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Review Article

Oxidative Stress, Inflammation and Echocardiographic Parameters as Predictors for Stress Right Ventricular Diastolic Dysfunction in Non-Severe Chronic Obstructive Pulmonary Disease

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ABSTRACT

Stress induced Right Ventricular DD (RVDD) precedes the clinical/echocardiographic manifestation of pulmonary hypertension and is an early marker of pulmonary vasculopathy. The timely detection of RVDD is important for the early diagnosis of pulmonary vasculopathy in COPD management and physical activity improvement. The simultaneous performance of stress-echocardiography and cardio-pulmonary exercise testing may provide early diagnosis of RVDD in COPD patients with exertional dyspnoea.

Oxidative stress and inflammation are both present in Chronic Obstructive Pulmonary Disease (COPD). In addition to intrathoracic and haemodynamic pressure oscillations, they have been considered as main factors for both right and left ventricular diastolic remodeling. The role of 8-isoprostane, prostaglandin E2 and resistin for stress induced Right Ventricular DD (RVDD) in non-severe COPD is still elusive.

We evaluated 104 patients with non-severe COPD (FEV1>50%) and preserved left ventricular ejection fraction >50%. Patients underwent Cardio-Pulmonary Exercise Testing (CPET). Our results showed a high prevalence of stress induced RVDD-78% of the patients, while only 14% showed RVDD at rest. Patients with stress RVDD demonstrate similar levels of oxidative stress (of 8-isoprostane). Prostaglandine E2 and resistin correlate to RV E/e'>6, but none of them is an independent predictor for it. None of these biomarkers could be used as a predictor for stress RVDD in clinical practice. In contrast, in multivariate regression analysis the echocardiographic parameters - RAVI, RVWT, RV E/A and RV E/e' ratio at rest independently predict stress RVDD.

Keywords: Inflammation; Oxidative stress; Stress echocardiography; Heart failure with preserved ejection fraction; Chronic obstructive pulmonary disease

INTRODUCTION

"Cardio-pulmonary continuum" is applied for Cardio-Vascular (CV) comorbidity in COPD. Oxidative stress and systemic inflammation are related to cardio-respiratory interactions and are not restricted to certain structural, haemodynamic, vascular or genetic parameters [1,2].

Cor pulmonale is classically considered as the cardio-vascular manifestation of COPD. However, subclinical RV abnormalities may be found even in mild form of the disease [3,4]. Contemporary investigational methods demonstrate that COPD patients have small RV dimensions and RV hypertrophy that predispose to Right Ventricular Diastolic Dysfunction (RVDD) [5-8] that is an early sign of pulmonary vasculopathy [9-11]. MRI shows that invasive Pulmonary Arterial Pressure (PAP) measurement delays the diagnosis of lung vascular pathology in the general population and in COPD patients [10,11]. Right ventricular diastolic dysfunction and pulmonary vessel impairment may be essential contributors for dyspnea and limited physical activity even in non-severe forms of COPD [12,13].

ECHOCARDIOGRAPHIC PREDICTORS AND STRESS RIGHT VENTRICULAR DIASTOLIC DYSFUNCTION IN NON-SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

"We confirm the concept of "cor pulmonale parvus" [14-17]. Our COPD patients have small RV dimensions, RV hypertrophy and RVDD at rest. Non-severe COPD patients with normal PAP at rest

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probably experience excessive haemodynamic PAP changes during exertion. Physical exertion could help for the dynamic assessment of diastoling filling pressures. They may be normal at rest but increase abnormally during exercise [18]. This may gradually result in RV structural changes that precede the clinical manifestation of RV dysfunction.

Although only a small proportion of patients have RVDD (14%) at rest, 78% show signs of RVDD after symptom limited incremental stress protocol. ROC analysis was performed in order to assess the predictive value of the right heart structural parameters that are usually measured in clinical practice and the stress induced RVDD (stress E/e' >6). RAVI and RVWT seem to be the parameters that have the best sensitivity and specificity. A cut-off value of 20.55 ml/m2 for RAVI may discriminate the patients with stress RVDD with a sensitivity of 86.36% and specificity 86.11%; E/A ratio at rest (cut-off 1.05) discriminates stress RVDD patients with sensitivity 79.7%; specificity 90.5%. RVWT of 5.25 mm is discriminative with a sensitivity 100% and specificity 63% (Table 1).

Table 1: Receiver operating characteristic curve analysis using RV echocardiographic parameters at rest to identify subjects with an stress RV E/e'>6.

	Area under the curve	95% CI	Cut-off value	Sensitivity	Specificity
RV basil diameter, mm	0.75	0.69-0.81	35.5	63%	71%
RVWT, mm	0.66	0.66-0.77	5.25	100%	63%
RAVI, m^1/m^2	0.91	0.84-0.97	20.55	86.36%	86.11%
E/A ratio at rest	0.9	0.83-0.96	1.05	79.70%	90.50%
E/e' ratio at rest	0.64	0.52-0.75	5.1	74.70%	61.90%
TAPSE, mm	0.7	0.58-0.82	21.62	68%	61%
PASP, mmHg	0.66	0.55-0.78	18.78	55%	81%
AT, msec	0.65	0.54-0.76	145	50%	75%

Abbreviations: FEV1: Forced Expiratory Volume in 1 sec; ICdyn: Dynamic Hyperinflatio; RVDD: Right Ventricular Diastolic Dysfunction; LV: Left Ventricle; RV: Right Ventricle; LVPWT: Left Ventricular Posterior Wall Thickness; RVWT: Right Ventricular Wall Thickness; RAVI: Right Atrium Volume Index; AT: Acceleration Time; PASP: Pulmonary Arterial Systolic Pressure; AT: Acceleration Time; TAPSE: Tricuspidal Annular Plane Systolic Excursion; PG E2: Prostaglandine E2.

Both functional (RV E/e' and RV E/A) and structural parameters (RAVI, RVWT, RV basilar and median diameter) correlate to stress RV E/e' ratio in univariate regression analysis they may be echocardiographic predictors for stress RVDD in non-severe COPD without PAH at rest. In multivariate regression analysis RAVI and rest RV E/e'>5.1 remained independent predictors for stress-RVDD (Table 2).

Table 2: Logistic regression analysis between ventilatory and echocardiographic parameters and stress RV E/e'.

Univariable regression analysis	p-value	OR	95% CI
Ventilatory parameters			
FEV1, l	0.78	2.01	0.86-3.87
ICdyn, l	0.04	5.29	2.68-9.18
LV parameters			
Septum, mm	0.67	1.98	1.62-2.86
LVPWT, mm	0.81	2.17	1.93-4.49
E/A ratio at rest	0.94	0.99	0.80-1.23
E/e' ratio at rest	0.99	1.89	1.59-1.99
E/A ratio after stress	0.04	1.54	1.00-2.35
E/e' ratio after stress	0	4.07	1.75-12.47
RV parameters			
RV basilar diameter, mm	0	1.48	1.23-1.78
RVmedian diameter, mm	0	1.83	1.38-2.48
RVWT, mm	0.74	0.98	0.78-1.02
RAVI, m^1/m^2	0	3.82	2.04-7.14
E/A ratio at rest	0	19.73	18.52-21.01
E/e' ratio>5.1 at rest	0.03	4.79	1.73-13.24
TAPSE, mm	0.37	21.56	1.20-38.91
S peak velocity, m/s	0.33	0.73	0.55-0.97
PASP, mmHg	0.12	0.7	0.07-75.08
AT, msec	0.49	2.39	0.20-28.67
Biomarkers			
Resistin, ng/ml	0.02	0.81	0.51-1.31
PG E2 , µmol/l/cre	0.04	0.7	0.34-1.07
Multivariable regression analysis			
E/e' ratio>5.1 at rest	0.02	9.03	1.32-63.73
RAVI, m^1/m^2	0	2.27	1.40-3.68

Abbreviations: FEV1: Forced Expiratory Volume in 1 sec; ICdyn: Dynamic Hyperinflatio; RVDD: Right Ventricular Diastolic Dysfunction; LV: Left Ventricle; RV: Right Ventricle; LVPWT: Left Ventricular Posterior Wall Thickness; RVWT: Right Ventricular Wall Thickness; RAVI: Right Atrium Volume Index; AT: Acceleration Time; PASP: Pulmonary Arterial Systolic Pressure; AT: Acceleration Time; TAPSE: Tricuspidal Annular Plane Systolic Excursion; PG E2: Prostaglandine E2.

INFLAMMATION, OXIDATIVE STRESS AND STRESS RIGHT VENTRICULAR DIASTOLIC DYSFUNCTION IN NON-SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In addition to intrathoracic and haemodynamic pressure oscillations during physical exertion, oxidative stress and inflammation have been assumed as leading factors for both right and left ventricular diastolic remodeling [19-21]. Systemic inflammation in COPD leads to elevated IL-6, TNF-α, hsCRP levels, which increase E-selectin, VCAM, endothelial reactive oxygen species and attenuate nitric oxide availability in the coronary microvasculature [22]. These biochemical reactions stimulate collagen deposition and myocardial stiffness [23]. Despite this, according to our results none of the inflammatory and oxidative stress markers is an independent predictor for it.

Indeed in our study resistin plasma levels correlated to stress RV E/e'>6, but are not independently associated with stress RVDD. Resistin plasma levels were higher in patients with RVDD, compared to those without (18.91 vs. 5.47 ng/ml, p-0.027). Resistin has been associated with vascular damage, insulin resistance, hypertension, left ventricular diastolic dysfunction, increased cardiovascular morbidity in the general population of patients [24-26]. Resistin and rodent resistin-like molecules (RELM) α are mechanistically critical to Pulmonary Hypertension (PH) etiology in lungs. Lin et al, prove that Resistin/RELMα is the pathogenic driver in the development of right cardiac dysfunction and maladaptive RV remodeling [27]. Lin et al, successfully established that anti-h Resistin neutralizing antibodies are novel therapy for PAH and the associated RV failure in an animal model [28]. Our findings also support the current notion. Although plasma resistin levels are not

independently associated with stress RVDD, they correlate to stress RV E/e' ratio.

The other inflammatory marker that significantly differed between both groups was prostaglandin E2. Urine levels of prostaglandin E2 are higher in the group without stress RVDD (62. 19 vs. 49.73 μmol/l/cre; p-0.014). However, urine levels of prostaglandin E2 did not show good sensitivity and specificity to distinguish the two patients with stress RVDD from those without. Our results, regarding urine prostaglandin E2 and plasma resistin levels should be validated in larger cohorts and their pathogenetic mechanisms should be further explored.

In addition to systemic inflammation, oxidative stress in COPD may also disturb calcium transport and myocardial relaxation [29]. Reactive Oxidative Species (ROS) are generated under inflammatory or hypoxic conditions and increase endothelin secretion and decrease NO/prostacyclin synthesis [30]. Thus, oxidative stress leads to endothelial damage of coronary, systemic, pulmonary vessels and contribute both to right (RVDD) and Left Ventricular Diastolic Dysfunction (LVDD) [31]. Though we applied a well-validated method and marker for oxidative stress – urine 8-isoprostanes, we did not find substantial difference in its concentrations between COPD subjects with/without RVDD (30.78 vs 30.41 μmol/l/cre, p-0.847). Neither a correlation between urine 8-isoprostanes and stress RV E/e' was found.

CONCLUSION

Patients with stress RVDD demonstrate similar levels of oxidative stress. Prostaglandine E2 may have protective role in RV remodeling, while resistin plasma levels contribute to RVDD pathogenesis. Only RAVI, RVWT, RV E/A and RV E/e' ratio at rest may be used as independent predictors for stress RVDD.

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