Dottorato in Scienze e Biotecnologie Mediche

Relazione attività scientifica

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Diagnostic accuracy of right atrial strain for the early detection of hemodynamic deterioration in patients with Pulmonary Hypertension.

INTRODUCTION

Right atrial (RA) enlargement and elevated mean RA pressure (mRAP) measured by catheterization are proved to be independent risk factors for mortality in patients with pulmonary arterial hypertension (PAH) (1-2). Furthermore, RA dilatation has been correlated with 6-minute walking test (6MWT) and New York Heart Association (NYHA) functional class (3). However, models for diagnosis of PH patients proposed so far, based on traditional Doppler and 2D echocardiographic derived criteria, showed weak correlations with invasive parameters, especially with pulmonary vascular resistances (PVR) or cardiac index (CI). On the other hand, atrial functional assessment using pressure catheters is limited by its invasive nature and may not actually reflect the true atrial characteristics. A noninvasive method capable of providing a comprehensive assessment of RA function may be of clinical value for early diagnosis and timely therapeutic interventions.

In this regard **two-dimensional speckle–tracking strain echocardiography (2D-STE)** is a novel, angle-independent method, that quantifies wall deformation relying on tracking of acoustic speckles rather than using Doppler myocardial velocities (4). In experimental animal and clinical settings, strain and strain rate imaging has proved valuable for real-time quantitative measurement of myocardial deformation with high spatial and temporal resolution (5-6). Indeed, 2D-STE has been validated against tagged magnetic resonance imaging (7-8-9) and implemented for left atrial (LA) functional assessment (10).

The potential of 2D-STE in the assessment of RA deformation in PH patients, however, has not been established yet.

AIMS

To determine **feasibility and accuracy of RA 2D-STE** in the assessment of **global RA function** in patients with PH, and to examine the **added value of RA 2D-STE** in the clinical evaluation of such patients compared to gold standard hemodynamic parameters.

METHODS

We studied 43 consecutive, naïve adult patients (32 female, 11 male), aged 42 to 82 years (mean 69±11 years) with suspected PH based on clinical and echo parameters, referred to our Center for first-line **right heart cardiac catheterization (RHC)**. Subjects were included if they fullfilled the contemporary diagnostic criteria for PH: mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest and PVR > 3 Woods units. We excluded nonsinus rhythm patients. **Hemodynamic assessment was performed within 48 hours of baseline standard evaluation** consisting of: 1) EKG, physical examination and routine blood tests; 2) evaluation of brain natriuretic peptide (BNP) with immunoenzymatic assay (ELISA); 3) conventional transthoracic echocardiography. 4) 6MWT, pulmonary function tests (PFTs), gas transfer analyses - diffusion lung CO (DLCO), arterial blood gases and chest X-ray. Sixteen normal subjects matched for age, gender, sex and BMI were included as controls.

Cardiac Catheterization

Routine readings of invasive cardiac pressure measurements were performed in the catheterization laboratory by an investigator blinded to all echocardiographic data. According to published guidelines (11) and the recent achievements of the fifth World Symposia on Pulmonary Hypertension (Nice, France, 2013) we evaluate the haemodynamic profile by measuring RA pressure, PAP (diastolic, systolic and mean), pulmonary artery wedge pressure (PAWP), transpulmonary gradient (TPG), pulmonary vascular resistance (PVR), diastolic pulmonary gradient (DPG), Cardiac output (CO) and cardiac index (CI).

Two-dimensional and Doppler echocardiographic variables

All two-dimensional conventional echo and Doppler measurements were included. Systolic pulmonary artery pressure (sPAP) was estimated from the maximal velocity of tricuspid regurgitation (TR) and RAP using Bernoulli's equation ($sPAP= 4TR^2 + RAP$). RAP was estimated by the respiratory motion and the size of the inferior vena cava (IVC) from the subcostal view. Traditional index transthoracic echocardiograms are also performed using standard methods: left

and right atrial area and volume, left and right ventricular volume and function, pulmonary vascular resistances. The RA area was measured at end-systole in a 4-chamber dedicated view. The RA maximum volume (RA Vmax) was calculated prior to tricuspid valve opening, according to the area-length method (12). LA area and volume were calculated in the same way.

Speckle Tracking Echocardiography

Real-time 2D color Doppler RA myocardial imaging data were recorded using a modified 4-chamber apical view at the highest frame rate available (30-80 Hz acquisitions) with the narrowest sector angle possible. For 2D-STE analysis a line was manually drawn along the RA endocardium. The software then automatically generates additional lines near the atrial epicardium and mid-myocardium, thus delineating a region of interest (ROI). Before processing, a cine loop preview feature visually confirmed that the internal line followed the RA endocardium throughout the cardiac cycle. If tracking of the RA endocardium was unsatisfactory, manual adjustments or changing software parameters could be made. Using such technique, we analyzed regional deformations of 6 equidistant segments located along the septum, the roof and the lateral wall of RA cavity. In each region, the mean values calculated from all points were color-coded and shown as a function of time throughout the cardiac cycle. **Quantitative curves representing each segment strain were divided into component parts representing a different phase of RA cardiac cycle**. RA strain was measured during both RA contraction and RA relaxation. Negative values indicate tissue shortening/contraction. Positive values indicate tissue lengthening. A curve plotting the average of the 6 segments' strain curves was also automatically generated: we called the integral of such curve global strain and the maximum value of the curve peak strain. Recordings were stored digitally and analyzed offline by a single experienced and independent echocardiographer, who was not directly involved with the image acquisition and had no knowledge of hemodynamic measurements.

RESULTS

We enrolled 41 patients. Five patients were excluded because echocardiographic images were inadequate for the assessment of RA 2D-STE. In our PH patients **echocardiographic estimated sPAP showed an excellent correlation with RHC derivate sPAP measurements (r=0.67, p<0.001)** (Fig 1). The **RA deformation indices**, in particular peak strain and global strain, were **significantly compromised in all patients compared to controls** (Fig 2).

In our study population we observed that **depressed RA global strain** was **significantly associated** with higher **BNP** (r=0.38, p=0.002), advanced **NYHA** functional class (p=0.027), poor **6MWT** (r=0.23, p=0.006), reduced **TAPSE** (r=0.32, p<0.001) and **TAPSE/sPAP ratio** (r=0.28, p=0.005) (Fig 3). Furthermore, worse RA performance indexes proved to be associated with more advanced stages of the disease and more serious hemodynamic impairment. Regression analysis showed a **strong correlation between RA global strain and RHC-derived measurements**. In particular, we observed a direct correlation with CI (r=0.43, p=0.001) and an inverse correlation with PVR that was significant in all patients, albeit stronger in subjects with pre-capillary PH (r=0.18, p=0.018; r=0.29, p=0.007 respectively) (Fig. 4). By contrast, traditional echocardiographic parameters such as **RA area and volume failed to show any significant association with invasive hemodynamic parameters**.

In order to assess the RA 2D-STE added value in the clinical and functional evaluation of the patients' population, we performed a **multivariate analysis** including those noninvasive parameters found to be significantly associated with CI and PVR in our study. As a result, RA functional indices compared to LA strain, BNP, TAPSE and RA volume, remained as independent predictors of RHC-derived CI variations, with **RA global strain showing the strongest correlation with hemodynamic parameters** (Tab. 1).

Finally, we found that a **RA global strain > 17%** could identify patients with preserved CI (≥2.4 l/min/m^2) with a sensitivity and specificity of 90% and 54%, respectively (AUC: 0.83, 95% CI 0.66 to 0.94, P<0.0001) (Fig. 5).

CONCLUSIONS

In summary, **RA function can be assessed using 2D-STE** in most of PH patients. Differences in RA strain can **predict hemodynamic and functional impairment** to an extent that can potentially **reduce the frequency of repeating RHC** and more accurately modulate proper treatment while **monitoring response to the specific therapy**. Although RA 2D-STE is not routinely used, it is clinically helpful and, as such, it should be implemented in the comprehensive right heart evaluation in PH patients.

WORK IN PROGRESS

To increase the sample size to confirm the diagnostic value of right atrial strain.

To identify a correlation between right atrial strain and hemodynamic response to therapy in patients with pulmonary hypertension.

FIGURES AND TABLES

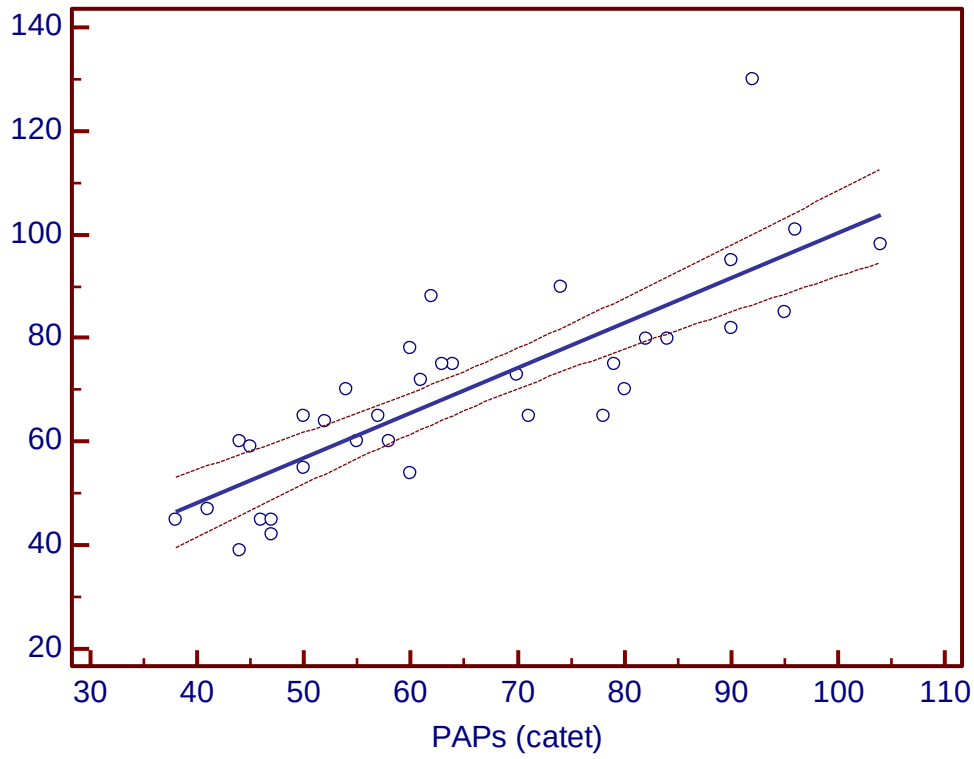

Figure 1. Correlation between echocardiographic and RHC systolic pulmonary artery pressure (sPAP).

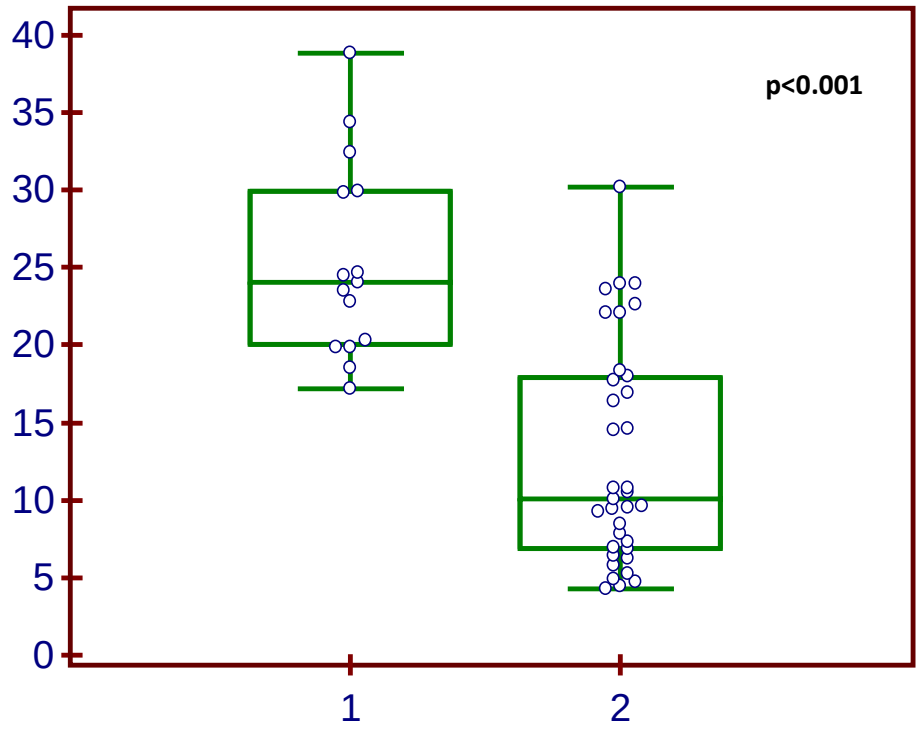

Figure 2. RA global strain in controls (1) versus PH patients (2).

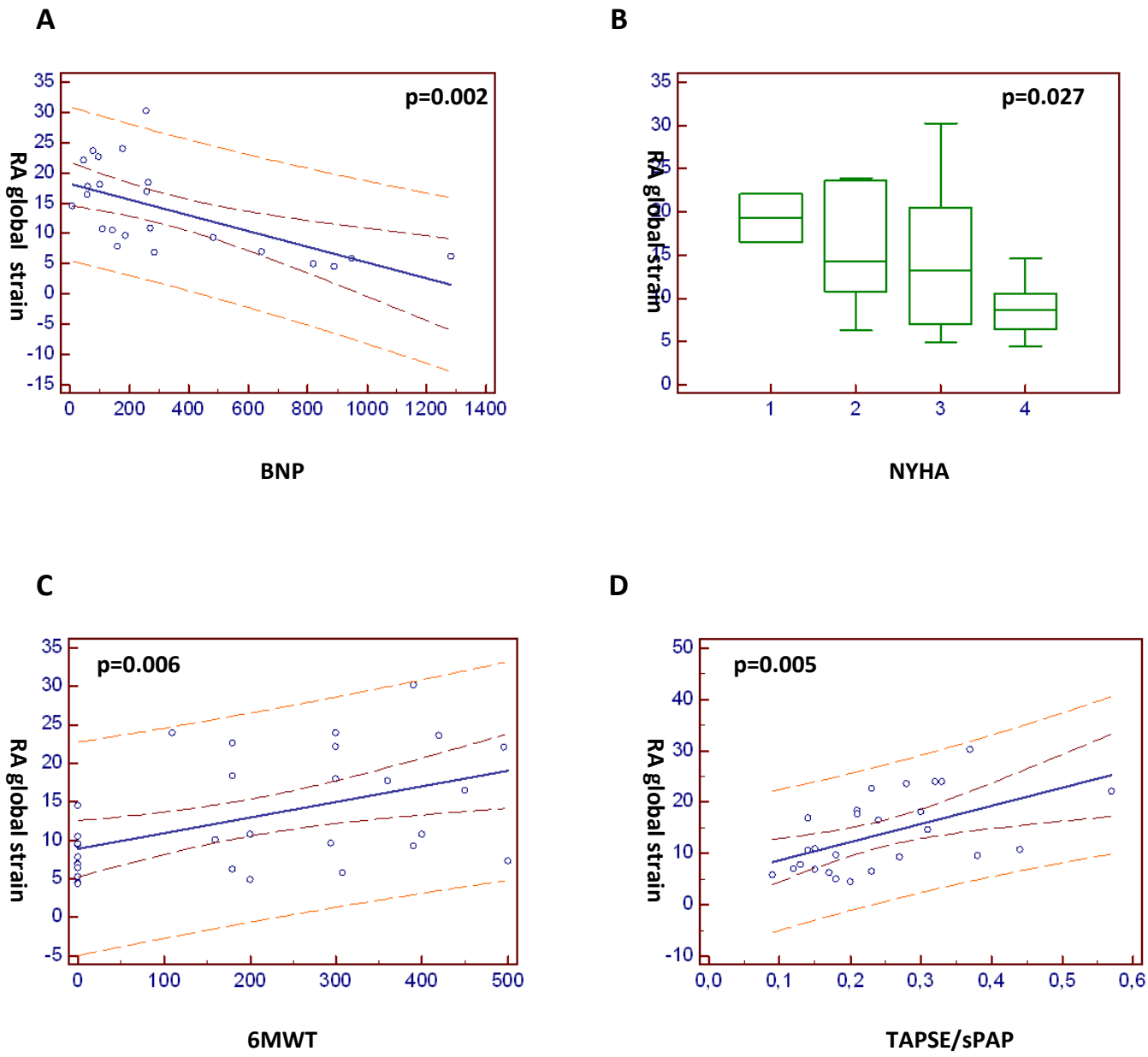

Figure 3. Correlation between right atrial global strain and functional (A, B, C) and standard echocardiographic parameters (D).

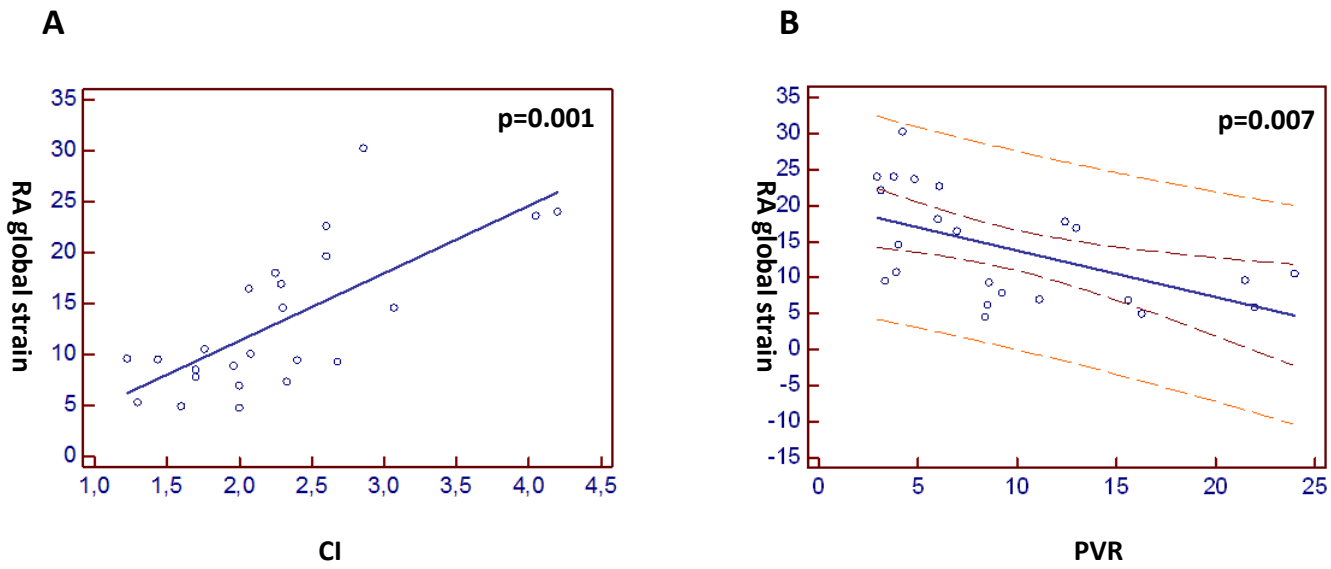

Fig. 4. Correlation between right atrial global strain and RHC measurements.

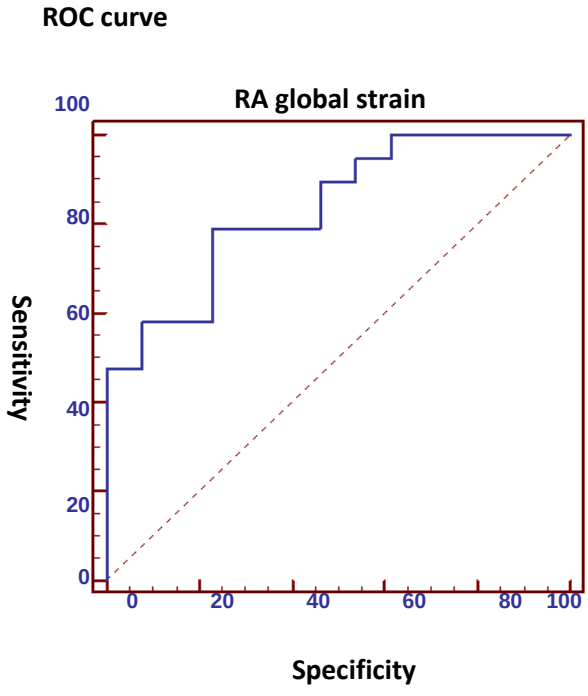

Figure 5. ROC curve between right atrial global strain and cardiac index (CI).

Table 1.

Simple size		**36**
Dependent variable		**CI (l/min/m^2)**
Indipendent variables	***r*** (coefficent of correlation)	***p*** (statistical significance)
RA global strain	**0,6655**	**0,0026**
RA time to peak strain	0,5204	0,0413
LA global strain	0,4268	0,3130
TAPSE	0,4061	0,9763
BNP	-0,3723	0,4979
Right atrial volume	-0,2149	0,2091

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SEMINARS

- Anticancer strategy Targeting cancer cell metabolism in ovarian cancer. January, Monday 19th 2015 (Prof.Dr.Yong-Sang Song)
- Regulation of hepatocytes differentiation during the transitions between epithelial and mesenchymal state. January, Tuesday 20th, 2015 (Dr Tonino Alonzi)
- Myeloid cells as therapeutic target in cancer. January Wednesday 27th, 2015. (Prof. Antonio Sica)
- Proof of principle for cell therapy: from autologous transplantation of tissue specific progenitors
  to gene corrected patient specific injured pluripotent stem cells. March 11th, 2015 (Prof. Bosnakovski)
- An Integrated Approach to the Diagnosis and Treatment of Ovarian Cancer. May Thursday 7th, 2015 (Prof John McDonald)
- Recent Developments in (cutaneous) Human Polyomavirus Research. June 5th, 2015 (Dr. Feltkamp)
- Infection susceptibility in medicine: examples from primary immunodeficiencies. October Thursday 8th, 2015. (Prof Raffaele Badolato).

CONGRESSES

1. International Meeting on Adult with Congenital Heart Disease" – S. Donato Milanese (in qualità di partecipante), March 2014.
2. Scientific Symposium "A New Horizon in Pulmonary Management" – Lisbon (in qualità di partecipante), April 2014.
3. "L'insufficienza mitralica funzionale e le nuove indicazioni al trattamento" – Novara (in qualità di partecipante), June 2014
4. ESC CONGRESS 2014 – Barcellona (in qualità di partecipante), August/September 2014.
5. Corso Ipertensione Polmonare. Linee Guida, nuovi orientamenti e mondo reale: una sfida quotidiana - Novara (in qualità di **relatore)**, Ottobre 2014.

6. 4^ CONVENTION GIOVANI SIC Piemonte e Valle d'Aosta. Dalla scuola al mondo del lavoro – Novara (in qualità di **relatore)**, Novembre 2014.
7. Third Focus on Pulmonary Hypertension – Capri (in qualità di partecipante), Maggio 2015.
8. Emoclinic Symposium. Sulle sponde del Ticino. Diagnostica e terapia cardiologica – Stresa (in qualità di partecipante), Maggio 2015.
9. Webinar Innovation. L'anticoagulazione tra FA e TEV – Apixaban nella SPAF – Novara (in qualità di partecipante), Maggio 2015.

POSTERS AND PRESENTATIONS

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

Additional value of right atrial strain in pulmonary hypertension diagnosis: correlation with clinical and invasive parameters and prognostic implications.

L. Ferrarotti, C. Piccinino, D. Sola, A. Giubertoni, Zanaboni J, PN. Marino.

POSTER PRESENTATION – 14th International Pulmonary Hypertension Forum (Copenaghen, 27-29/3/2015).

Clinical value of right atrial strain in predicting early hemodynamic deterioration in patients with pulmonary hypertension.
L. Ferrarotti, C. Piccinino, D. Sola, A. Giubertoni, J. Zanaboni, P. Marino.
POSTER PRESENTATION – ESC Congress 2015.

PUBLICATIONS

Correction of Chronotropic Incompetence with Rate-Responsive Device in a Ddd Pacemaker Population: Results from a Pilot Screening Study

E. Occhetta, M.V. Di Ruocco, E. Facchini, **L. Ferrarotti**, A. Magnani, L. Plebani, P. Marino – Journal of Atrial Fibrillation.

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. doi: 10.1097/MBC.0000000000000084.

Diagnostic accuracy of right atrial strain for the early detection of hemodynamic deterioration in patients with Pulmonary Hypertension.

C. Piccinino**, L. Ferrarotti**, P.E. Balbo, A. Giubertoni, J. Zaniboni, D. Sola, R. Nicali, PN. Marino – Journal of the American Society of Echocardiography (submitted, 6/2015).