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Conference Paper · May 2020

DOI: 10.1164/ajrcm-conference.2020.201.1_MeetingAbstracts.A2066

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Exercise Capacity in Patients with Pulmonary Arterial Hypertension: Multicentric Analysis of Aerobic Capacity and Survival

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Rationale: Reduced exercise capacity is common in pulmonary arterial hypertension (PAH) and has prognostic value. Whether or not patients with idiopathic or associated PAH present a similar pattern of exercise response has not been fully explored. The study aimed to 1) analyze the response to cardiopulmonary exercise test in patients with idiopathic and associated PAH, and 2) identify exercise predictors of survival in the different forms of PAH. **Methods:** We evaluated 181 patients: 102 with idiopathic/heritable (PAH-IH), 25 with connective tissue disease-associated PAH (PAH-CTD), and 54 with other types of associated PAH (PAH-Others) (associated with congenital heart disease: 23; associated with human immunodeficiency virus infection: 12; pulmonary veno-occlusive disease: 10; associated with portal hypertension: 9), from two national reference centers, who had performed a cardiopulmonary exercise test (CPET). We described anthropometric measures, functional class, pulmonary function tests, biomarkers, and hemodynamic measurements, and we compared CPET variables among groups. We also identified the predictors of survival by the construction of the receiver operating characteristic (ROC) curves and the analysis of the area under the curve (AUC). **Results:** Patients with PAH-CTD had worse peak oxygen uptake (VO_2 peak) and lower maximum workload than PAH-IH (table 1). The cumulative survival of all patients was 97%, at 1 yr, 90% at 3 yr, and 86% at 5 yr. The 5-year mortality by group was: 10% in PAH-IH, 27% in PAH-CTD, and 27% in PAH-others. The CPET predictors for survival were >13.9 ml/min/Kg for VO_2 peak, <39.75 in ventilatory equivalent (VE/VCO_2), and >6.96 ml/beat for oxygen pulse (O_2 pulse). Additionally, the diffusion capacity of CO (DLCO) $<52.6\%$ was a survival predictor factor. **Conclusion:** Patients with PAH-CTD showed lower exercise tolerance compared to PAH-IH. Mortality was higher in patients with PAH-CTD and PAH-others. VO_2 peak, VE/VCO_2 , O_2 pulse and DLCO were predictors of survival.

Table 1. Description of groups

	Overall	PAH-IH	PAH-CTD	PAH-Others	p
	n = 181	n = 102	n = 25	n = 54	
Age (years)	41.6 ± 13.0	41.4 ± 12.2	46.3 ± 15.5	40.0 ± 13.1	0.264
Sex (M/F)	60/121	29/73	5/20	26/28	
NYHA (I/II/III/IV)	38/94/47/2	23/53/26/0	5/10/9/1	10/31/12/1	
Weight	67.7 ± 13.6	69.8 ± 13.6	66.7 ± 13.6	63.9 ± 12.5	<0.001*
Height	164 ± 13	164 ± 9	163 ± 9	168 ± 10	0.019*
Body mass index	24.8 ± 5.0	26.5 ± 5.2	24.7 ± 3.7	22.5 ± 4.4	0.002*
<i>Pulmonary Function</i>					
FVC	89.8 ± 15.8	90.5 ± 14.2	86.8 ± 15.3	90.1 ± 18.6	0.597
FEV ₁	85.9 ± 16.2	88.2 ± 15.4	84.8 ± 14.8	82.4 ± 17.7	0.250
FEV ₁ /FVC	77.8 ± 10.4	78.6 ± 7.7	81.1 ± 17.3	74.7 ± 9.9	0.142
TLC	93.9 ± 13.7	93.0 ± 14.1	89.5 ± 12.9	96.6 ± 14.4	0.036*
DL _{CO}	65.6 ± 19.7	71.5 ± 17.9	58.4 ± 18.4	54.7 ± 18.8	<0.001*
<i>Hemodynamics</i>					
Cardiac Index	2.8 ± 0.7	2.7 ± 0.7	2.9 ± 0.8	2.9 ± 0.8	0.058
mPAP	50.1 ± 16.2	52.6 ± 15.1	40.6 ± 11.2	49.9 ± 18.1	<0.001*
PCP	9.4 ± 3.5	9.1 ± 3.6	9.8 ± 3.0	9.6 ± 3.6	0.783
PVR	9.2 ± 5.3	10.0 ± 5.2	7.1 ± 4.9	8.9 ± 5.4	<0.001*
PAD	7.0 ± 4.3	7.5 ± 4.4	5.9 ± 3.3	6.9 ± 4.3	0.347
<i>Biomarkers</i>					
BNP	83.1 ± 97.3	82.9 ± 96.0	144 ± 210	65.3 ± 53.0	0.785
NTpro-BNP	954 ± 1473	873 ± 1237	1084 ± 2396	977 ± 1267	0.640
<i>Exercise Capacity</i>					
6MWD	481 ± 97	492 ± 92	443 ± 99	480 ± 101	0.034*
SpO ₂ basal	95.4 ± 3.1	96.1 ± 2.7	93.5 ± 3.5	95.1 ± 3.2	0.004*
SpO ₂ at the end	90.8 ± 7.2	92.1 ± 6.5	90.7 ± 7.2	88.7 ± 8.0	0.128
<i>CPET</i>					
Wmax	72.8 ± 30.7	73.6 ± 33.1	58.6 ± 19.3	76.8 ± 28.7	0.195
VO _{2peak} (ml/Kg/min)	15.7 ± 5.0	15.8 ± 5.3	13.5 ± 4.0	16.4 ± 4.6	0.006*
HRmax	146 ± 22	145 ± 21	142 ± 20	148 ± 26	0.052
O ₂ pulse	7.5 ± 2.4	7.8 ± 2.4	6.2 ± 1.8	7.6 ± 2.5	0.044*
VE/VCO ₂ slope	38.2 ± 9.4	37.6 ± 9.4	38.5 ± 11.6	39.1 ± 8.4	0.206

Abbreviations: FVC: Forced vital capacity; FEV₁: Forced expiratory volume at the first second; TLC: Total lung capacity; DL_{CO}: Diffusion capacity of the lungs for carbon monoxide; mPAP: mean pulmonary arterial pressure; PCP: Pulmonary capillary pressure; PAD: pulmonary artery diameter; PVR: pulmonary vascular resistance; BNP: B-natriuretic peptide; NT-proBNP: Biologically inactive fragment of BNP; 6MWD: Six-minute walk distance; SpO₂: Oxygen saturation; VO_{2peak}: peak oxygen consumption; Wmax: Maximum workload; HR: Heart rate; O₂pulse: Pulse of Oxygen; VE/VCO₂: Ventilatory equivalent. The test used for this analysis was ANOVA.

This abstract is funded by: The study was supported by grants from the Fondo de Investigaci3n Sanitaria, Instituto de Salud Carlos III (PI17/1515), Fondo Europeo de Desarrollo Regional (FEDER), Uni3n Europea "Una manera de hacer Europa". Sociedad Espaola de Neumologaa y Cirugaa Torcica (SEPAR) and Societat Catalana de Pneumologia (SOCAP)

Am J Respir Crit Care Med 2020;201:A2066

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