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ORIGINAL ARTICLE

Non Invasive Assessment of Pulmonary Artery Stiffness and Right Ventricular Function in Patients with Obstructive Sleep Apnea

MH Shah, MD[1], MM Elzaki, MD[1], AS Eldamanhory, MD[1], MA Abdel-Rashid, MD[1], DM Elsayed, Msc[1]*.
[1]Cardiology Department, Faculty of Medicine, Zagazig University, Sharkia, Egypt.

***Corresponding author:**

Doaa Mohamed Elsayed
Cardiology department, faculty of medicine, Zagazig University.
E-mail: doctordo@yahoo.com

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ABSTRACT

We aimed to evaluate pulmonary artery stiffness by Doppler studies and to use speckle derived study to assess function of right ventricle to predict early RV functional changes in obstructive sleep apnea (OSA) patients. In addition, we aimed to assess when we can use anticoagulants in patients with elevated pulmonary artery pressure and OSA.

Methods: This study was performed on one hundred cases with OSA who did overnight sleep (polysomnography) study detecting the complete cessation of respiration and hypoventilation episodes, then patients were subjected to blood sampling of serum fibrinogen, platelets, hepatic and renal function tests, and random blood sugar (RBS) was measured, conventional echocardiography was done to measure right ventricular ejection fraction (RVEF), tricuspid annular plane systolic excurtion (TAPSE), myocardial performance index (MPI), fractional area change (FAC), linear diameters of right ventricular inflow tract (RVOT), right ventricular (RV) free wall thickness, Doppler assessment of pulmonary artery stiffness (PAS) and speckle tracking echocardiography (STE)

Results: There was a statistically high difference among the study groups regarding Fibrinogen, platelet count, global longitudinal strain, RVEF, TAPSE, and PAS. There was a positive relation between fibrinogen and apnea-hypopnea index (AHI) (r= 0.686, p< 0.001), a positive relation between PAS and AHI (r= 0.515, p< 0.001), a negative relation between RVEF and AHI (r= -0.639, p< 0.001) and a negative relation between GLS and AHI (r=-0.663, p< 0.001). We found that GLS was important with PAS for prediction of RV failure.

Conclusions: OSA patients may have a hidden RV systolic impaired function detected by STE. PAS may contribute to the development of RV impaired function. Elevated fibrinogen is important risk factor for cardiovascular and cerebrovascular pathology and may direct attention for starting anticoagulation in OSA patients.

Keywords: Obstructive sleep apnea, Apnea hypopnea index, right ventricular function, pulmonary artery stiffness, Speckle tracking echocardiography.

INTRODUCTION

OSA patients develop many cardiovascular and cerebrovascular events due to night episodes of hypoventilation and cessation of ventilation that expose circulatory system to negative variations in intra thoracic pressure which lead to diminished oxygenation and increase in preload [1]. RV function plays an important role in the morbidity and mortality in patients who develop cardiopulmonary disease. Early detection of RV decreased function before rise of pulmonary pressure help to prevent progression to morbid failure and death [2].

In OSA there is a hyper coagulant state. Fibrinogen is the most important coagulation protein involved. So there is a relation between fibrinogen and risks of thromboembolism [3].

METHODS

This cross-section study was performed in Cardiology Department, Faculty of Medicine, Zagazig University, on obstructive sleep apnea patients who did polysomnography in Zagazig university hospitals from March 2017 to September 2019.

The study was approved by the medical research and ethics committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of

Helsinki) for studies involving humans. A written consent was obtained from each patient after clear explanation of the study protocol.

Methods: All cases were subjected to complete History taking, Electrocardiogram (ECG) to detect signs of increased pulmonary pressure e.g. P-pulmonale or RV hypertrophy, Laboratory tests including fibrinogen level using venous blood sample by immunoassays with normal levels being (1.5-3 gm/L) [4], platelet count with normal level range (150-450 X 106 /L) [5], ALT, AST, creatinine levels and random blood sugar with value ≥200 mg/dl was considered abnormal [6]. We also performed 2-D transthoracic echocardiographic examination using a 5 MHz phased-array transducer Vivid E9 commercial ultrasound scanner with phased-array transducers (M5S-D). Examinations were done; utilizing left parasternal long axis, short axis, apical 4, apical 5 and apical 2 chamber views. Recorded data calculated by different parameters was performed according to the recommendations of the American Society of Echocardiography [7]. Data obtained by echocardiography was RVOT diameters measured using the apical 4 chamber view by tracing the endocardial border at end-diastole, with trabeculations and papillary muscles included. Measurements obtained were RVd1 which is the maximal transverse dimension in the basal one third of RVOT at end diastole, RVd2 which is the transversal RV diameter in the middle third of RV inflow, approximately halfway between the maximal basal diameter and the apex at the level of papillary muscle at end-diastole and RVd3 from base to apex of RV length [7], RV free wall thickness using M-mode in subcostal view at end-diastole and focus on the RV mid-wall below tricuspid annulus with value 1-5 mm was normal [7], RVEF in Apical 4 chamber view by Tracing of endocardial border at end-diastolic and end-systolic frames. RVEF value >45% reflects normal RV systolic function [7], Myocardial performance index or Tie index using pulsed wave Doppler on tricuspid flow in apical 4 chamber view to assess tricuspid rapid filling velocity and peak atrial velocity along with ejection time. MPI was calculated using the following formula; RV MPI = (IVRT+IVCT) / ET. Normal values are set as less than 0.3 [7], Tricuspid annular plane systolic excursion (TAPSE) by Measuring tricuspid annular excursion from end diastole to end systole by m-mode on lateral annulus in apical 4 chamber view [7], RV fractional area change (RV FAC) was defined as (RV end diastolic area − RV end systolic area) / end diastolic area × 100 in apical 4 chamber view [7], RV global longitudinal strain (RV GLS) was calculated as a percentage of shortening of the RV free wall from base to apex and the septal segments during systole. Data suggest that GLS >-20% is likely abnormal [7] and Pulmonary artery stiffness (PAS) was measured in short axis view using pulsed wave Doppler 1 cm distal to pulmonic valve to assess maximal frequency shift and acceleration time. PAS (kHz/sec) = maximal frequency shift of pulmonary flow / acceleration time [8].

STATISTICAL ANALYSIS

Analysis of the study data was performed using (SPSS) version 23. Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics: Mean, Standard deviation (± SD) for numerical data. Frequency, percentage and chi square tests of categorical data. Analytical statistics: analysis of variance ANOVA was used to assess the statistical significance of the difference among the three groups. (P>0.05) was non-significant, (p <0.05) was significant. Pearson's correlation test was applied to estimate and test the relationship between AHI and significant echo parameters. Simple linear regression and then multiple regression was used to detect the associated independent variables for PAS.

RESULTS

Out of 129 patients who underwent overnight sleep study, 10 patients were out of the study due to atrial fibrillation, 10 patients were discarded due to being on anticoagulant therapy, and 9 patients were out of study due to bad echo window which is unfit for speckle tracking. The study was conducted with 100 patients.

Patients were classified into 3 categories according to AHI;

Group (1) mild (AHI < 5 -14), Group (2) moderate (AHI 15-30), and Group (3) sever (AHI > 30)

Regarding to demographic data, there was no noticed difference among the study groups regarding sex, age and elevated blood pressure (p>0.05).

Regarding laboratory data there was high significant difference among the study groups regarding fibrinogen level and platelet count p<0.001 but there was no significant difference among the study groups regarding hepatic function, renal function and blood glucose (p > 0.05).

Regarding to echocardiographic data there was high significant difference among the study categories at GLS, RVEF, TAPSE and PAS (p <0.001) but there was no significant difference

among the study groups regarding RV diameters, RV free wall, FAC and MPI (p <0.05) table1.

There was positive relation between fibrinogen and AHI (r= 0.686, p< 0.001) fig 1, positive relation between PAS and AHI (r= 0.515, p< 0.001) fig 2, negative relation between RVEF and AHI (r= -0.639, p< 0.001) fig 3. And negative relation between GLS and AHI (r= -0.663, p< 0.001) fig4.

By simple linear regression analysis, we found that, RV STE, RVEF, fibrinogen and AHI were significant predictors of PAS table2. But multiple regression analysis found that GLS was the independent predictor of PAS table3.

Table 1: shows Echo data among the study groups (1,2&3) according to AHI

Variable	Group (1) (n=19)	Group (2) (n=21)	Group (3) (n=60)	P-Value
	X ±SD	X ±SD	X ±SD	
RV (STE)	17.8±3.3	15.5±2.7	12.3±3.2	**<0.001 High .sig**
RV (EF)	45±0.041	43±.047	38±0.063	**<0.001 ,High .sig**
MPI	0.2679±**0**. 067	0.363±**0**.063	0.370±**0**.18	0.20, N.sig
FAC	46.2±**0**.093	58.2±13.5	55.5±13.27	0.24, N.sig
TAPSE	17.05±2.63	15±2.7	10.1±3.72	**0.001, sig**
RV free wall	1.20±**0**.05	1.22±**0**.09	1.23±**0**.11	0.451, N.sig
RVbasal	3.64 ±0.20	3.60 ±0.18	3.63 ± 0.19	0.85, N.sig
RV mid	3.44 ± 0.20	3.40± 0.25	3.39 ± 0.25	0.73, N.sig
RV longitudinal	7.30 ±**0**.14	7.27 ±**0**.15	7.26±0.37	0.89, N.sig
PAS	0.009±0.001	0.008±0.001	0.010±0.002	**<0.001, High .sig**

RV (STE): right ventricular speckle tracking echocardiography; RVEF: right ventricular ejection fraction; FAC: fractional area changes; TAPSE: tricuspid annular plane systolic excursion; PAS: pulmonary artery stiffness, MPI: myocardial performance index

Table 2: shows simple linear regression analysis for predictors of PAS

Variables	Adjusted R square	Beta Co-efficient	Sig	Lower bond	Upper Bond
RV(STE)	0.246	-0.503	<0.001	0.012	0.015
RV(EF)	0.157	-0.407	<0.001	0.013	0.019
Fibrinogen	0.201	0.457	<0.001	0.005	0.008
AHI	0.257	0.515	<0.001	0.006	0.008

RV (STE): right ventricular speckle tracking echocardiography; RVEF: right ventricular ejection fraction; AHI: apnea hypopnea index

Table 3: shows multiple linear regression analysis for predictors of PAS

Variables	Adjusted R square	Beta Co-efficient	Sig
RV(STE)	**0.322**	-0.294	**0.009**
RV(EF)		-0.171	0.119
Fibrinogen		0.224	0.054
AHI		0.056	0.723

RV (STE): right ventricular speckle tracking echocardiography; RVEF: right ventricular ejection fraction; AHI: apnea hypopnea index

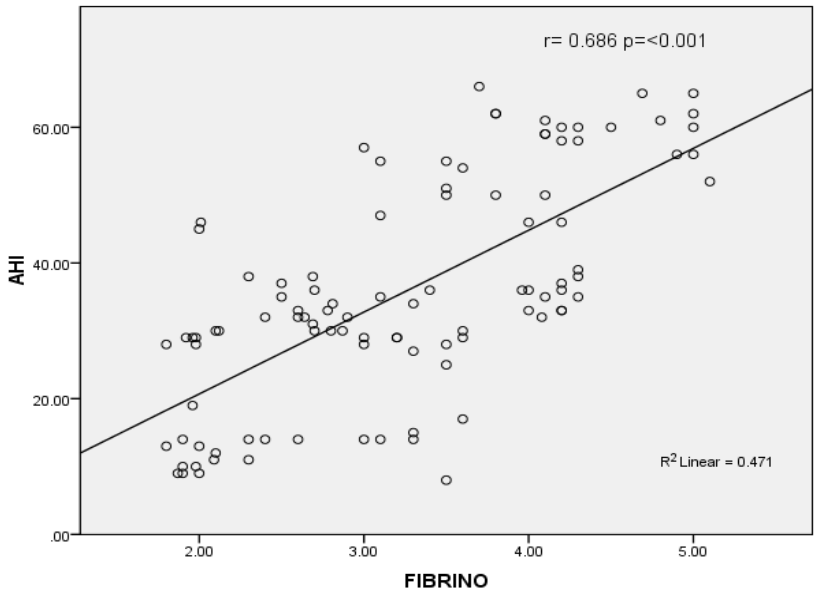

Figure 1: a scatter diagram showing strong positive correlation of high statistical significance between AHI and fibrinogen

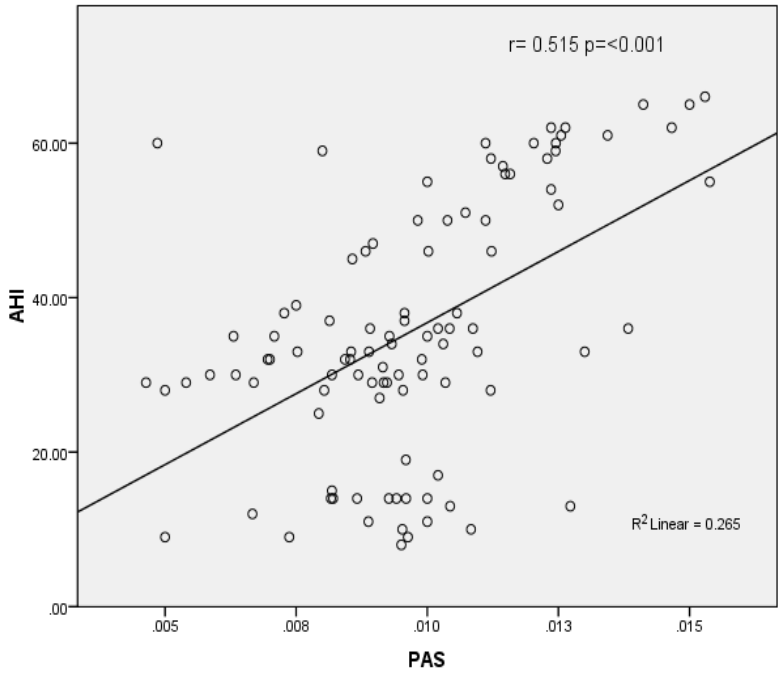

Figure 2: a scatter diagram showing significant strong positive correlation between AHI and PAS

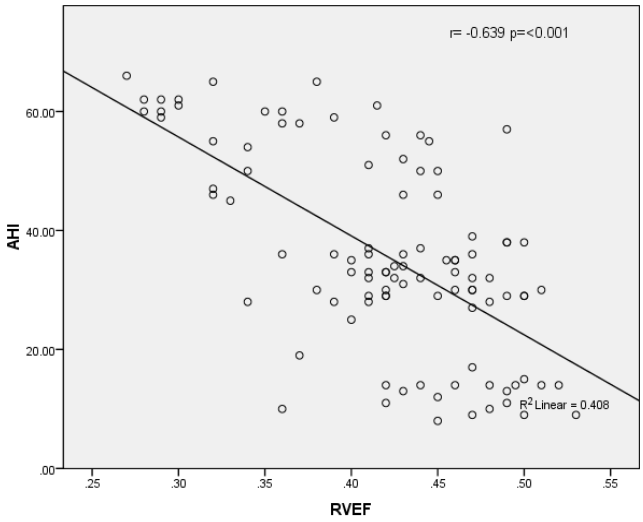

Figure 3: a scatter diagram showing negative correlation of high statistical significance between AHI and RV(EF)

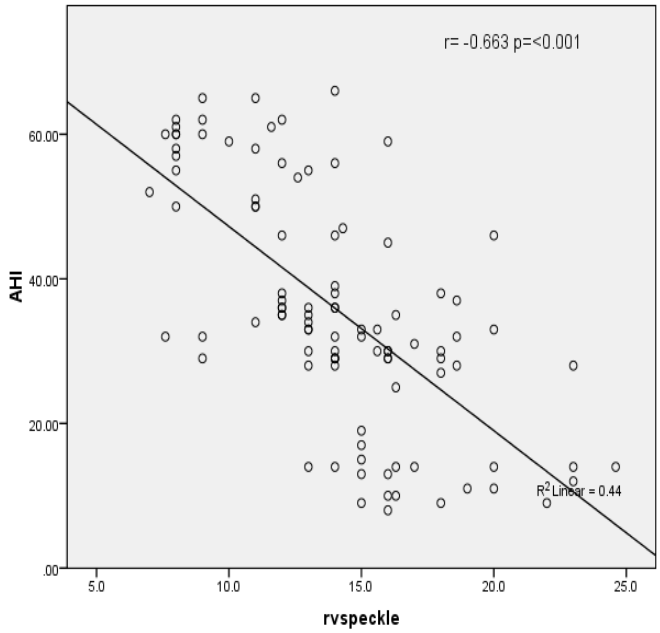

Figure 4: a scatter diagram showing negative correlation of high statistical difference between AHI and RV(STE)

DISCUSSION

The present study was performed on one hundred cases who did an overnight sleep study (polysomnography) in chest department, with calculation of the apnea-hypopnea index AHI. Patients with AHI was more than 5 events per hour are present in our study, then patients were investigated in cardiology department, echocardiography unit for measuring RV function.

This study aimed to detect pulmonary artery stiffness by Doppler studies and RV functions by STE in predicting early RV impaired function in OSA patients. In addition, we aimed to assess when we can use anticoagulation in patients with raised pulmonary arterial pressure and OSA.

Patients in the present study were divided into three categories according to AHI, Group (I): Mild OSA (AHI 5-14 events per hour), Group (II): moderate OSA (AHI 15-30 events per hour) and Group (III) severe OSA (AHI >30 events per hour).

There was no significant difference among the study groups based on age, sex and hypertension. This was matched with Buonauro et al. [1] who found non-significant difference regarding age, sex and hypertension.

There was highly significant difference among the study groups in fibrinogen level and we noticed higher levels in group (II) & (III)

compared to group (I); this finding was powered in our study by the strong positive relation between fibrinogen and AHI (r= 0.686, p= <0.001). This was matched with Shamsuzzaman et al. [3] who found that fibrinogen levels were highly raised in patients with severe OSA compared to mild OSA (P=0.02) this agrees that fibrinogen is an acute phase protein that influences platelet aggregation and fibrin clot formation so, fibrinogen is a important mediator of coagulation and is a risk factor for cardiovascular and cerebrovascular thromboembolism [9].

In addition, there was highly significant difference among the study groups regarding platelet count and we noticed high significant value in group (III) compared to other groups this was matched with Akinnusi et al. [10] who found significant difference among the study groups. This suggests that platelets have an important role in preventing bleeding; however, they also contribute to the development of thrombosis, which lead to vascular complications [11]. On the contrary, this was mismatched with Reinhart et al. [12] who found no relation between platelet activation and OSA.

This study showed highly significant difference among the study groups based on RVEF and we noticed that RV function was upper normal in group (I) with progressive impairment in groups (II & III); this finding was powered in our study by the strong negative relation between RVEF and AHI (r= -0.639, p< 0.001) This was matched with Oliveira et al. [13] who found highly significant difference in his study groups regarding RVEF, this agrees that in OSA cessation of respiration during sleep give rise to increased intra-thoracic negative pressure, and increase venous return into right heart, and cause increased right ventricular preload [14]. On the contrary, this was mismatched with Buonauro et al. [1] who found no noticed difference between his study groups; this may be explained by performing his study on OSA and control groups.

Also, there was highly significant difference among the study groups regarding TAPSE and we noticed that its value was upper normal in group (I) while there was progressive impairment in group (II) & (III) meaning that there was progressive drop in systolic function. This was matched with Li et al. [15] who found highly significant difference among his study groups regarding TAPSE, this agrees that RVEF decreases due to periods of hypoventilation and cessation of respiration result in intermittent hypoxemia, disturbed autonomic nervous system function, and consequently affect RV myocardial function as TAPSE is also an indicator of RV systolic function like EF [14]. On the contrary, this was mismatched with Altıparmak et al. [8] who found no significant difference between his study groups based on TAPSE; this may be explained by performing his study on OSA and control groups.

In addition there was no significant difference among the study groups regarding Tie index, FAC, RV free wall thickness, RV linear diameters and we noticed that all values were in normal reference in the three groups, this was mismatched with Sascău et al. [16] who found highly noticed difference regarding Tie index. Li et al. [15] found highly noticed difference regarding FAC and free wall thickness. Buonauro et al. [1] found highly noticed difference regarding basal, mid and longitudinal RV diameters [17].

Interestingly, there was statistically high difference among the study groups regarding RV STE with slight impairment in group (I) while progressive impairment in group (II) & (III); this finding was powered in our study by the strong negative relation between RV STE and AHI (r= -0.663, p< 0.001). This was matched with Sascău et al. [16] who found significant difference in their study groups regarding RV STE.

In addition, we noticed that although RVEF and TAPSE were upper normal in group (I), RV strain was impaired. This means that early affection of right ventricle is detectable by speckle derived ECHO study.

It is proven that decreased pulmonary elasticity decreases the ejection time of pulmonary systolic flow resulting in reduction in acceleration time of pulmonary flow trace with increase in maximal flow velocity making PAS a new parameter to detect rise in pulmonary arterial pressure [18].

With development of PAS and PH functional capacity and patient survival will be affected [19].

Interestingly, there was highly significant difference among the study groups regarding PAS and we noticed higher value in group (III) compared to other groups, a finding that was powered by the strong positive relation between PAS and AHI (r= 0.515, P <0.001), so elevated PAS should alert the clinicians to early deterioration of RV function. This was accepted with Altıparmak et al. [8] who found significant difference in his study groups regarding PAS.

Furthermore, the present study showed that PAS is an important predictor for early RV impaired function in OSA patients this was matched with Buonauro et al. [1] who found that

RV longitudinal strain was independently associated with PAS. (B co-efficient= 0.26, p-value= 0.035).

CONCLUSIONS

OSA patients have early affection of RV function which is not detected by standard ECHO parameters but easily detected by STE. Increased PAS due to decreased elasticity is important factor to predict early RV dysfunction as it is easy and simple predictor to be used. Moderate to severe OSA patients had rising levels of fibrinogen that may urge to start anticoagulation in this category.

Conflict of interest: Non.

Financial disclosure: Non.

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