**Online supplement**

# Exercise hemodynamics in the prognosis of patients with pulmonary arterial hypertension

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***Methods***

**Patients**

We studied 49 patients referred to the Nancy University Hospital, Nancy, France between March 1, 2006 and December 15, 2012. Twenty-one patients with idiopathic, heritable or drug-induced PAH who were included in a previous published study (8) were excluded.

**Measurements**

**Exercise test during right heart catheterization**

All pulmonary hemodynamic measurements were performed in the supine position. A 7.5F Swan-Ganz catheter was advanced via the internal right jugular vein into the pulmonary artery. The mid-chest level served as the zero reference. Correct Swan-Ganz catheter position was confirmed by fluoroscopy and by the presence of characteristic pressure waveforms. Heart rate (HR) was determined from a continuous ECG monitoring lead. Cardiac output obtained by thermodilution, right atrial pressure (RAP), systolic pulmonary artery pressure (PAP), mean PAP, pulmonary artery wedge pressure (PAWP), and derived parameters were recorded at rest and during a constant-workload exercise for 8 to 10 minutes on a cycle ergometer in the supine position. All pulmonary artery pressures at rest and during exercise, including PAWP, were averaged over a period of 3 to 5 respiratory cycles corresponding to approximately of 10 cardiac cycles. Cardiac index was calculated as cardiac output divided by body surface area. Stroke volume was adjusted to body surface area. Measurements during exercise were performed in the stable state.

The constant workload used for exercise testing was 0 to 40 W, with 0 W corresponding to unloaded cycling. In each patient, the workload to be used was determined on the day before right heart catheterization, using the same cycle ergometer, according to the level of exertional dyspnea and the heart rate during the first minute of the exercise test to allow the patient to exercise in a stable state condition for at least 8 minutes. The workload was adjusted from 0 to 40 W with an electromagnetic brake, patients pedaling at 70 rpm. Just before starting exercise test the operator inflated the balloon of the Swan-Ganz catheter to examine the pressure curve of PAWP with appropriate respiratory contour then we deflated the balloon and asked the patient to start pedaling. PAWP was measured first at 3 minutes. Subsequently, PAP, RAP and cardiac output were measured. All measurements were performed within 5 minutes, which correspond to a total duration of exercise of approximately 8 minutes. The same workload was used during repeat right heart catheterization 3 to 5 months after initiating specific PAH therapy.

**Statistical analysis**

Survival rates were compared in subgroups of patients using the log-Rank test.

**Results**

**Exercise pulmonary hemodynamics at baseline**

The series was stratified into two subgroups, the first consisting of 20 patients with idiopathic (n=17) or heritable (n=3) PAH and the second consisting of 29 patients with PAH associated with the scleroderma spectrum (n= 10) or another disease. Age, sex ratio, NYHA class and 6MWD were similar between the 2 subgroups (data not shown). Conversely, mPAP at rest, exercise mPAP, exercise CI and exercise PVR were less altered in the subgroup of patients with the scleroderma spectrum or another disease.

Survival rates were statistically lower in the patients with a ΔHR lower than the median value (33 beats/min) compared to the remainders (Log Rank test, *p*=0.043). The same difference was observed for ΔsPAP (median value 27 mm Hg, Log Rank test, *p*=0.040).

**Changes of pulmonary hemodynamics under treatment**

Twelve patients did not undergo an exercise hemodynamic study at the follow up evaluation. These patients were significantly older and had a higher CI compared to the remainders at baseline. The comparison of other variables at baseline showed no significant difference.

PAH treatments at the time of the follow-up pulmonary hemodynamic studies (T1) were endothelin receptor antagonist (n=23), phosphodiesterase type 5 inhibitor (n=5), combination of endothelin receptor antagonist and phosphodiesterase type 5 inhibitor (n=8), combination endothelin receptor antagonist and prostacyclin analogue (n=1). No patient was acute responder to inhaled nitric oxide, therefore none was treated with a calcium channel blocker.

At T1, 3 patients and 14 patients had a decrease of 2 and 1 NYHA classes, respectively. Eighteen patients had an unchanged NYHA class and 2 patients worsened of 1 NYHA class. Six-minute walk distance improved significantly from 395 ± 102 meters to 418 ± 124 meters (*p*<0.001). The increase in 6MWD was significantly higher in 16 patients with idiopathic or heritable PAH compared to 21 remainders (+51.2 ± 22.2 meters versus +1.8 ± 24.7 meters, Mann-Whitney U test, *p*=0.05).

***Online supplement Figure 1***

Determination of changes in isoflow mean PAP at T1

In this example mean PAP and cardiac output at exercise were 64 mm Hg and 4.9 L/min, at T0, respectively. At T1 mean PAP at the same cardiac output was calculated at 49 mm Hg. Thus, the treatment-induced change in isoflow mean PAP was - 15 mm Hg. Pressure-flow slopes at T0 and at T1 in blue and in red, respectively.



***Online Supplement Figure 2***

Significant correlation between exercise stroke volume (SVI) and isoflow mean pulmonary artery pressure (mPAP) changes from T0 to T1 in the 37 patients who had an exercise hemodynamic study at the follow up evaluation.

r= -0.735, r2= 0.54, *p*< 0.001

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