Mitral Valve Prolapse and Sudden Death

JF Avierinos
Hôpital Timone
Marseille
January 27th, 2017
Mitral Valve Prolapse
Between Benign and Malignant
the Long Story of an Ongoing Controversy

… of a Pathologic disease … defined by echo

JF Avierinos
Hôpital Timone
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January 27th, 2017
MVP: Four decades of controversy

From Pathology to stethoscope

Dr Barlow

“The significance of late systolic murmurs and mid-late systolic clicks”

MVP: Four decades of controversy
From stethoscope to echo

Prevalence: 5% to 17% ???
MVP Prevalence with current diagnostic criteria

0.6% to 2.4%

150 Million subjects worldwide

Freed, NEJM, 1999
### MVP: Four decades of controversy

#### Outcome

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº</td>
<td>237</td>
<td>300</td>
<td>456</td>
<td>316</td>
<td>229</td>
<td>84</td>
</tr>
<tr>
<td>Age</td>
<td>44</td>
<td>42</td>
<td>47</td>
<td>42</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6.2</td>
<td>6.1</td>
<td>Backwards</td>
<td>8.5</td>
<td>?</td>
<td>Backwards</td>
</tr>
<tr>
<td>Patients with Complic. (%)</td>
<td>22</td>
<td>39</td>
<td>17</td>
<td>10</td>
<td>44</td>
<td>5</td>
</tr>
<tr>
<td>Linearized Rates (%/year)</td>
<td>3.4</td>
<td>6.4</td>
<td>?</td>
<td>1.2</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
MVP : Four decades of controversy

Sudden Death

Sudden Death in the Mitral Valve Prolapse-Click Syndrome

Am J Cardiol, 1976

Sudden death in mitral valve prolapse with Holter monitoring documented ventricular fibrillation: evidence of coexisting arrhythmogenic right ventricular cardiomyopathy

Martini, Int J Cardiol, 1994

Life-Threatening Arrhythmias in the Mitral Valve Prolapse Syndrome

Am J Med, 1976

Arrhythmias in mitral valve prolapse: Relation to anterior mitral leaflet thickening, clinical variables, and color Doppler echocardiographic parameters

Zuppiroli, Am H J 1994

DeMaria, Ann Int Med, 1976

Prevalence, Nature, and Frequency

ANTHONY N. DeMARIA, M.D.; EZRA A. AMSTERDAM, M.D.; LOUIS A. VISMARA, M.D.; ALEXANDER NEUMANN, B.S.; and DEAN T. MASON, M.D.; Davis, California
MVP: Four decades of controversy

Sudden Death

**Figure 1.** Percent distribution of 118 serious complications in 100 of 300 patients with idiopathic mitral valve prolapse.


MVP: Four decades of controversy
Sudden Death

Figure 1. Percent distribution of 118 serious complications in 100 of 300 patients with idiopathic mitral valve prolapse.


Prevalence and Clinical Outcome of Mitral Valve Prolapse

The New England Journal of Medicine July 1st, 1999

**Table 2. Prevalence of Various Clinical Findings According to the Presence or Absence of Mitral-Valve Prolapse.**

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Mitral-Valve Prolapse (N=84)</th>
<th>No Mitral-Valve Prolapse (N=3407)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>25 (0.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (1.2)</td>
<td>58 (1.7)</td>
</tr>
<tr>
<td>Cerebrovascular disease*</td>
<td>1 (1.2)</td>
<td>52 (1.5)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (3.6)</td>
<td>103 (3.0)</td>
</tr>
</tbody>
</table>

*Cerebrovascular disease refers to stroke or transient ischemic attack.*
Mitral Valve Problems Are Not So Serious After All

As many as 28 million Americans who were told they are in danger of stroke, heart failure and other problems because of mitral-valve prolapse probably do not have to worry. A new study showed that about 2.4 percent of the population — not the 5 percent to 15 percent previously estimated — have the condition, an abnormally long, floppy valve that can cause blood leakage in the heart. And in those who do have it, it was found no more likely to cause the feared complications than those who do not.

HOLCOMB B. NOBLE

THE NEW YORK TIMES, SUNDAY, JULY 4, 1999

MVP: a benign condition
MVP: a benign condition?

MVP = 70% surgical severe MR in western countries

Olson, Mayo Clin Proc. 1987
MVP with flail leaflet

Clinical outcome

Excess mortality

Survival (%)

Expected

Observed

P=0.016

Ling, Enriquez Sarano, NEJM, 1996
Changes in Diagnostic criteria
# MVP: Four decades of controversy

## Outcome

<table>
<thead>
<tr>
<th></th>
<th>Series from referral centers (n=1538)</th>
<th>Population-based study (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognosis</strong></td>
<td>Variable, often severe</td>
<td>Benign</td>
</tr>
<tr>
<td><strong>Complications (%)</strong></td>
<td>10 to 44</td>
<td>5</td>
</tr>
<tr>
<td>Linearized rates of complications (%/year)</td>
<td>1.2 to 6.4</td>
<td>?</td>
</tr>
<tr>
<td><strong>Predictor</strong></td>
<td>Mitral thickening</td>
<td>None</td>
</tr>
<tr>
<td><strong>Criticism</strong></td>
<td>Outdated criteria</td>
<td>Small sample size</td>
</tr>
<tr>
<td></td>
<td>Referral bias</td>
<td>No FU</td>
</tr>
</tbody>
</table>
MVP: Clinical outcome in the community

Risk Stratification

833 Community MVP

Overall Survival

Cardiac Survival

**Overall Survival**

- **Low risk = 50% of pts**
  - $P(\text{exp})=0.17$
  - Survival at 10 years: $95 \pm 2$

- **High risk = 18% of pts**
  - $P(\text{exp})=0.20$
  - Survival at 10 years: $70 \pm 5$

- $P(\text{dif})<0.001$

**Cardiac Survival**

- **No or 1 minor RF**
  - Survival at 10 years: $87 \pm 4$

- **≥2 minors RF**
  - Survival at 10 years: $66 \pm 10$

- **major RF**
  - Survival at 10 years: $55 \pm 9$

- $P(\text{dif})<0.001$

*Avierinos, Circ, 2002*
MVP: Clinical outcome in the community

Sudden Death

*Does it exist?*

*Is it the leak?*  *Is it MVP?*
MVP: Sudden Death and severe MR due to Flail Leaflet

348 Flail, 67yo, FU=48±41 months, 99 deaths

25 SD

1.8%/year

Table 2. Multivariate Predictor of Sudden Death*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unit</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>Per percent</td>
<td>0.94</td>
<td>0.91–0.97</td>
<td>0.0001</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>Per class</td>
<td>1.91</td>
<td>1.20–3.04</td>
<td>0.006</td>
</tr>
<tr>
<td>AF</td>
<td>Per AF present</td>
<td>2.40</td>
<td>0.97–5.95</td>
<td>0.059</td>
</tr>
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Grigioni, JACC, 1999
MVP: Sudden Death and severe MR due to Flail Leaflet

Yearly Rate of Sudden Death

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Rate (%/year)</th>
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<tbody>
<tr>
<td>I</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>II</td>
<td>3.1 ± 1.0</td>
</tr>
<tr>
<td>III-IV</td>
<td>7.8 ± 3.2</td>
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Sudden Death Events/Group

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<tr>
<td>I</td>
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</tr>
<tr>
<td>II</td>
<td>9</td>
</tr>
<tr>
<td>III-IV</td>
<td>6</td>
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10 / 25 SD in asymptomatic patients
17 / 25 SD in patients with normal EF
MVP: Sudden Death and severe MR due to Flail Leaflet

Yearly Rate of Sudden Death

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There is probably more than just the hemodynamic consequences of MR
MVP: Clinical outcome in the community
Risk Stratification
833 Community MVP

16 sudden deaths
3±0.9% at 10 years
0.35%/year
NS from expected rates of SD

70% belonging to the low risk group

There is more than just MR to explain SD
MVP: Sudden Death without severe MR

1200 Out-of-hospital SD with documented arrhythmia
24 unexplained SD after initial assessment –
10/24 with MVP - 0.83% of all OH SD; 50% of unexplained SD

* Female (90%)

* Frequent/complex ventricular arrhythmias
  (Outflow tract/Papillary Muscles/Fascicular Origin)

* Inverted T waves in inferior leads

* Bileaflet MVP (100%)
  only 1 with severe MR

MVP : Sudden Death without severe MR

Malignant MVP?

* Female (90%)

* Frequent/complex ventricular arrhythmias (Outflow tract/Papillary Muscles/Fascicular Origin)

* Inverted T waves in inferior leads

* Bileaflet MVP (100%)
  only 1 with severe MR

MVP: Sudden Death without severe MR: impact of fibrosis

650 SD with autopsy (North Italy), 43 with isolated MVP (MVP=7% of all SD)

- 60% females, 32 yo, 21% with BBBlockers
- 70% with Bileaflet MVP
- 100% with replacement-type fibrosis

- at PM level
- & 90% under posterior leaflet

Basso, Arrhythmic MV prolapse and sudden cardiac death, circulation, 2015, 132, 556-566
MVP: Sudden Death without severe MR; impact of fibrosis

30 MVP alive patients with complex arrhythmia (VF & VT, including 2 resuscitated SD)

* 73% Female, 41 yo

* 70% with Bileaflet MVP

* 93% with MRI Late Gadolinium Enhancement at PM level and under post leaflet

Arrhythmic MVP?

Basso, Arrhythmic MV prolapse and sudden cardiac death, circulation, 2015, 132, 556-566
MVP: Sudden Death without severe MR: origin of Fibrosis

36 arrhythmic MVP with no or mild MR + LGE
(27 females, 44 yo)
Vs. 16 MVP without LGE (6 females, 40 yo)

Annulus disjunction correlates with Fibrosis
MVP : Sudden Death without severe MR: origin of Fibrosis

36 arrhythmic MVP with no or mild MR + LGE (27females, 44yo) 
Vs. 16 MVP without LGE (6females, 40 yo)

Annulus curling correlates with MAD & Fibrosis
MVP: Sudden Death without severe MR: origin of Fibrosis

36 arrhythmic MVP with no or mild MR + LGE
(27females, 44yo)
Vs. 16 MVP without LGE (6females, 40 yo)

MAD creates curling which creates fibrosis
MVP: Sudden Death

- Multi-center Case-control study (8 french academic centers + Mayo Clinic)

- Inclusion Criteria
  - ICD for Secondary Prevention after idiopathic aborted cardiac arrest
  - MVP: only abnormality found after initial assessment

- MVP with SUD vs. matched MVP without SUD

42 Patients with MVP and SUD
Ventricular Fibrillation in all

Frequency Matched 1:2

84 Controls with MVP Alive at Last Follow up

Matched for Age, sex, MR, Afib and EF

Hourdain, Enriquez Sarano…
## MVP : Sudden Death

<table>
<thead>
<tr>
<th></th>
<th>Sudden Death patients (n=42)</th>
<th>Control patients (n=84)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Female, n</td>
<td>28</td>
<td>56</td>
<td>1</td>
</tr>
<tr>
<td>Age, years</td>
<td>53.36±14.4</td>
<td>53.88±14.2</td>
<td>0.85</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62.2±5.2</td>
<td>62.2±5.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Mitra Regurgitation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: None or trivial</td>
<td>8</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>2: Mild or Mild-Moderate</td>
<td>29</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>3: Moderate or Moderate-Severe</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>4: Severe</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>History of Atrial Fibrillation, n</td>
<td>7*</td>
<td>15</td>
<td>1</td>
</tr>
</tbody>
</table>

Most SUD patients belong to the low risk group !!
MVP: Sudden Death

Cases vs. Controls

Clinical

ECG

Echo

• Syncope (60%)

• Pre syncope (95%)

• Family Hx of SUD

↑ LVED; ↑ LVES

Hourdain, Enriquez Sarano...
MVP: Sudden Death Determinants

- Past History of Syncope
- % of Posterior PM PVCs
- Severe Myxomatous Disease

[Images of medical scans and data charts]

Hourdain, Enriquez Sarano...
Conclusion

MVP: benign or malignant?

* Heterogeneous, not uniformly benign or malignant
* A same diagnosis for different diseases:
  - single vs. bileaflets, flail vs. no flail, non thickened
  - vs. severe myxomatous changes, no MR vs. severe MR
* Most complications driven by severe MR and its consequences on LA and LV
* Small subset at risk of Sudden Death despite no MR
Conclusion

MVP: Sudden Death Risk Profile

* Clinical:
  Young females, Syncope, palpitations, familial history of SD

* Electrocardiographic:
  Complex and frequent ventricular arrhythmia from posterior papillary Muscle

* Echocardiographic:
  Thickened bileaflet MVP, annulus disjunction, curling

Potential role of mechanical traction by deep MVP on PPM generating localized fibrosis
Conclusion

MVP: proposed pathway for SD in MVP