Diastolic dysfunction in patients with lymphangioleiomyomatosis: the role of exercise stress echocardiography.

Andrea Sonaglioni[1], Massimo Baravelli[1], Roberto Cassandro[2],

Olga Torre[2], Davide Elia[2], Claudio Anzà[1], Sergio Harari[2].

[1]Unità operativa di Cardiologia, Ospedale San Giuseppe Multimedica IRCCS, Milan, Italy.

[2]Unità operativa di Pneumologia e Terapia semi-intensiva Respiratoria - Servizio di Fisiopatologia Respiratoria e emodinamica polmonare, Ospedale San Giuseppe Multimedica IRCCS, Milan, Italy.

The pathogenesis of pulmonary hypertension (PH) in patients with lymphangioleiomyomatosis (LAM)

- Previous studies[1,2] demonstrated that hypoxic pulmonary vascular vasoconstriction and a reduction in pulmonary vascular capacitance caused by the cystic lung lesions are involved in causing PH during exercise in patients with LAM.

- However, the pathogenesis of PH in LAM has not been fully clarified.

- The last Guidelines for the diagnosis and treatment of PH (2015 ESC/ERS Guidelines) classify LAM-PH in the group 5 (PH with unclear and/or multifactorial mechanisms).

[1]**Taveira-DaSilva AM et al**. Chest 2007;132:1573–1578.

[2]**Cottin V et al.** Eur Respir J 2012;40:630–640.

OUR STUDY PROTOCOL

- A single-center case-control observational study.

- **Aim of this study** was a non-invasive evaluation of the main pulmonary and cardiac hemodynamic parameters, assessed by Exercise Stress Echocardiography (ESE), in LAM patients compared to those of a matched healthy control group.

- Fifteen consecutive LAM patients (mean age 48.2 ± 14.3 years) without resting echocardiographic signs of pulmonary hypertension were enrolled into the study protocol and compared to 10 consecutive healthy controls (mean age 43.5 ± 9.1 years, p = 0.39).

METHODS

A complete echocardiographic study with tissue Doppler imaging (TDI) was performed at baseline and during semi-supine symptom-limited exercise test to evaluate:

- the occurrence of symptoms and/or ECG changes;
- the left ventricular (LV) systolic and diastolic function;
- the right ventricular (RV) contractile function;
- the pulmonary capillary wedge pressure (PCWP);
- the systolic (SPAP) and mean (MPAP) pulmonary artery pressure and;
- finally the pulmonary vascular resistance (PVR).

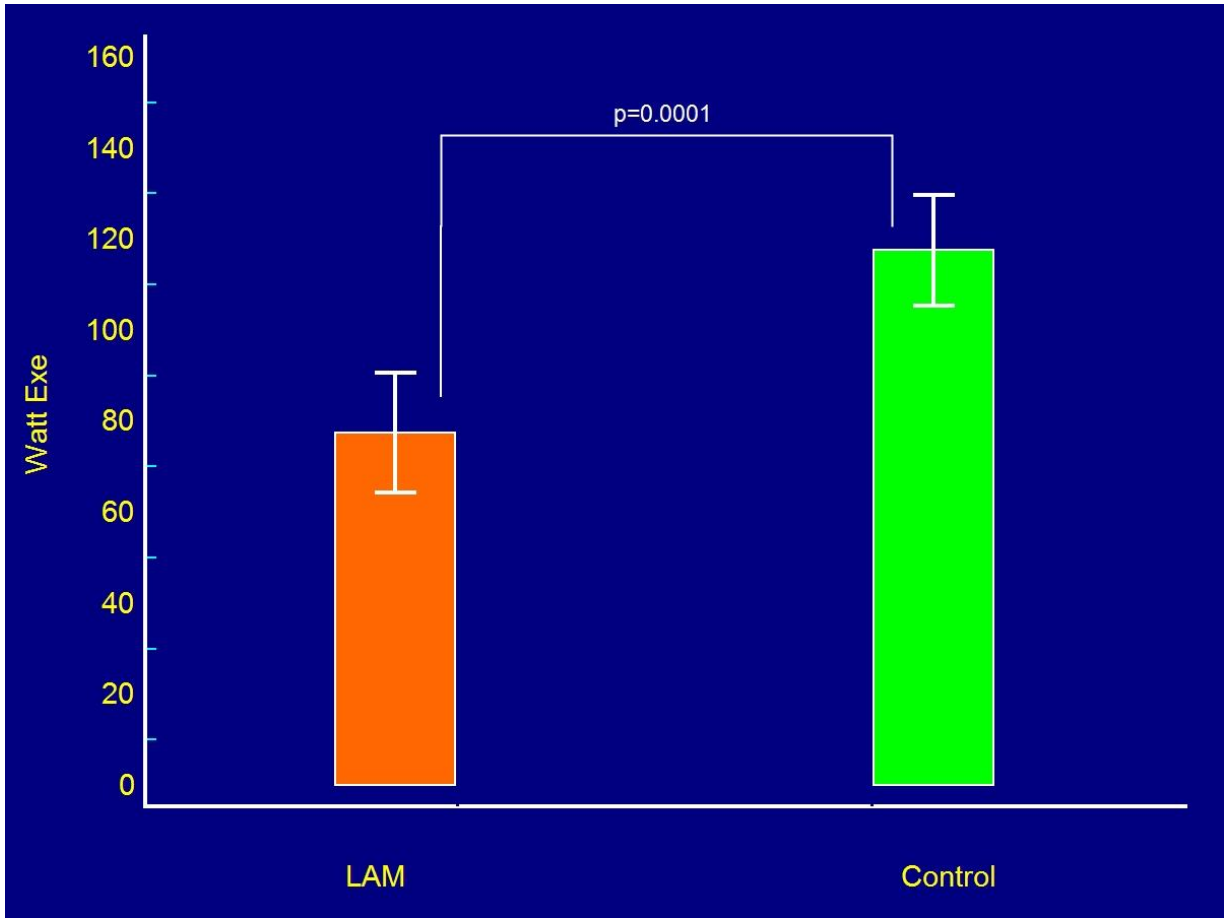
M-mode, 2D and Doppler echocardiographic parameters assessed by ESE in LAM patients and in healthy controls

M-mode and 2D parameters[11]	LV systolic function	LV diastolic function	RV systolic function	Pulmonary hemodynamics
LVEDDi, LVESDi, IVS, PWT by 2D-guided M-mode	LVEF (%), by the modified biplane Simpson's method[11]	E/A ratio by transmitral PW-Doppler technique	TAPSE (mm), by M-mode[12]	SPAP (mmHg) = 4 x TRV^2 + RAP[16]
RWT = (2 x PWT)/LVEDD	SV (ml)= VTIlvot x CSAlvot[14]	E/average e' ratio by PW-TDI[13]	Tricuspid S'-wave velocity by TDI (cm/sec)	RAP (mmHg) = IVC size and collapsibility
LVEDVi, LVESVi by the modified biplane Simpson's method	CO (l/min/m^2 BSA)= SV x HR[15]	PCWP (mmHg) = 1.9 + 1.24 x E/average e'[13]	Tei Index = (IVRT + IVCT)/ET[12]	MPAP (mmHg) = 79 – 0.45 x ATrvot[17]
LAVi by the monoplane Simpson's method				PVR (WU) = TRV x 10/TVIrvot + 0.16[18]
RVIT by Echo 2D using the 4-chamber view				

LUNG DATA FUNCTION OF LAM PATIENTS

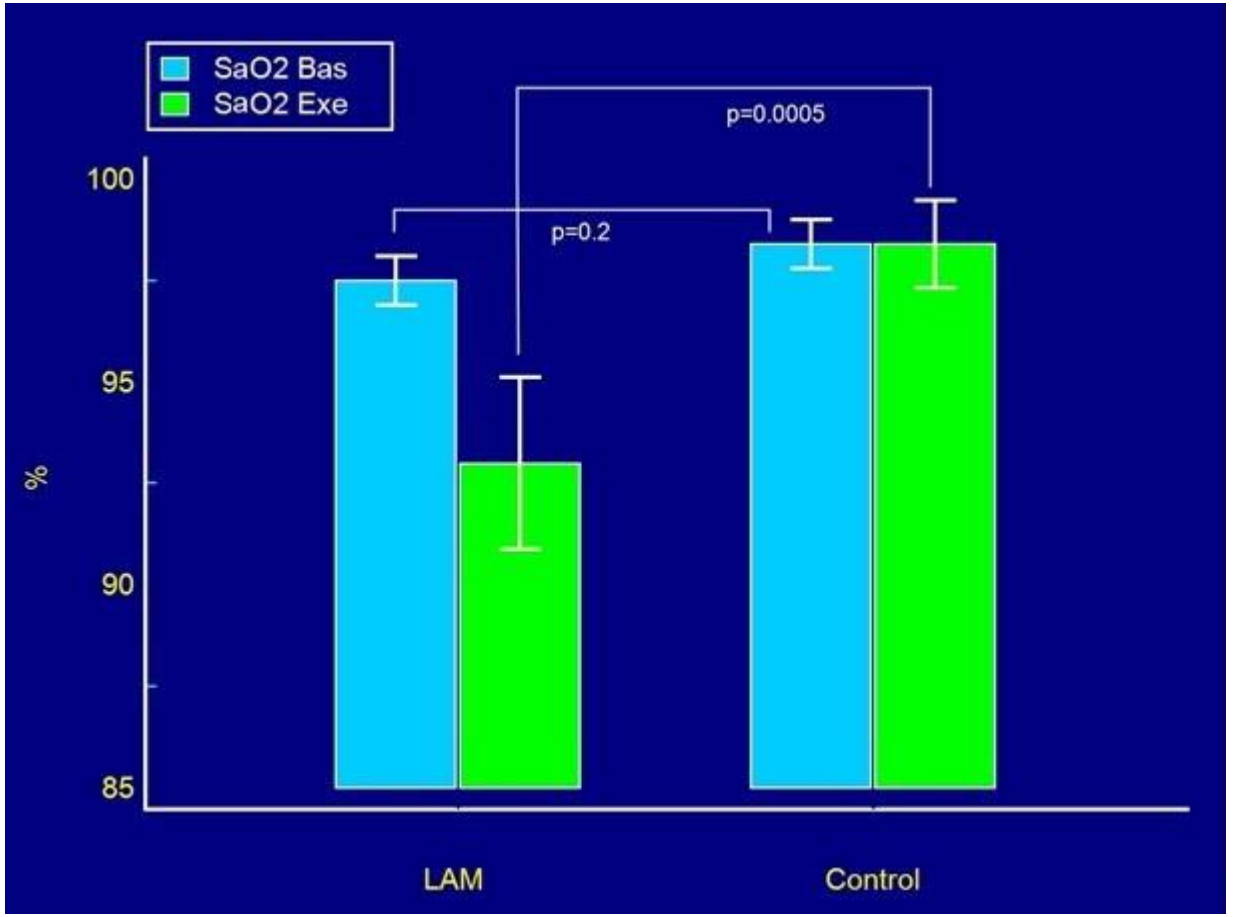
SPIROMETRIC PARAMETERS										
FVC (l)	FVC %	FEV1 (l)	FEV1 %	TLC (l)	RV (l)	IC/TLC	DLCO (ml/min/mmHg)	DLCO%	6MWT (m)	DeltaSaO2 (%)
3,27 ± 0,48	104,66 ± 19,17	2,24 ± 0,73	81,8 ± 25,7	5,82 ± 1,21	2,41 ± 1,34	0,60 ± 0,12	12,84 ± 3,88	51,06 ± 15,48	538,33 ± 89,57	-4,2 ± 3,56

WORKLOAD REACHED, WATT



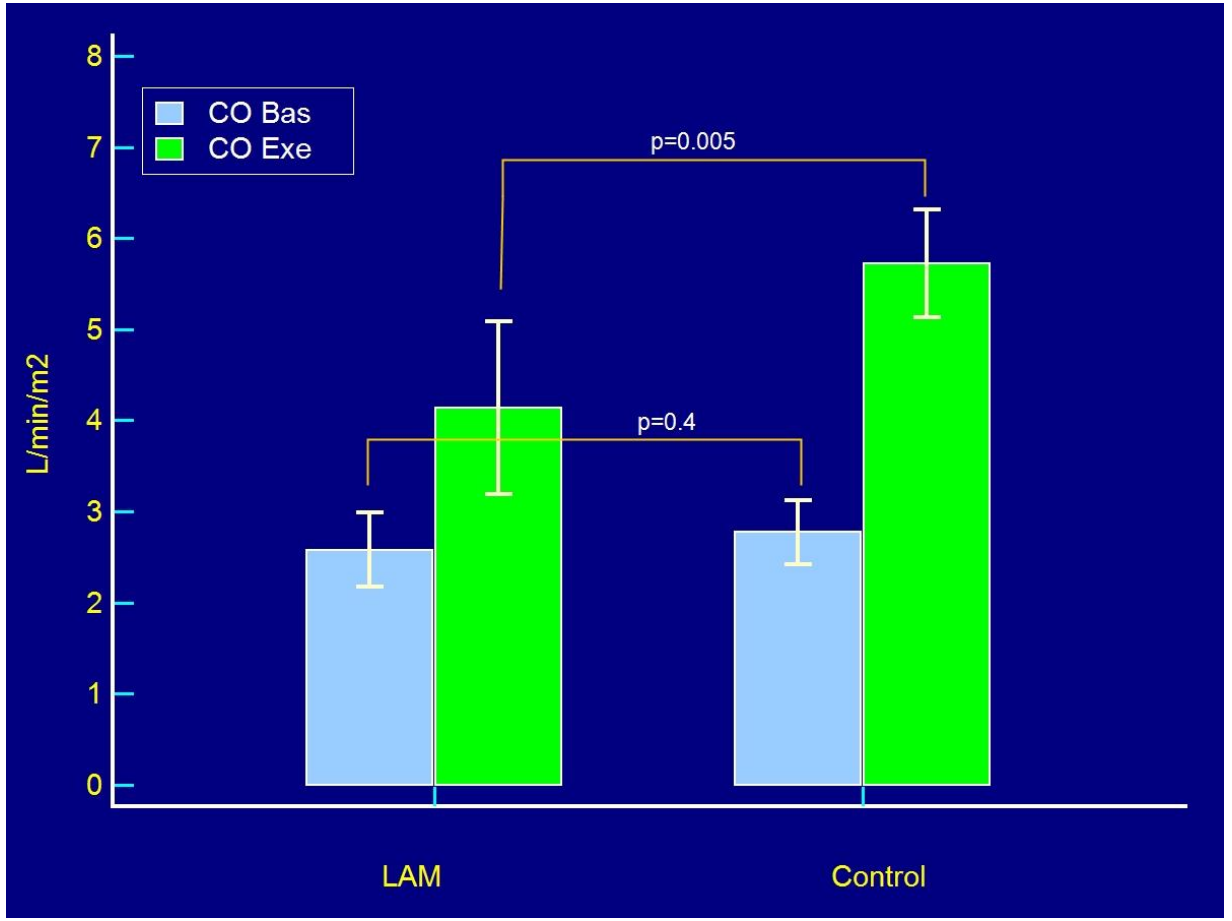
Compared to healthy controls, LAM patients exhibited a reduced effort tolerance

Oxygen saturation (SaO2), %



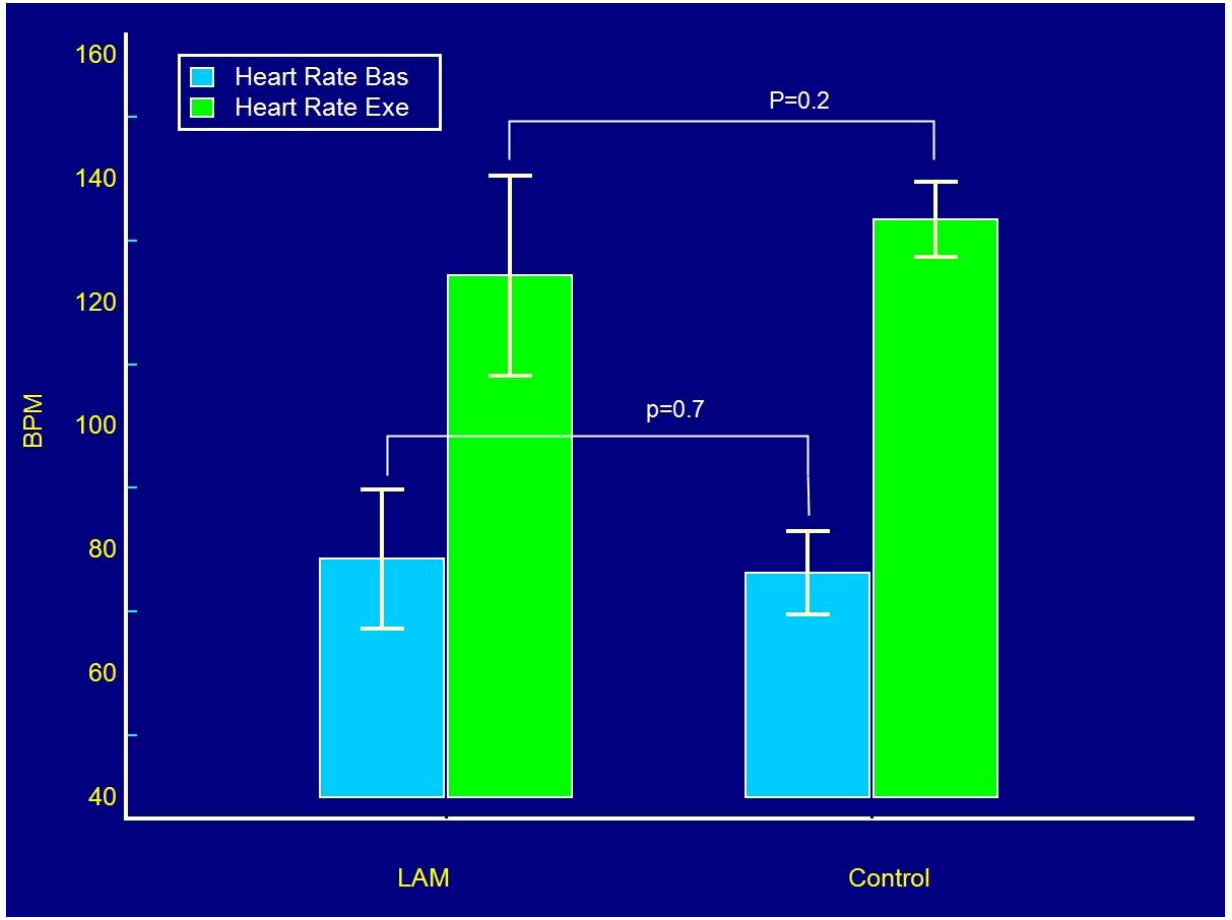
LAM patients showed a rapid decline in SaO2 (%) at peak exercise >3%

Cardiac Output (CO), l/min/m2



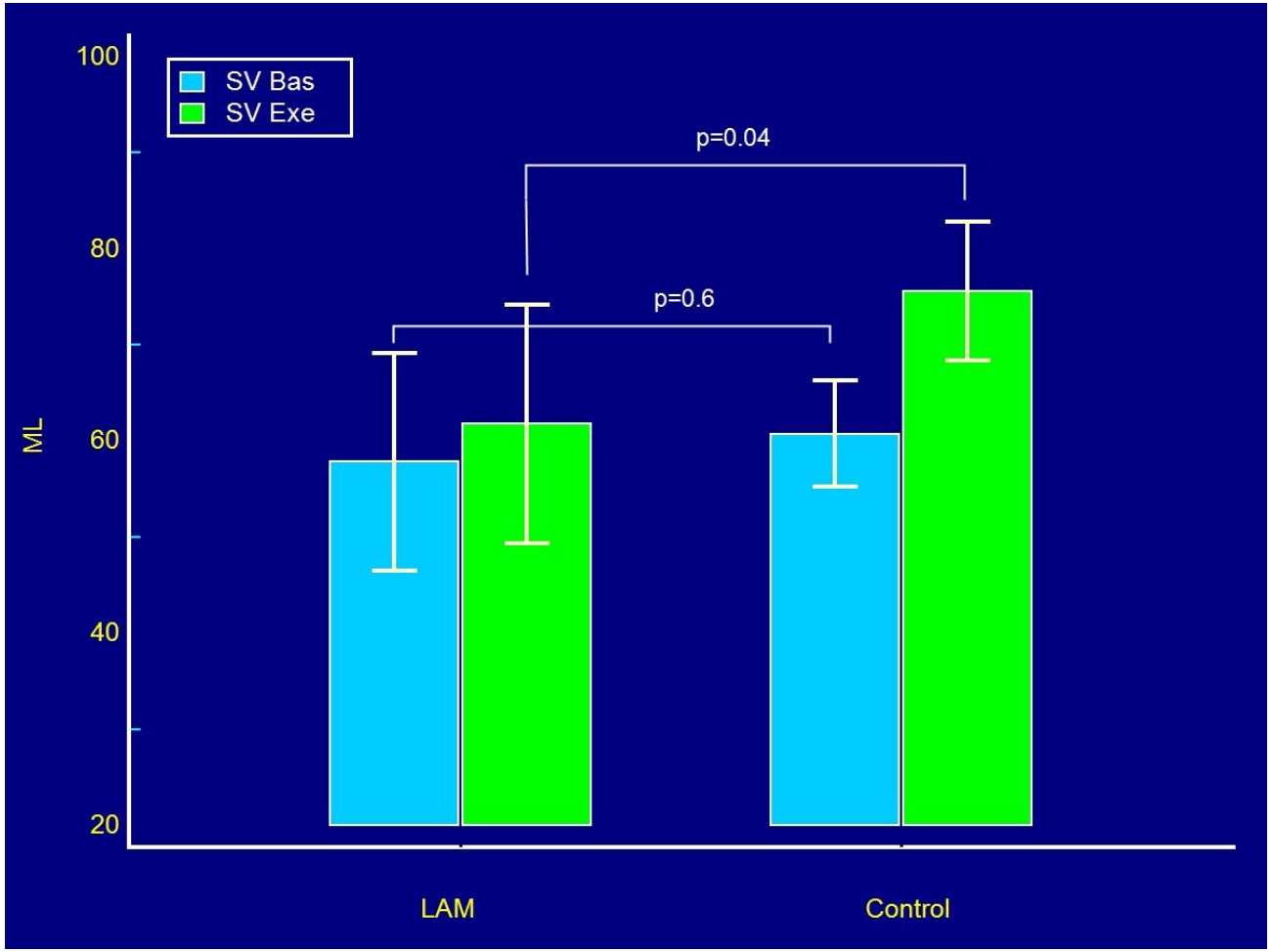
LAM patients showed a lower cardiac output (CO) reserve

Heart rate, bpm



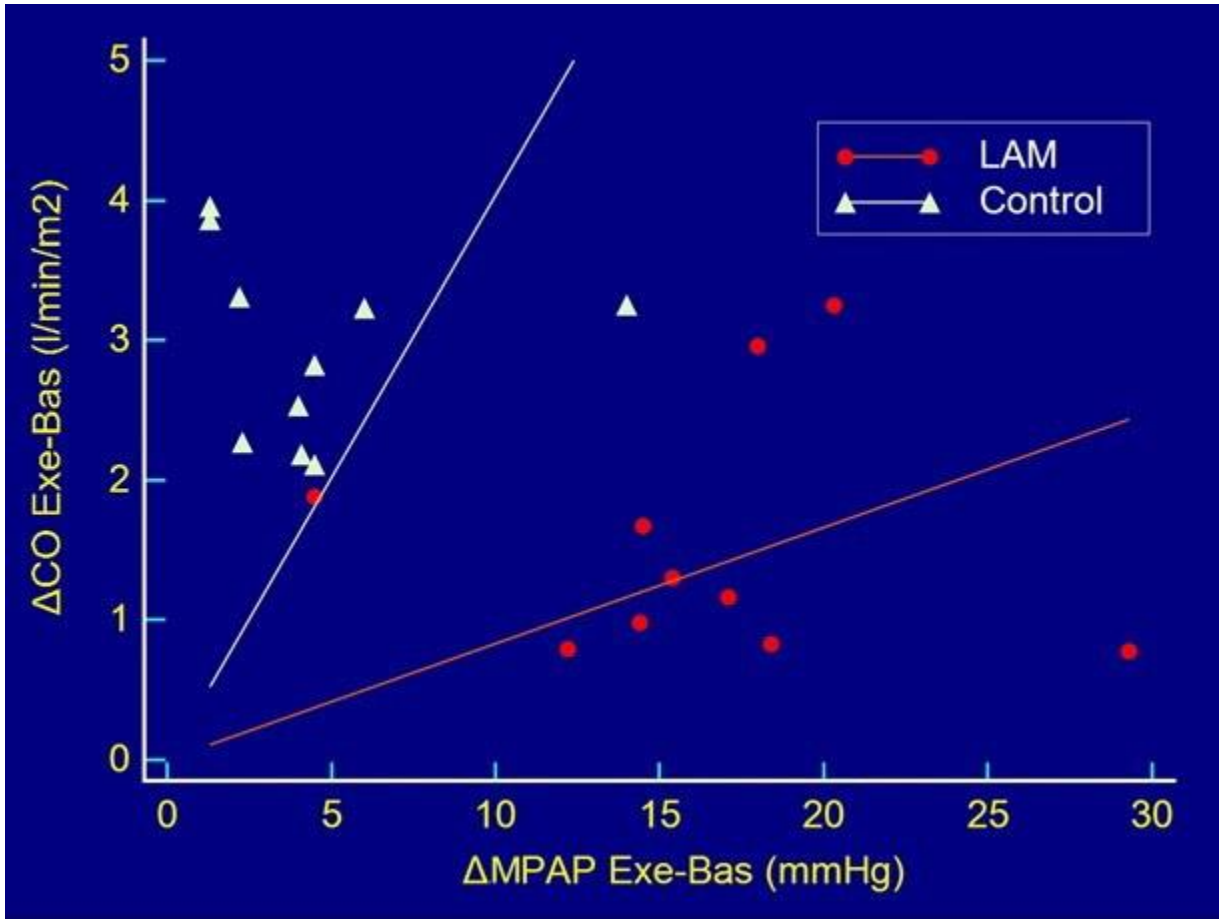
The chronotropic response to exercise was adequate in both groups of patients

Stroke Volume (SV), ml



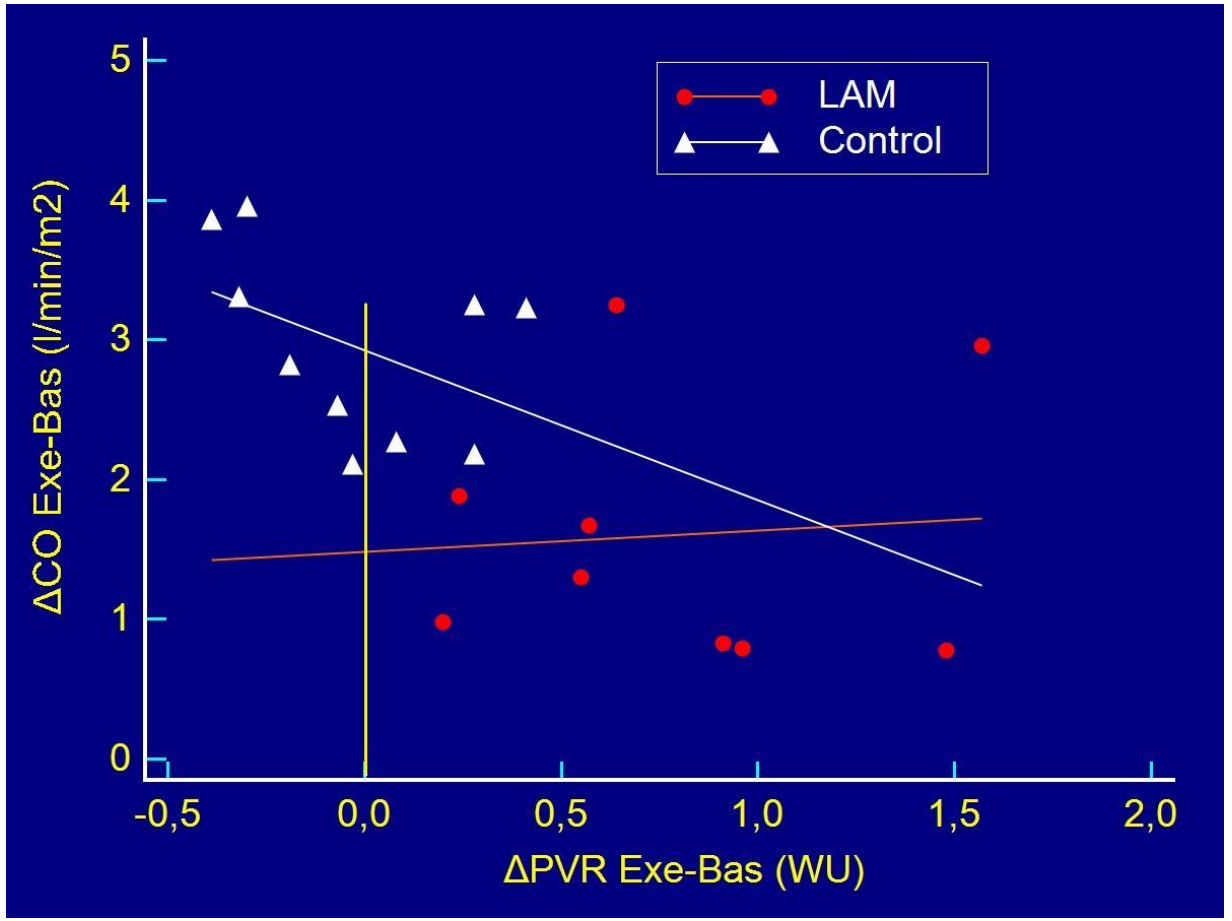
The LV stroke volume reserve was lower in LAM patients

ΔCO (Exe-Bas) VS ΔMPAP (Exe-Bas)



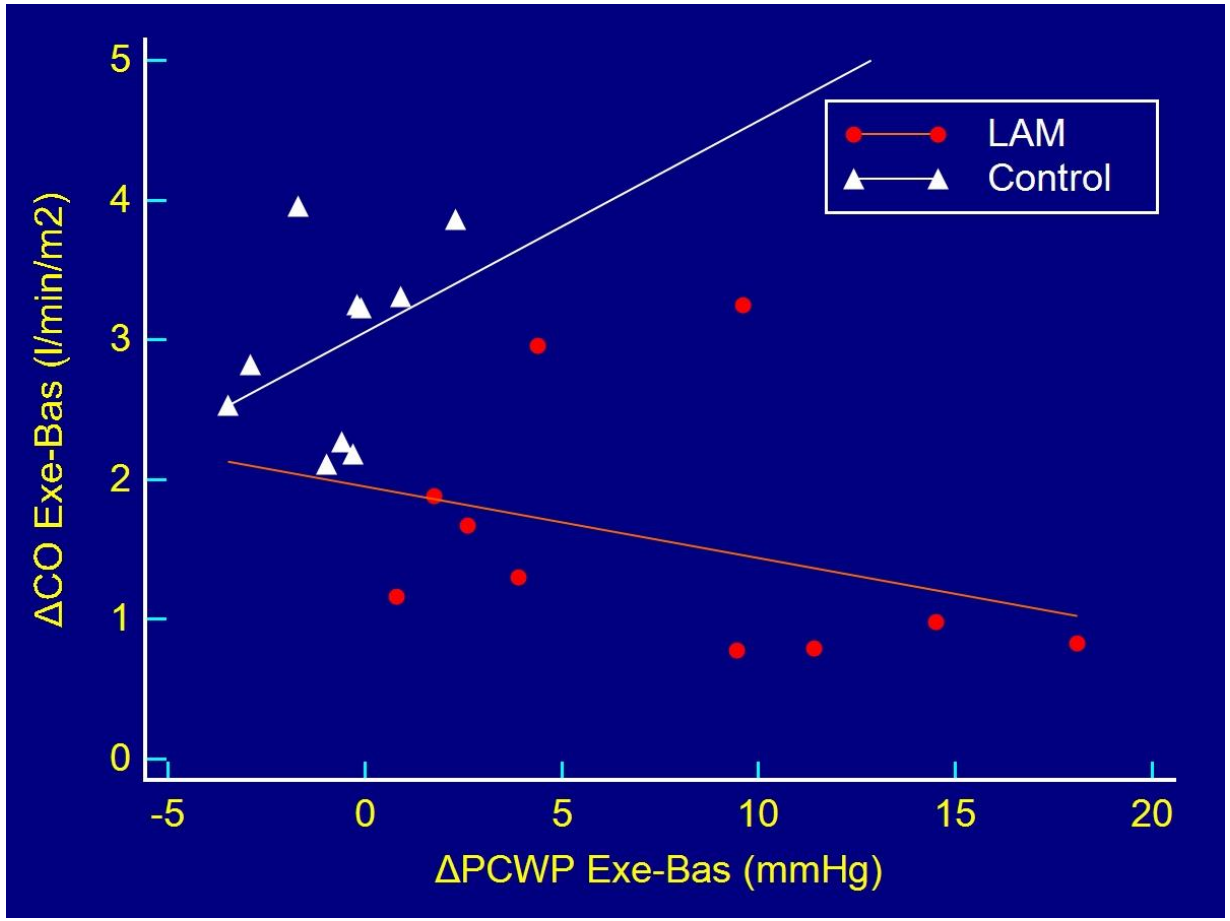
Compared to healthy controls, LAM patients exhibited a lower cardiac output (CO) reserve, secondary to a lower LV stroke volume reserve (the chronotropic response to exercise was adequate), and showed a significant exercise-induced increase in MPAP.

ΔCO (Exe-Bas) VS ΔPVR (Exe-Bas)



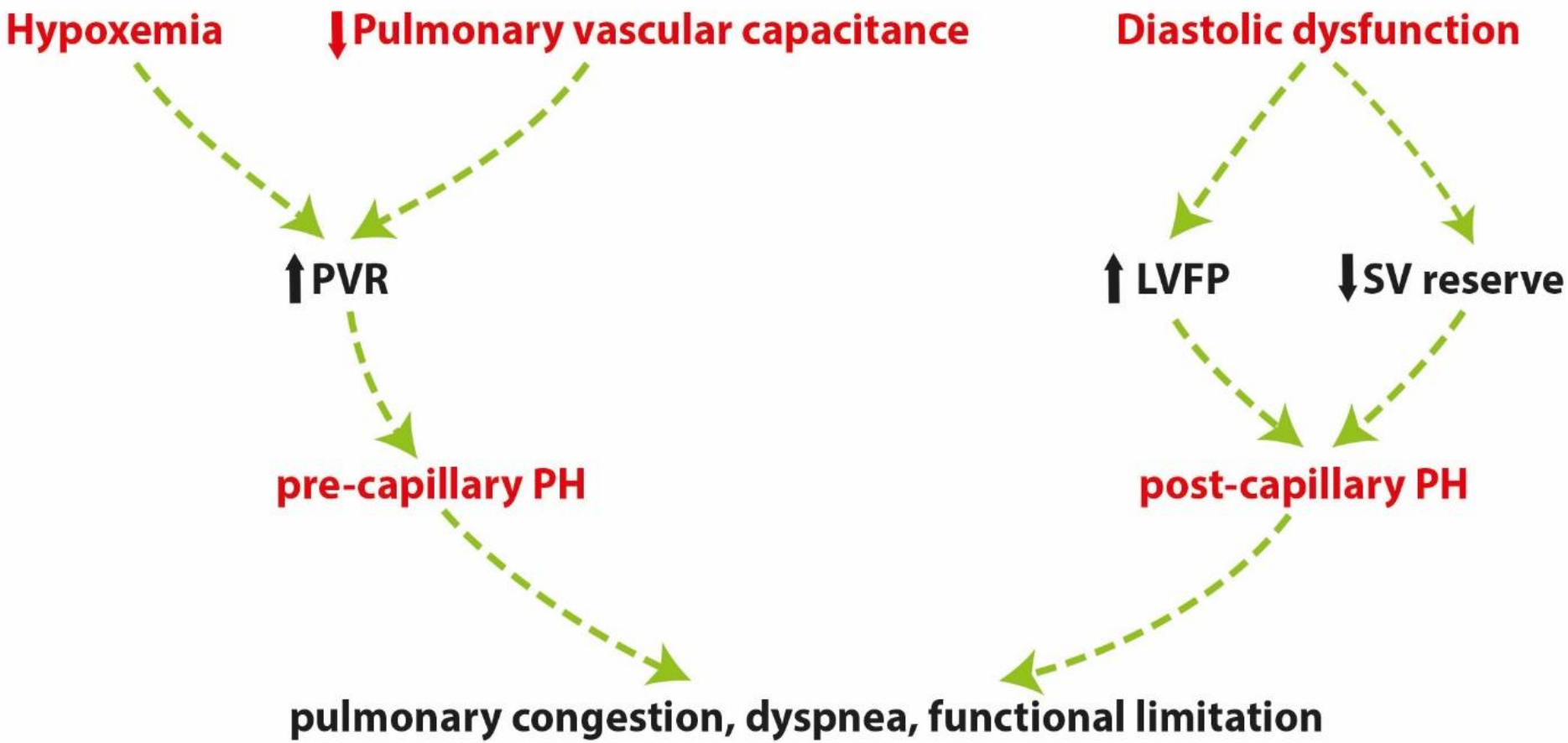
One of the two major pathophysiological components underlying the increase in MPAP in LAM patients was a significant exercise-induced increase in PVR (pre-capillary component).

ΔCO (Exe-Bas) VS ΔPCWP (Exe-Bas)



The second major pathophysiological component underlying the increase in MPAP in LAM patients was a significant exercise-induced increase in PCWP (post-capillary component).

PATHOGENETIC MECHANISMS



What are the possible pathophysiological mechanisms underlying this LV diastolic dysfunction?

- An exercise-induced acute RV pressure overload, secondary to a significant increase in the systolic and mean PAP, and consequently an acute RV dilatation and a leftward shift of the interventricular septum, with a decrease in LV volume and LV compliance.

- The presence of a pulmonary constraint on the heart: an exercise-induced increase in lung stiffness and/or dynamic hyperinflation could interfere with either RV and LV preload as well as the external work of the heart and may cause a mechanical extrinsic compression of the heart .

CONCLUSIONS

- Exercise-induced PH in LAM patients could be related not only to a hypoxic pulmonary vascular vasoconstriction during exercise (**pre-capillary PH**), but also to a significant exercise-induced increase in LV filling pressures, probably secondary to a diastolic dysfunction (**post-capillary PH**).

- Assessment of pulmonary and cardiac haemodynamics using ESE provides incremental and more detailed pathophysiological information than that obtained by resting echocardiography in such patients.

- It's important to remark the ability of ESE to physiologically unmask latent pulmonary hypertensive tendencies, that may antedate progression to resting PH.


THANK
YOU!