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# *S.C.D.U. Clinica Cardiologica*

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*Incidence, clinical features, hemodynamic and outcomes of residual pre-capillary pulmonary hypertension after surgical correction of mitral valve diseases: prognostic value of rest and exercise echocardiographic assessment, compared with clinical and biochemical markers and conventional and novel invasive hemodynamic parameters.*

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# STUDY

## ***Background***

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterization (RHC). PH can be found in multiple clinical conditions. Different pathobiological features characterize the diverse clinical PH Group. According to various combinations of values of pulmonary wedge pressure (PWP), pulmonary vascular resistance (PVR), and cardiac output (CO), different haemodynamic definitions of PH are considered: pre-capillary PH includes the clinical groups with mean PAP ≥ 25 mm Hg, PWP ≤ 15 mmHg and CO normal or reduced, post-capillary PH includes the clinical group with PAP ≥ 25 mm Hg, PWP ≥ 15 mmHg and CO normal or reduced.

PH carries a poor prognosis for patients with chronic heart failure. In the literature the mortality rate after 28 months of follow-up was 57% in patients with moderate PH compared with 17% in patients without PH. In left-sided valvular diseases, the prevalence of PH increases with the severity of the defect and of the chronic heart failure symptoms. Mitral valve disease is a common cause of post-capillary pulmonary hypertension and PH can be found in virtually all patients with severe symptomatic mitral valve disease. However, there is no consensus about the outcome of patients with PAH after mitralic valve replacement in the literature. The mechanisms responsible for the increase in PAP are multiple and include the passive backward transmission of the pressure elevation; in these cases the transpulmonary pressure gradient (TPG = mean PAP minus mean PWP) and PVR are within the normal range. In other circumstances the elevation of PAP is greater than that

of PWP (increased TPG) and an increase in PVR is also observed (post-capillary reactive or 'out of proportion' PH); the elevation of PVR is due to an increase in the vasomotor tone of the pulmonary arteries and/or to fixed structural obstructive remodelling of the pulmonary artery resistance vessels: the former component of reactive PH is reversible under acute pharmacological testing while the latter, characterized by medial hypertrophy and intimal proliferation of the pulmonary arteriole, does not respond to the acute challenge. Which factors lead to reactive (out of proportion) PH and why some patients develop the acutely reversible vasoconstrictive or the fixed obstructive components or both is poorly understood. Pathophysiological mechanisms may include vasoconstrictive reflexes arising from stretch receptors localized in the left atrium and pulmonary veins, and endothelial dysfunction of pulmonary arteries that may favour vasoconstriction and proliferation of vessel wall cells.

## ***Aim of the study***

To **a**ssess the incidence of residual "reactive" pre-capillary pulmonary hypertension after surgical correction of mitral valve disease (valvuloplasty or valve replacement) and the hemodynamic chenges after elective mitral valve surgery in patients with severe and mild pulmonary arterial hypertension. To assess, also, clinical, functional and hemodynamics characteristics and prognostic significance of the "prosthetic valve-patient mismatch" (PPM).

## ***Methods***

In this prospective observational study all consecutive patients undergoing elective mitral valve surgery in "Maggiore della Carità" Hospital Novara are enrolled the study and undergo echocardiographic evaluation of pulmonary artery pressure before surgery. With continous-wave Doppler, the maximum peak tricuspid regurgitant velocity (TRV) recorded from any view is used to determine the PASP with the simplified Bernoulli's equation [PASP = 4*(peak TRV)2 + mean right atrial pressure]; mean right atrial pressure (RAP) is estimate from the respiratory changes of the inferior vena cava diameter with inspiration as follow: complete collapse RAP=5 mm Hg, partial collapse RAP=10 mmHg, and no collapse RAP=15 mmHg. Pulmonary artery systolic pressure was assumed to equate the right ventricular systolic pressure in the absence of pulmonic stenosis and right ventricular outflow tract obstruction.

In keeping with current guidelines, PH was defined using the pre-specified cut-off of PASP ≥ 50 mmHg at rest. In the present study, the term PH refers to an increased PASP associated with left heart diseases (Group 2 clinical classification of PH).

Traditional index transthoracic echocardiograms are also performed using standard methods: left and right atrial volume, left and right ventricular volume and function.

Patients with PASP ≥ 50 mmHg are addressed to the preoperative right heart catheterization, in order to confirm pulmonary hypertension (PAMP ≥ 25 mmHg) and to evaluate the hemodynamic profile by measuring mean pulmonary artery, pulmonary wedge pressure, pulmonary vascular resistence and cardiac index. These patients are studied six months after mitral valve surgery with clinical and echocardiographic follow-up. The right heart catheterization will be performed in patients with echocardiographic PASP ≥ 50 mmHg, and indirect signs of pulmonary hypertension, in order to select "reactive" pre-capillary pulmonary

hypertension. In patients with PAMP < 50mmHg will be performed stress echo, to increase diagnostic sensitivity. It will be also evaluated the relationship between body surface area and prosthesis size, as predictor factor of persistent post-operative pulmonary hypertension.

## ***End points***

Primary end point: analysis and prevalence of residual pre-capillary pulmonary hypertension 6 months after mitral valve surgery.

Secondary end point: evaluation of the "valve prosthesis-patient mismatch" (PPM) in patients with residual post-capillary pulmonary hypertension.

## ***References***

1. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: A Multicenter Long-term International Study. Andrea Barbieri, et all. European Heart Journal (2011) 32, 751–759.
2. Guidelines for the diagnosis and treatment of pulmonary hypertension The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). European Heart Journal (2009) 30, 2493–2537.
3. Early hemodymamic changes after mitral valve replacememt in patients with severe and mild pulmonary artery hypertension. Fatemeh Bayat, et all. Ann. Thorac Cardiovasc Surf. October 15,

2012.

4. Pulmonary artery hypertension in mitral stenosis: role of right ventricular stroke volume, atrio-ventricular compliance, and pulmonary venous complicance. Letter to Editor. Praveen Kumar Neema, Ramesh Chandra Rathod. Journal of Anesthesiology Clinical Pharmacology. Aprile-June 2012,Vol 28,Issue 2.
5. Evaluation of pulmonary hypertension and surgical outcome by dynamic pulmonary perfusion imaging in patients with valvular disease. Wang X, et all. Clin. Nucl. Med 2011. May; 36(5):337-40.
6. Echocardiographic indexes for the non-invasive evaluation of pulmonary hemodynamics. Alberto Milan, et all. Journ of the Am Sic of Echocardiography. March 2010.

## CONGRESS

1. International Meeting on Adult with Congenital Heart Disease" – S. Donato Milanese, March 2014.
2. Scientific Symposium "A New Horizon in Pulmonary Management" – Lisbon, April 2014.
3. "L'insufficienza mitralica funzionale e le nuove indicazioni al trattamento" – Novara, June 2014
4. ESC CONGRESS 2014 – Barcellona, August/September 2014.

## POSTER PRESENTATION

1. **Additional value of right atrial in pulmonary hypertension diagnosis: correlation with clinical and invasive parameters and prognostic implication.**
   **L. Ferrarotti**, E. Maggi, C. Piccinino, D. Sola, F. Pastore, PN. Marino - Euro Echo Imaging 2014 (Vienna, 6/12/2014).

## SCIENTIFIC PUBLICATION

1. **Prevalence of undiagnosed chronic thromboembolic pulmonary hypertension after pulmonary embolism.**

Livio Giuliani, C. Piccinino, A. D'Armini, S. Manganiello, **L. Ferrarotti**, P.E. Balbo, A. Lupi, P.N. Marino – Blood coagulation and fibrinolysis. 2014 Oct;25(7):649-53.

# ***SEMINARS***

## Prof. Follenzi

1. July 15

   Gene therapy application

## The Borghese Sessions

**2.** September 8

Skin as an organ

Layers of skin, cell types, developmental origine

**3.** September 9

Cell-Cell Interactions – anchoring junctions

Cell-Cell Interactions – occluding junctions, tight junctions

**4.** September 10

Cell Matrix Interactions – basal lamina

Epithelial-mesenchymal transizione

**5.** September 11

Angiogenesis

Innervation

**6.** September 15

Basal layer stem cells, symmetric versus asymmetric divisions, transient amplifying cells

Solar radiation, nucleotide excision repair

**7.** September 16

Basal and squamous cell carcinomas

Melanoma – biology

8. September 17

   Melanoma - treatment

   Contact dermatiti

9. September 22

   Other skin disorders

   Other components of skin