0.20</td>
<td>AVA = 0.76cm²</td>
</tr>
</tbody>
</table>

DOI = 0.20
AVA = 0.76cm²
DOI = 83/250 = 0.33; AVA= 1.0
DOI = 1.05/2.66 = 0.39; AVA = 1.2cm²
Assessment of Patients with AS and Low Flow--Outcome

- **136 patients studied**
  - Group 1 = 92 pts with ICR
  - Group 2 = 44 pts without ICR

- **Operative mortality**
  - Group 1 = 5%
  - Group 2 = 32%

- **Outcomes in patients (7) discovered to have moderate AS treated medically**
  - 57% alive during f/u

Summary

• Exercise Echo in Dyspnea
  • Can separate pulmonary from cardiac causes of dyspnea

• Exercise Echo in Valvular Disease
  • Evaluates dynamic change in echo markers of severity
  • Evaluates PA pressure with graded exercise
  • Correlates severity with symptoms
  • Can detect latent LV dysfunction
  • Adds prognostic information

• Dobutamine challenge in Low Gradient AS
  • Separates true from pseudo stenosis
  • Adds prognostic information prior to AVR
References

• Braunwald’s Heart Disease, 9th Edition


• Anderson KM, Murphy DL and Balaji M. Essentials of non-invasive cardiac stress testing. Journal of the American Association of Nurse Practioners 2014; 26:59-69