Exercise Pulmonary Hypertension predicts the Occurrence of Symptoms in Asymptomatic Degenerative Mitral Regurgitation

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Conflict of Interest Disclosure

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Pr Lancellotti P: None
Introduction

✓ The management and the timing of surgery of patients with asymptomatic degenerative mitral regurgitation (MR) is controversial.

✓ Resting (≥50mmHg) and exercise (≥60mmHg) pulmonary hypertension (PHT) are criteria for surgical decision-making (ACC/AHA: IIa, C) in patients with severe degenerative MR.

✓ Exercise PHT may develop in patients with degenerative MR, even when resting systolic pulmonary arterial pressure (SPAP) is normal.
Objectives

✓ The determinants of exercise-induced PHT in patients with asymptomatic degenerative MR have not been evaluated.

✓ The aims of this study were to identify

(1) the echocardiographic determinants of exercise SPAP and PHT and

(2) the impact of exercise PHT on symptom-free survival in asymptomatic patients with degenerative MR.
Methods

✓ Consecutive asymptomatic patients (n=78) with ≥ moderate MR (effective regurgitant orifice area [ERO] >20mm²; regurgitant volume [RV] >30ml) and with preserved LV systolic function (LV ejection fraction >60%; LV end-systolic diameter <45mm).

✓ Resting and exercise Doppler–echocardiography

✓ MR quantification:

**PISA Method**

- ERO = 28mm²
- RV = 43ml
- r = 8.1 mm

**Doppler Method**

- RV = Mitral SV – LVOT SV
- ERO = RV/ MR
- TVI = 152cm
Impact of Exercise on SPAP

Exercise-induced changes in SPAP

- Resting SPAP: 30±11 mmHg
- Exercise SPAP: 53±17 mmHg

Prevalence of PHT

- Resting PHT (SPAP ≥ 50mmHg): 16%
- Exercise PHT (SPAP ≥ 60mmHg): 46%

p<0.0001
p=0.0003
## Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (n=78)</th>
<th>No Ex-PHT (n=42, 54%)</th>
<th>Ex-PHT (n=36, 46%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61±13</td>
<td>57±14</td>
<td>65±11</td>
<td>0.006</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>44 (58)</td>
<td>19 (45)</td>
<td>25 (69)</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index, kg.m⁻²</td>
<td>26±4</td>
<td>27±4</td>
<td>26±4</td>
<td>0.27</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73±11</td>
<td>73±11</td>
<td>72±11</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>43 (55)</td>
<td>18 (43)</td>
<td>25 (69)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>16 (20)</td>
<td>7 (17)</td>
<td>9 (25)</td>
<td>0.53</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>8 (10)</td>
<td>3 (7)</td>
<td>5 (14)</td>
<td>0.72</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>27 (35)</td>
<td>13 (30)</td>
<td>14 (39)</td>
<td>0.62</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior, n (%)</td>
<td>5 (7)</td>
<td>2 (5)</td>
<td>5 (14)</td>
<td>0.24</td>
</tr>
<tr>
<td>Posterior, n (%)</td>
<td>37 (47)</td>
<td>17 (40)</td>
<td>20 (56)</td>
<td>0.27</td>
</tr>
<tr>
<td>Both, n (%)</td>
<td>36 (46)</td>
<td>23 (55)</td>
<td>13 (36)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mitral Flail, n (%)</td>
<td>8 (10)</td>
<td>3 (7)</td>
<td>5 (14)</td>
<td>0.46</td>
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</tbody>
</table>
## Echocardiographic Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Patients (n=78)</th>
<th>No Ex-PHT (n=42, 54%)</th>
<th>Ex-PHT (n=36, 46%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting LV function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVES volume, ml</td>
<td>36±11</td>
<td>35±12</td>
<td>38±12</td>
<td>0.27</td>
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<tr>
<td>LVED volume, ml</td>
<td>114±35</td>
<td>109±34</td>
<td>123±37</td>
<td>0.015</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>69±6</td>
<td>68±5</td>
<td>69±6</td>
<td>0.42</td>
</tr>
<tr>
<td>E/Ea ratio</td>
<td>14±5</td>
<td>13±4</td>
<td>16±5</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Exercise LV function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVES volume, ml</td>
<td>31±16</td>
<td>33±20</td>
<td>31±11</td>
<td>0.59</td>
</tr>
<tr>
<td>LVED volume, ml</td>
<td>106±39</td>
<td>103±39</td>
<td>111±39</td>
<td>0.37</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>72±9</td>
<td>70±9</td>
<td>71±10</td>
<td>0.64</td>
</tr>
<tr>
<td>E/Ea ratio</td>
<td>14.5±5</td>
<td>14±5</td>
<td>15±5</td>
<td>0.38</td>
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<tr>
<td><strong>Resting LA volume, ml</strong></td>
<td>71±24</td>
<td>74±27</td>
<td>73±21</td>
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<tr>
<td><strong>Exercise LA volume, ml</strong></td>
<td>81±29</td>
<td>83±35</td>
<td>87±26</td>
<td>0.56</td>
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<tr>
<td><strong>Mitral regurgitation</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting ERO, mm²</td>
<td>43±20</td>
<td>43±23</td>
<td>42±16</td>
<td>0.83</td>
</tr>
<tr>
<td>Exercise ERO, mm²</td>
<td>48±26</td>
<td>42±27</td>
<td>55±23</td>
<td>0.03</td>
</tr>
<tr>
<td>Resting RV, mm</td>
<td>71±27</td>
<td>73±35</td>
<td>69±20</td>
<td>0.55</td>
</tr>
<tr>
<td>Exercise RV, ml</td>
<td>73±36</td>
<td>65±39</td>
<td>83±28</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Exercise-induced Changes in Degenerative MR

32% of patients increased significantly MR severity (RV>15ml, ERO>10mm$^2$) during exercise.
Exercise-induced changes in MR according to Exercise PHT

Regurgitant Volume

Changes in RV, ml

<table>
<thead>
<tr>
<th></th>
<th>No Ex-PHT</th>
<th>Ex-PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes, ml</td>
<td>-5±3.6</td>
<td>12.6±4</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
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</table>

Effective Regurgitant Orifice

Changes in ERO, mm²

<table>
<thead>
<tr>
<th></th>
<th>No Ex-PHT</th>
<th>Ex-PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes, mm²</td>
<td>-1±2</td>
<td>9±2.5</td>
</tr>
<tr>
<td>p</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>
Correlations between Exercise-Induced Changes in MR and in SPAP

- Stop for dyspnea

\[ r = 0.64, \quad p < 0.0001 \]

\[ r = 0.63, \quad p < 0.0001 \]
**Determinants of Exercise PHT**

**Impact of resting SPAP on Changes in SPAP**

- Increase in MR
- No change in MR
- Decrease in MR

**Multivariate analysis to determine Exercise PHT**

- Δ LVEF
- Δ LVEDV
- Age
- Ex. ERO
- Rest. SPAP

- OR=0.87, p=NS
- OR=0.93, p=NS
- OR=1.05, p=NS
- OR=1.1, p=0.02
- OR=1.15, p=0.01

Correlation:
- r=0.09, p=NS

**Changes in SPAP, mmHg**

- Resting SPAP, mmHg
- Odds-ratio (OR)
**Impact on Symptom-free Survival**

**Resting PHT** (SPAP ≥ 50mmHg)

- Symptom-free survival, %
  - 100
  - 80
  - 60
  - 40
  - 20
  - 0

Follow-up, months

- p=0.04
- Adjusted HR=2.1, p=NS

**Exercise PHT** (SPAP ≥ 60mmHg)

- Symptom-free survival, %
  - 100
  - 80
  - 60
  - 40
  - 20
  - 0

Follow-up, months

- 75±7%
- 35±8%

p<0.0001

Adjusted HR=3.4, p=0.002
Exercise PHT to Predict Onset of Symptoms

**ROC curves**

- **Sensitivity**
  - Exercise SPAP >56mmHg
  - Exercise SPAP >60mmHg
  - Resting SPAP >36mmHg
  - Resting SPAP >50mmHg

- **100-Specificity**
  - Exercise SPAP
  - Resting SPAP

- **Prediction of symptoms**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensi.</th>
<th>Specif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise SPAP &gt;56mmHg</td>
<td>82</td>
<td>73</td>
</tr>
<tr>
<td>Exercise SPAP &gt;60mmHg</td>
<td>71</td>
<td>78</td>
</tr>
<tr>
<td>Resting SPAP &gt;36mmHg</td>
<td>72</td>
<td>56</td>
</tr>
<tr>
<td>Resting SPAP &gt;50mmHg</td>
<td>25</td>
<td>95</td>
</tr>
</tbody>
</table>

- **AUC**: 0.67 vs. 0.77
- **p=0.032**
Conclusions

✓ Exercise PHT (SPAP ≥60 mmHg) is frequent in patients with asymptomatic degenerative MR.

✓ Exercise-induced changes in SPAP are unrelated to resting SPAP.

✓ Changes in MR severity during exercise are the main determinants of exercise-induced changes in systolic PAP and in exercise PHT.

✓ Exercise PHT is associated with reduced symptom-free survival and is more accurate than resting PHT to predict the occurrence of symptoms.
Thank you for your attention.
**Prediction of Exercise SPAP**

Predicted Ex. SPAP =

$$0.3 \times \text{Resting SPAP} + 0.1 \times \text{Age} + 0.07 \times \text{LVED vol} + 0.6 \times \text{E/Ea} + 0.08 \times \text{TP Sa} + 36$$

Exercises SPAP, mmHg (measured)

$r=0.91$

$p<0.0001$
Prediction of Exercise PHT

- LVED volume: AUC=0.83
- Resting SPAP: AUC=0.80
- E/Ea ratio: AUC=0.90
- Mean TP Sa: AUC=0.82
- Age: AUC=0.65

- Predicted Ex. SPAP AUC=0.97 (p<0.01)

Best cut-off:

- Predicted Ex. SPAP: 58 mmHg
- Sensitivity: 98%
- Specificity: 85%
Outcome

✓ Follow-up (FU) collection was complete in 78 patients (100%) with a mean FU = 22±13 months

✓ During FU: 38 (49%) patients developed symptoms, 4 (5%), atrial fibrillation

✓ Hospitalization: 5 patients for congestive heart failure
  1 patients for syncope
  1 patients for acute pulmonary edema

✓ Surgery: 25 (32%) patients underwent mitral valve surgery
  20 mitral valve repair vs. 5 mitral valve relacement

✓ No operative mortality and 5 long-term postoperative deaths, 20 patients with no cardiac event following surgery
Agreement between PISA and Doppler Methods at Rest

Larger ERO and RV with Doppler than with PISA method

$r=0.87; p<0.0001$
Agreement between PISA and Doppler Methods at Peak Exercise

Similar results during exercise than at rest

$r = 0.84; p < 0.0001$
Exercise-induced changes in MR

Regurgitant Volume, ml

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77±22</td>
<td>81±31</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Effective Regurgitant Orifice, mm²

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48±14</td>
<td>53±20</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Impact of Exercise-induced increase in MR on Symptom-free Survival

Follow-up, months

Symptom-free survival, %

Changes in RV<15ml

Changes in RV≥15ml

Unadjusted HR=1.8, 95% CI: 1.2-2.4

p=0.0015

53±12%

67±8%

81±6%

26±11%
Conclusion (1)

• As in functional MR, degenerative MR due to mitral valve prolapse can be dynamic.

• Degenerative MR may significantly increase (RV≥15ml, ERO≥10mm²) during exercise in > 30 % of patients.

• Changes in MR severity are associated with reduced symptom-free survival.

• How to manage asymptomatic patients with preserved LV function and significant exercise-induced changes in MR?
Exercise Pulmonary Hypertension

✓ Exercise pulmonary hypertension (PHT) may develop in patients with degenerative MR, even when resting systolic pulmonary arterial pressure (SPAP) is normal.

✓ Exercise PHT (≥60mmHg) is a criterion for surgical decision-making in patients with severe degenerative MR (Class IIa, ACC/AHA).

✓ There is very few studies to support this recommendation.

✓ What is the impact of exercise-induced changes in MR on systolic pulmonary arterial pressure?
**Impact of Exercise on SPAP**

**Exercise-induced changes in SPAP**

- **Resting SPAP**: 30 ± 11
- **Exercise SPAP**: 53 ± 17

Significance: p < 0.0001

**Prevalence of PHT**

- **Resting PHT**: 16%
- **Exercise PHT**: 48%

Significance: p = 0.0003