Floppy Mitral Valve (FMV)/Mitral Valve Prolapse (MVP) and the FMV/MVP Syndrome: Pathophysiologic Mechanisms, Diagnostic and Therapeutic Considerations

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Editorial

Floppy Mitral Valve and Mitral Valve Prolapse: Lack of Precise Definition (The Tower of Babel Syndrome)

Boudoulas KD, Boudoulas H. Cardiology 2011;118:93-96
Floppy mitral valve (partial to complete involvement) is the central issue in the mitral valve prolapse, mitral valvular regurgitation story.
Floppy Mitral Valve (FMV) Genetics

- Gene map loci:
  - 16p12.1 – p11.2
  - 11p15.4
  - 13q31.3 – q32.1
  - xq28

- Clinical trials.gov (2012-2020)

Four generations pedigree of a family with floppy mitral valve/mitral valve prolapse/mitral regurgitation
FMV/MVP/Mitral Valvular Regurgitation: Diagnostic Considerations

Imaging: (echo, angio, MRI)
- Thick redundant valve with prolapse
- 3rd chamber

Skeletal abnormalities
- Thinner than normal
- Height/weight > normal
- Arm span > height

Auscultation:
- Click-murmur

Hemodynamic:
- (angio/Doppler, MRI, mitral regurgitation)
 Floppy Mitral Valve/Mitral Valve Prolapse Association with Other Disorders/Diseases

• Heritable connective tissue disorders
  – Marfan
  – Ehlers-Danlos
  – Adult polycystic kidney diseases
  – Multi valve prolapse
  – MASS (mitral, aorta, skeleton, skin)

• Other
  – Graves disease
  – Atrial septal defect?
FMV/MVP/MVR: Classification

- Normal
- FMV/MVP – no MVR
- FMV/MVP: - mild MVR
- FMV/MVP: - moderate MVR
- FMV/MVP: - severe MVR

Dynamic spectrum

Time (years)
FMV/MVP/MVR: Symptoms/Complications

- Infective endocarditis
- Cardiac arrhythmias
- Sudden cardiac death
- Thromboembolic complications

- Progressive MVR
- Ruptured chordae tendineae
- Increased LV-LA size
- CHF
• Thrombus formation
• Infective endocarditis
  – Oral hygiene
  – Antibiotic?
FMV/MVP: Sudden Cardiac Death

- Very rare (more common in female)
- Bileaflet prolapse – floppy mitral valve
- History of complex ventricular arrhythmias and/or syncope
FMV/MVP: Natural History

![Bar Graph: Number of Patients vs Patient Age]
FMV/MVP: Progression of Mitral Valvular Regurgitation (MVR) Precipitating Factors

Mild MVR

Moderate MVR

Severe MVR

LA-LV dilatation/dysfunction

- Infective endocarditis
- Chordae tendinae rupture
- Stiff aorta
- Papillary muscle displacement
MVR: Aortic-Ventricular-Pulmonary Interrelationship

- Left Atrium
- Mitral Valve
- Left heart
- Pulmonary veins
- Left heart
- Arterioles
- Right heart
- Pulmonary artery
- Vena cava
- Alveolar capillaries
FMV/MVP/MVR: Therapeutic Considerations

The Heart Team and Heart Valve Center of Excellence

Medical
FMV/MVP/MVR: Therapeutic Considerations

Mitral Valve Clip

Echocardiographic and clinical outcomes of central versus noncentral percutaneous edge-to-edge repair of degenerative mitral regurgitation.

FMV/MVP/MVR: Therapeutic Considerations

Surgical Approach

- Significant MVR
- Symptoms
- Left ventricular (LV) ejection fraction <60
- LV end systolic diameter >40 mm
- Pulmonary hypertension ≥50 mm Hg, rest
- Left atrial enlargement
- Chordae tendinae rupture
- Atrial fibrillation
- The role of exercise
- Reconstructive vs valve replacement
- Leaflet prolapse
  - Posterior 67%, 51%
  - Anterior 10%, 11%
  - Both 23%, 37%
## FMV/MVP Syndrome (n = 313)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Female (n=227)</th>
<th>Male (n=86)</th>
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<tbody>
<tr>
<td>Chest pain</td>
<td>60</td>
<td>60</td>
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<tr>
<td>Palpitations</td>
<td>75</td>
<td>46</td>
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<tr>
<td>Fatigue</td>
<td>48</td>
<td>28</td>
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<tr>
<td>Dyspnea</td>
<td>34</td>
<td>16</td>
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<tr>
<td>Postural phenomena</td>
<td>15</td>
<td>15</td>
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<tr>
<td>(syncope/presyncope)</td>
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<tr>
<td>Symptoms</td>
<td>Count</td>
<td></td>
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<tr>
<td>----------------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>25</td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Postural phenomena (syncope/presyncope)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms consistent with FMV/MVP syndrome (n=101)
FMV/MVP Syndrome: Age of Onset and Duration of Symptoms

• Median age of onset 30 years
  (Range 10-65 years)

• Median time of duration 16 years
  (Range 3-50 years)
FMV/MVP Syndrome: Pathogenetic Mechanisms

- Papillary muscle traction / Stretch receptor activation
- Mitral valve-brain interaction
- Development of third chamber
- Hypersensitivity to adrenergic stimulation
- Other
FMV/MVP: Papillary Muscle Traction/Stretch Receptor Activation

- Abnormal Mitral Apparatus
  - Mitral Leaflet Prolapse
    - Papillary Muscle Traction
      - Activation of Stretch Receptors
        - Papillary Muscle and Subendocardial Ischemia
          - Pain
          - Ventricular Arrhythmias

Stretch Receptor
FMV/MVP: Mitral Valve-Brain Interactions
FMV/MVP: Third Chamber
Floppy Mitral Valve/Mitral Valve Prolapse
Normal Mitral Valve

Floppy Mitral Valve / Mitral Valve Prolapse

Courtesy Vlasis Ninios, Agios Loukas Hospital, Thessaloniki
Floppy Mitral Valve / Mitral Valve Prolapse

Courtesy Subha Raman, MD, The Ohio State University
Left Ventricular End-Diastolic Volume Index (LVEDVI) in the Supine and Upright Posture, at Rest and During Exercise

FMV/MVPS (n=16)
Control (n=12)

Symbols:
- Supine
- Upright

Graph shows the LVEDVI values for FMV/MVPS and Control groups in the supine and upright postures, with data points for Rest, 300 Kpm/min, and Peak.
Effect of Isoproterenol Infusion on Heart Rate (HR)

Δ HR (beats/min)

- Control (n = 12)
- FMV/MVPS (n = 16)

- 0.5 μg/min: p < 0.01
- 1 μg/min: p < 0.01
- 2 μg/min: p < 0.01

### β₁-Adrenergic Receptor Polymorphism in FMV/MVP: Frequency of CC (Arginine 389) Genotype

#### Table

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>FMV/MVP</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>Female</td>
<td>48%</td>
<td>61%</td>
</tr>
<tr>
<td>Total</td>
<td>45.5%</td>
<td>51%</td>
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</tbody>
</table>

#### Graph

- **X-axis:** Total, Male, Female
- **Y-axis:** %
- **Legend:**
  - Control
  - FMV/MVP
- **Data:**
  - Total: 45.5% Control, 51% FMV/MVP
  - Male: 48% Control, 48% FMV/MVP
  - Female: 48% Control, 61% FMV/MVP
β₁-Adrenergic Receptor Polymorphism in Females. Frequency of CC (Arginine 389) Genotype

- Control: 48%
- FMV/MVP: 61%
- FMV/MVP Syndrome: 81%

p = 0.025
Floppy Mitral Valve: Factors Contributing to Symptoms in FMV/MVP Syndrome

- Development of 3rd Chamber
- ↓ Stroke Volume (especially in upright position)
- ↑ β₁-Receptor Sensitivity
- FMV Nerve Ending Stimulation
- ↑ Papillary Muscle Traction
- Neurohumoral Activation
- Brain-Heart Interaction
- Stretch Receptor Activation
- Orthostatic Phenomena
- Tachycardia
- Arrhythmia
- Chest Pain
Floppy Mitral Valve/Mitral Valve Prolapse Syndrome: Pathogenesis of Symptoms
FMV/MVP Syndrome: Therapeutic Considerations

The Superior Physician
He is skeptical toward the data of his own profession, welcomes discoveries which upset his previous hypothesis, and still animated by human sympathy and understanding. Alfred North Whitehead, *Dialoges* (Lucien Press) 1954

- Explain and reassure
- Avoid caffeine, catecholamines or other cyclic - AMP stimulants
- Avoid volume depletion and diuretics
- Avoid long-term drug therapy
- Treat the specific symptoms if persistent (chest pain, postural phenomena, etc.)
- Management requires understanding the underlying pathophysiologic mechanisms, natural history of the disease and caring for the patient.
FMV/MVP: Individual Patient Analysis

Initial Diagnostic Evaluation

Heritable Connective Tissue Disorder

Isolated FMV/MVP

Diagnostic Classification

Symptoms / Events

Periodic Evaluation

Frequent Evaluation

Intervention

Time (years)

FC

IV

III

II

I

FMV/MVP/MVR

FMV/MVP Syndrome

Diagnostic Classification

FMV/MVP: Individual Patient Analysis
FMV/MVP: Individual Patient Analysis

Initial Diagnostic Evaluation

Heritable Connective Tissue Disorder

Isolated FMV/MVP

Diagnostic Classification

Symptoms / Events

Time (years)

FC

IV

III

II

I

Frequent Evaluation

Periodic Evaluation

Intervention
FMV/MVP/MVR: The Role of the Aorta

Stiff Aorta

Normal Aorta
A randomized controlled phase IIb trial of beta\textsubscript{1}-receptor blockade for chronic degenerative mitral regurgitation.
Ahmet MI, et al. *JACC* 2012;60:833-838 (FMV/MVP/MVR, n=38; Toprol-XL, MRI, 2 year study)

Modulation of transforming growth factor-\(\beta\) signaling and extracellular matrix production in myxomatous mitral valves by angiotensin II receptor blockers.
Geirsson A, et al. *Circulation* 2012;126(Suppl 1):S189-S197 (Cultured valve tissue obtained from patients undergoing mitral valve repair or organ donors without mitral valve disease)
# Mitral Valve Repair vs Replacement

Medicare database 47,279, >65 years, 2000-2009

<table>
<thead>
<tr>
<th></th>
<th>MV Repair</th>
<th>MV Replacement</th>
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<tbody>
<tr>
<td>Surgical Mortality</td>
<td>3.9%</td>
<td>8.9%</td>
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<tr>
<td>Survival</td>
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<td></td>
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<tr>
<td>1 year</td>
<td>90.9%</td>
<td>82.6%</td>
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<tr>
<td>5 years</td>
<td>77.1%</td>
<td>64.7%</td>
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<tr>
<td>10 years</td>
<td>53.6%</td>
<td>37.2%</td>
</tr>
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FMV/MVP/MVR: Late Outcome of Mitral Valve Repair

Survival

Freedom from moderate and severe MVR

Hemodynamics in Acute Mitral Regurgitation
FMV/MVP Syndrome

- Diffuse thickening (3rd chamber) – 40 patients
  - Symptoms consistent with FMV/MVP syndrome - 21 (52.5%)

- Regional thickening – 61 patients
  - Symptoms consistent with FMV/MVP syndrome – 19 (31%)

p = 0.025
Mitral Valve Prolapse (MVP): Definition

MVP results from the systolic movement of portion(s) or segments of the mitral valve leaflet(s) into the left atrium during left ventricular systole.