The Role of New Pulmonary Artery Wedge Pressure Formula to Predict Diastolic Dysfunction in Obstructive Sleep Apnea

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ABSTRACT

Background: *Heart failure (HF) is a common condition with high morbidity and mortality in Obstructive Sleep Apnea (OSA), especially in obese patient. The causes of HF are often abnormal conduction pathways, pump filling and/or heart valves. Right heart catheterization using Swan-Ganz catheter remains the gold standard to determine pulmonary hemodynamics, but it is costly and invasive. Herein, we propose a new formula for non-invasive Pulmonary artery wedge pressure (PAWP) measurement using tissue Doppler echocardiography. The purpose of this research is to explore the correlation between the new formula to calculate PAWP to predict diastolic dysfunction in OSA patients.* ***Methods:*** *A cross-sectional study was conducted in Jakarta, in March until October 2021. Eighty-two subjects were enrolled in the study, consist of 34 females and 48 males. All subjects underwent polysomnography and tissue Doppler echocardiography. Noninvasive measurement of PAWP were obtained from combined assessment of E/e'and left atrial parameters.* ***Results:*** *Based on 82 subjects included, 66 subjects (80.5%) had obstructive sleep apnea, and 16 subjects (19.5%) did not have it. There was a significant difference in PAWP between patients with and without OSA (p value <0.01). Ten subjects OSA (12.1%) had diastolic dysfunction, while all non-OSA subjects had normal diastolic function, with no statistical significance between two groups (p value = 0.20). Diastolic dysfunction significantly associated with PAWP measured using proposed formula (R = 0.240, p value = 0.030).* ***Conclusion:*** *The new formula could be used to indirectly calculate PAWP and predict diastolic dysfunction in OSA. Obstructive sleep apnea is associated with elevated PAWP. The increased risk of diastolic dysfunction in OSA, especially in obesity patient may indicate for the risk of cardiovascular morbidities.*

Keywords**:** *pulmonary artery wedge pressure, obstructive sleep apnea, diastolic dysfunction.*

INTRODUCTION

Heart failure (HF) is a common condition with high morbidity and mortality, which places a significant financial burden on the community due to reduced productivity, repeated hospitalizations and treatment costs. Moreover, 40% to 50% of patients who now present with heart failure with preserved ejection fraction (or HFpEF) are reported to have sleep apnea.[1] Left ventricular diastolic dysfunction, defined by impaired relaxation of the myocardium, is a hallmark of heart failure in patients who present with heart failure reduced ejection fraction (HFrEF) or heart failure preserved ejection fraction (HFpEF). This classification of HF causes is important, when one has to assess

patients with HF for the possibility of sleep apnea and develop a treatment plan as some HF types may be more sensitive to obstructive sleep apnea (OSA).[2]

Diastolic dysfunction is a condition that reflects an impairment of the filling properties of the left ventricle (LV) that has been demonstrated to be a predictor of future development of heart failure. The association between OSA and diastolic dysfunction is not well studied, although OSA is frequent in heart failure patients. Proposed mechanisms that affect left ventricular performance in patients with OSA include several mechanical, neurohumoral, inflammatory, endothelial, and oxidative effects. More research is required to determine basic mechanisms by which OSA exerts its adverse effects on the cardiovascular system. Such investigations could include studies of the impacts of intermittent hypoxia on cardiovascular function at both cellular and molecular levels, and genetic susceptibilities to adverse cardiovascular risks of OSA.[3]

Left ventricular filling can be measured directly by placing a catheter in the left ventricle to obtain the end-diastolic pressure (LVEDP), or indirectly by placing a catheter in the pulmonary artery to measure the pulmonary capillary wedge pressure (PCWP). Both of these invasive techniques involve cardiac catheterization with its attendant risk and expense.[1] Echocardiography is essential to the evaluation of heart failure, and guidelines exist to identify diastolic dysfunction non-invasively. However, up to 50% of patients with HFpEF have normal resting diastolic function parameters. On echocardiographic examination with Doppler, the velocity of V_E and V_A can be determined, where V_A is the rate of filling of the end-diastolic blood phase from LA to LV due to LA contraction as seen with P waves on the ECG. With this V_A velocity component, it can be used to determine the conversion formula from V_A to pulmonary artery wedge pressure (PAWP), so that it is enough with a non-invasive examination to determine PAWP pressure (PC = Pulmonary Capillary) indirectly, and there is no need to perform invasive catheterization again.[2]

Extensive technical improvements in echocardiography have increased its sensitivity for quantifying PAWP and it is now recognized as a safe and available alternative to right heart catheterization. PAWP represents an alternative measure to left ventricular end-diastolic pressure (LVEDP), which is the gold standard for determining left ventricular filling pressure.[4] The mean PAWP that integrates the atrial pressure tracing throughout systole and diastole provides an integrated measure of the hemodynamic burden imposed by the left atrial (LA) operating compliance on the pulmonary circulation.[5] PAWP is a surrogate marker of left atrial pressure (LAP).

Sleep apnea is often found in patients with heart failure. Obstructive sleep apnea patients reveal acute and chronic hemodynamic changes. Nevertheless, the combination of sleep apnea and heart failure is different to the previously mentioned combinations (i.e. OSA with hypertension and CAD) as the majority of the sleep apnea cases are central or mixed in heart failure patients.[3] Nevertheless, OSA can cause heart failure: systolic heart failure as after a myocardial infarction, or diastolic heart failure as is often the case in hypertensive patients. Almost half of heart failure patients have a preserved systolic function, i.e. a left ventricular (LV) ejection fraction (LVEF) >45%. LV hypertrophy (LVH) often seems to be associated with this LV diastolic dysfunction.[6]

Several predisposing factors for OSA include obesity, neck circumference size, age, sex, hormones, and airway anatomic abnormalities. Another study reported that neck circumference (>42.5 cm) was associated with an increase in Apnea-Hypopnea Index (AHI).[7] Obesity can change the volume and anatomical shape; the tongue can be raised thereby reducing the volume of the upper airway. Four large-scale prevalence studies suggest that one in five white adults with an average body mass index (BMI) of 25–28 kg/m^2 has an AHI 5 times per hour. It is reported that one in fifteen of OSA patients has an AHI of 15 or more.[8]

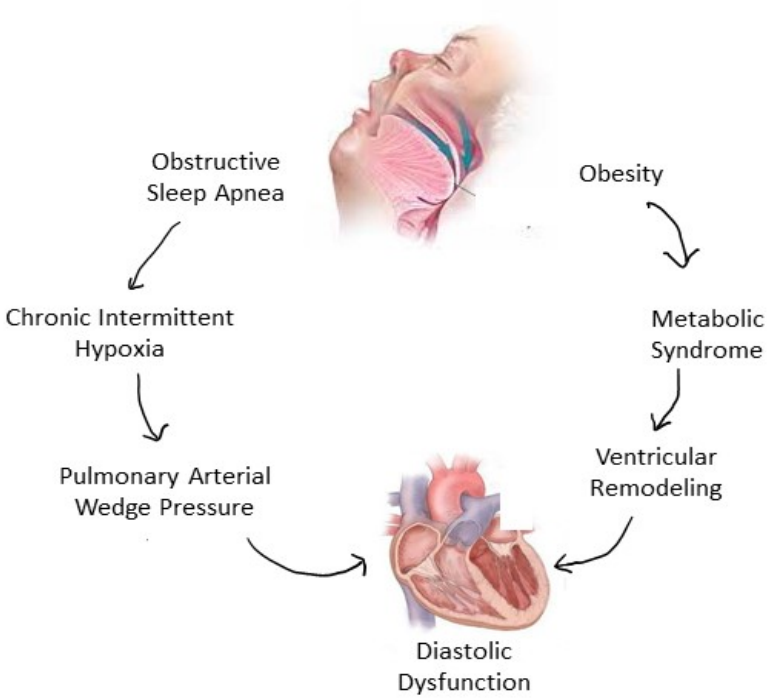

Figure 1. Pathophysiology of diastolic dysfunction in obstructive sleep apnea and obesity[6]

Since the PAWP is a substitute marker of left atrial pressure and chronic airflow obstruction is the most important cause of pulmonary artery remodeling that can lead to diastolic dysfunction, the main purpose of this study was to obtain the pulmonary artery wedge pressure (PAWP) based on echocardiography, which was estimated using a new mathematical model formula based on measurements of left atrial pressure and the influencing factors with parameters related to the OSA incidence. In addition, to build a new PAWP formula using a mathematical model that functions as a non-invasive procedure to predict diastolic dysfunction and compare the new formula with the existing formula.

METHODS

This cross-sectional study was conducted in Jakarta, between March until October 2021. The study was approved by Universitas Indonesia, Faculty of Medicine Ethic Committee (KET-1205/UN2.F1/ETIK/PPM.00.02/2020). This formula has been registered to the Indonesian Copyright Service for predicting diastolic dysfunction in obstructive sleep apnea the new pulmonary artery wedge pressure (PAWP) formula by Lukman H. Makmun (Reg. no. EC00202297046 and Reg. no. EC00202297063).

We included obese subjects aged from 18 to 65 years. In Asia-Pacific countries, the agreed cut-off point for obesity was defined as BMI (kg/m^2) between 25.0 and 29.9. Written informed consent was obtained from all subjects. Exclusion criteria included the following: unstable cardiorespiratory status, defined as the existence of respiratory failure, congestive heart failure, or if they were unable to participate. Patient demographic data were obtained, including age, gender, body mass index, and blood pressure.

Each subject underwent polysomnography (SomnoMedics type 2) according to well-established procedure. The monitoring included recording from surface leads for electroencephalography, bitemporal electro-oculography, submental and leg electromyography, and electrocardiography. Oxygen saturation and respiration was monitored by oronasal airflow and finger-pulse oximeter. Polysomnography recordings were scored for sleep, breathing, and oxygenation. We took the average number episodes of apnea and hypopnea per hour of sleep (apnea/hypopnea index) and the time during sleep spent with an oxygen saturation below 90%. OSA was diagnosed if the apnea-

hypopnea index (AHI) was more than 5 times in 1 hour of sleep.

Echocardiography was performed with an ultrasound system (General Electronics Ultrasound Vivid E95) using 2.5- and 3.5-mHz. Images were stored digitally for off-line analysis using EchoPAC software (General Electronics). Standard M-mode and 2-dimensional views were used. The following measurement were determined, such as peak early (E) and late (A) diastolic mitral annular velocity, the ratio of E and A velocities (E/A), and the deceleration time (DT). e' ≤ 8 was used as an indicator of left ventricular diastolic dysfunction and E/e' was calculated for the prediction of PCWP.[9]

Diastolic dysfunction was classified according to recent guidelines: 1) normal diastolic function (e' (lateral) >10 cm/s, e' (medial) >8 cm/s and LAVI <34 mL/m^2 ; 2) mild diastolic dysfunction (E/A <0.8, e' (lateral) <10 cm/s and e' (medial) <8 cm/s and; 3) diastolic dysfunction with elevated filling pressures (E/e' >13 cm/s or E/e' >9 and LAVI >34 mL/m^2).[9]

During end diastolic phase, left atrium contracts to empty the remaining early and mid-diastolic blood volumes that remain in the left atrium (LA-V_{ed} = LA-Volume end diastolic). There are amounts of blood transferred from the LA into the LV. When the afterload has reached the maximum load, there is no further increase in the dimension length (maximum isometric), so it can be assumed that the magnitude of *S* and the LA- V_{ed} is constant.[10]

The systolic left atrial pressure determined as depicted previously relates to strain in the left atrium during the pulmonary *S* wave. Essentially, diastolic left atrium pressure is the pressure during the pulmonary D wave.[10] Since pulmonary S and D waves have generally a similar duration, we estimated mean left atrial pressure as the average between systolic and diastolic left atrial pressure.[10]

At this end diastolic time, the LA space is also filled with blood volume which will be partially flowed at a smaller speed, namely V_A which is normally smaller than V_E. Because after this phase, there is an isometric contraction phase, where there is no change in the size of the magnitude again, the volume of the heart chambers do not change. Thus, the components for measuring LA pressure can be collected, namely: - geometric LA volume, so that the blood volume in LA can be calculated, so that the amount of blood mass that will press against the LA stereometric wall is a force (F = Force). - LA area dimensions can be calculated using stereometric mathematics. Blood flow or displacement from LA to LV, defined from LA midpoint to LV midpoint or modified from LA basal to mitral valve cross section, the distance or distance (d) can be determined.[11]

In the phase of ejection of blood into the Aorta is also due to LV contraction which is an electrical stimulation of the LV, seen from the ECG picture with QRS complex. Then begins the relaxation phase (diastole), in which LV pressure decreases and muscle tone decreases. Meanwhile the LA is filled with blood volume that has returned from oxygenation in the lungs, the pressure in the LA increases while the pressure in the LV decreases, so that the Mitral valve opens, massive LV filling occurs.[11] While filling the LV, there is a replenishment of blood to the LA. At the end of diastole, LA contraction occurs which is indicated by a P wave on the EKG and a wave on the LA pressure curve, and LV filling is seen which is described as an A wave which is a velocity so it is named VA. The final pressure in the LV is LVEDP (Left ventricular end diastolic pressure). This LVEDP pressure is equivalent to LA pressure and is also equivalent to PAWP (Pulmonary Artery Wedge Pressure).[12]

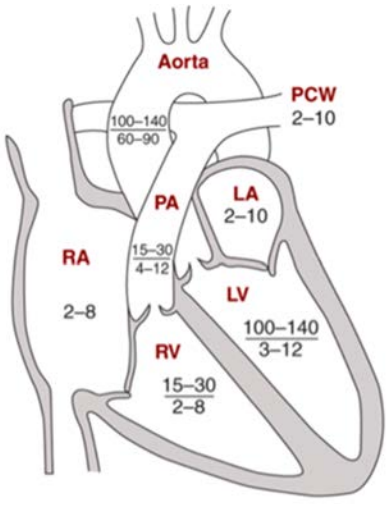

Figure 2. Normal Cardiac Pressure.[5]

Based on that condition, Pulmonary artery wedge pressure (PAWP) can be estimated using new formula that we proposed using calculation of the conversion of the value of V_A to the PAWP value (PC) equivalent to P_{LA} (pressure on the LA area). This pressure stereometrically caused by the suppression of the blood volume contained in the LA in the end diastolic phase. The final new simplified equation formula to calculate PAWP:

$$P_{LA} = 18{,}525 \times V_A^2 \text{ mmHg } (V_A \text{ on m/s})$$

In determining the geometry calculation, because the shape of the heart resembles the shape a tube and also the length of the outer curved line is approximately equal to the height, it will have an error factor value for the final number of the constant 18.525. To determine the value of this error factor, it is actually necessary to compare it with the Swan Ganz catheter examination, which is the gold standard method for determining PAWP. However, it is expensive, invasive, and there is also no medical indication for healthy people.

Amr Abbas et al, using subjects with cardiovascular and pulmonary disease, compared the results of Echo directly, namely TRV (Tricuspidal Regurgitas Velocity) with a right heart catheter and obtained PVR (Pulmonal Vascular Resistant) values.[13] The Amr Abbas Formula would be (sensitivity 77% dan specivicity 81%):

$$PVR = TRV/TVI_{RVOT} \times 10 + 0{,}16$$

Nagueh S et al, performed simultaneous examination of HF patients with Doppler echo and invasive.[10] The researcher used the components: e' and E velocity of the Mitral valve. The Nagueh formula is as follows:

$$PCWP = 1{,}24^* (E/ e') + 1{,}9$$

$$e' = (e'_{lat} + e'_{med}) /2.$$

The mean value of the early diastolic velocity of the mitral annulus is e'. E is the mitral inflow velocity in early diastolic. The Echo mode used to determine e' is TDI (Tissue Doppler Imaging), by measuring the velocity of blood flow in the myocardial tissue at the angles of the mitral annulus septal and lateral during the early diastolic phase. By using the ratio E/e', it is possible to determine the approximate size of the PCWP, the sensitivity and specificity are 66% and 50%. It is necessary to compare the PAWP results according to the new formula with the Nagueh formula as validation.

Statistical analyses were performed with SPSS version 25.0 for Windows. The baseline subject characteristics were expressed as mean and minimum-maximum values or frequency and percentages for categorical data. Normally distributed data were presented as mean and analyzed using Student's t test for comparisons of baseline characteristics and parameters between groups. Non-parametric data were analyzed with Mann-Whitney U test. Fisher's exact test was used for univariate analysis to look for association between various factors. A value of $p < 0.05$ was considered significant. Spearman's correlation analysis was used to assess the possible correlation between OSA and clinical data or echocardiographic variables.

To identify significant independent determinants of resting and dynamic LV diastolic function in OSA patients, their individual association with echocardiographic variables was assessed by multivariate analysis, using a bidirectional stepwise regression.

RESULTS

Of 82 patients in this study, 48 (58%) were male and 34 (41%) female, with mean age was ± 49 (40-51) years. Subjects in the OSA group were 65% male and 34% female with mean age ± 49 (42-52) years than those in the non-OSA group 31% male and 68% female with mean age ± 40 (30-49) years with p value < 0.01. The mean BMI measured in all study subjects was 32.60 ± 4.76 kg/m^2. Subject in the OSA Group had a BMI 32.87 ± 5.24, while those in the non-OSA group 32.42 ± 3.81 but BMI did not significantly different between the 2 groups (p=0.75).

The following variables were included into the analysis: age, gender, systolic and diastolic blood pressure, body mass index (BMI), neck circumference, mid upper arm circumference, waist circumference, fat percentage, muscle mass, visceral fat, Mallampati score, and laboratory parameter such as HbA1c and soluble ST-2 and standard echocardiographic measurements.

From all obese subjects included in this study, there were 66 subjects (80.5%) had obstructive sleep apnea, and 16 subjects (19.5%) did not have obstructive sleep apnea. The mean AHI was 9 to 47 events per hour in OSA group and 5 to 34 events per hour in all subjects. Baseline subject characteristics are presented in **Table 1**.

Fat percentage was found to be higher in the non-OSA group (37.95 (30.68-42.23)) than in the OSA group (30.70 (28.55-38.90)) and were considered significant with p value 0.04. While for muscle mass and visceral fat was found to be higher in the OSA group 28.30 (22.70-29.95) and 19.83 ± 6.33 respectively, although that two variable were not significant with p value 0.07 and 0.32.

There were 10 (15.2%) subjects with OSA have abnormal diastolic dysfunction, while all 16 subjects without OSA have normal diastolic function, without significant correlation among subjects with OSA and no OSA. According to the standard classification, all 10 subjects with OSA are considered to have diastolic dysfunction grade I. However, derived indices of diastolic dysfunction showed significant differences (p value = 0.01), with E/e' as a central parameter, increased with presence of OSA. Left atrial volume as a marker of left atrial size correlated significantly with OSA (p value = 0.01).

Table 1. Subject characteristics.

Variable	All n = 82	No OSA (AHI < 5) n = 16	OSA (AHI ≥ 5) n = 66	p value
Age (years)	49 (40-51)	40 (30-49)	49 (42-52)	< 0.01
Gender, Male	48 (58%)	5 (31%)	43 (65%)	
Gender, Female	34 (41%)	11 (68%)	23 (34%)	
Systolic Blood Pressure (mmHg)	140 (128-147)	132 (128-139)	141 (127-149)	0.05
Diastolic Blood Pressure (mmHg)	90 ± 11	87 ± 9	91 ± 11	0.18
Waist Circumference (cm)	105.03 ± 10.03	102.88 ± 11.47	106.02 ± 10.24	0.28
Mean Upper Arm Circumference (cm)	35.72 ± 3.65	35.41 ± 3.33	36.01 ± 3.96	0.58
Neck Circumference (cm)	40.00 (36.58-43.00)	38.50 (36.25-41.63)	41.00 (36.80-43.00)	0.32
BMI	32.60 ± 4.76	32.42 ± 3.81	32.87 ± 5.24	0.75
Fat Percentage (%)	31.90 (28.65-40.25)	37.95 (30.68-42.23)	30.70 (28.55-38.90)	0.04
Muscle Mass	27.45 (22.03-29.78)	23.00 (21.30-28.78)	28.30 (22.70-29.95)	0.07
Visceral Fat	19.39 ± 6.20	18.06 ± 5.84	19.83 ± 6.33	0.32
Mallampati Score	2 (1-3)	2 (1-2)	2 (1-3)	0.09
HbA1c (%)	5.80 (5.40-6.23)	5.55 (5.40-5.98)	5.80 (5.50-6.30)	0.13
sST2 (ng/mL)	13.12 (10.49-18.43)	12.28 (9.12-16.87)	13.13 (10.72-18.65)	0.39

Table 2. Polysomnographic variables.

Variable	All n = 82	No OSA (AHI < 5) n = 16	OSA (AHI ≥ 5) n = 66	p value
AHI (events/hour)	12 (5-34)	3 (2-3)	20 (9-47)	< 0.01
Lowest SaO2 (%)	81 (75-87)	87 (84-90)	79 (72-85)	< 0.01
ODI (%)	21 (11-42)	8 (6-11)	27 (17-58)	< 0.01
Arousal Index (events/hour)	42 (34-48)	43 (36-48)	41 (33-51)	0.75
Sleep Duration (minute)	300.73 ± 161.43	340.69 ± 116.92	286.77 ± 166.67	0.23

Table 3. Echocardiographic characteristics.

Variable	All n = 82	No OSA (AHI < 5) n = 16	OSA (AHI ≥ 5) n = 66	p value
Ejection Fraction (%)	71.34 ± 6.29	71.44 ± 5.60	71.09 ± 6.61	0.85
Diastolic Dysfunction	10 (12.2%)	0 (0%)	10 (15.2%)	0.20
TAPSE	2.40 (2.18-2.60)	2.50 (2.33-2.98)	2.40 (2.10-2.60)	0.07
E/A Ratio	1.04 (0.51-2.39)	1.28 (0.62-2.39)	0.98 (0.51-1.72)	0.04
E/e'	7.78 (0.47-14.85)	6.41 (0.53-9.42)	8.11 (0.47-14.85)	0.01
S'	13 (11-14)	13 (12-14)	12 (11-14)	0.96
Deceleration Time	193.17 (77-311)	176.50 (119-303)	197.21 (77-311)	0.03
LA Volume (ml/m^2)	23.04 (11.94-34.92)	20.47 (13.45-28.46)	23.67 (11.94-34.92)	0.01
Pulmonary Artery Wedge Pressure (mmHg)	10.14 (8.01-13.07)	8.07 (6.07-9.48)	10.70 (8.07-13.07)	< 0.01

**Using New PAWP Formula*

Of note, this study time measured in both groups also showed difference with p value 0.03. There was a significant difference in non-invasive measurement of PAWP between OSA group and non-OSA group with p value <0.01 and measured higher in the subjects with OSA (10.70 (8.07-13.07)) than in the non-OSA group (8.07 (6.07-9.48)). Echocardiographic measurements are outlined in **Table 3**.

The equation derived was then tested prospectively in obese population for the prediction of PAWP. Further analysis was performed to compare subjects with high PAWP and group with normal PAWP, in OSA group study. Of the 66 subjects with OSA, there were 23 subjects who had higher PAWP.

In subjects with OSA, there were significant differences in systolic blood pressure, HbA1c, and ejection fraction between subject group with abnormal PAWP and normal PAWP. Systolic blood pressure was found to be significantly higher in the OSA group with high PAWP values (146 (139-155)) compared to the OSA group with normal PAWP values (140 (122-145)). HbA1c values were also found to be significantly higher in the OSA group with high PAWP values (6.00 (5.50-7.43)) than in the OSA group with normal PAWP values (5.70 (5.40-6.05).

In addition, the OSA group with high PAWP values had a significantly higher ejection fraction value (74.22 ± 5.54) compared to the OSA group with normal PAWP values (69.42 ± 6.58).

Multiple stepwise logistic regression analysis was performed with variables, including age, fat percentage, AHI, ODI, lowest SaO2, and echocardiographic variables such as E/e', E/A, LA volume, deceleration time, and pulmonary artery wedge pressure calculated. This analysis showed that E/e' and deceleration time was the predictor of diastolic dysfunction.

Table 4. Multivariate analysis to identify predictors of diastolic dysfunction.

Variable	OR (95% CI)	Correlation Matrix (R^2)	p value
Age	0.967 (0.662-1.236)	-0.449	0.69
Fat Percentage (%)	1.000 (0.840-1.191)	-0.352	0.99
AHI	1.003 (0.906-1.112)	0.061	0.94
ODI	1.017 (0.909-1.137)	-0.259	0.77
Lowest SaO2	1.015 (0.904-1.139)	-0.554	0.80
E/e'	1.874 (1.052-3.340)	-0.169	0.03
E/A	0.001 (0.000-1.027)	-0.380	0.05
LA Volume (ml/m^2)	1.149 (0.879-1.502)	0.009	0.30
Deceleration Time	1.032 (1.005-1.059)	-0.393	0.02
Pulmonary Artery Wedge Pressure	0.904 (0.662-1.236)	-0.060	0.52

DISCUSSION

The mean LA pressure is the source pressure for LV filling, determining the LV filling pressure is a key element in the diagnosis and management of patients with suspected decompensated heart failure. Measurement of the pulmonary capillary wedge pressure with the Swan-Ganz catheter has become the gold standard for determining LV filling pressure. This invasive procedure is more expensive and produce complications, especially in critically ill patients. Two randomized clinical studies found no benefit from the use of the Swan-Ganz catheter to manage critically ill patients. Thus, A reliable non-invasive method for determining LV filling pressure is needed.[9]

Although right heart catheterization remains the gold standard for measurement of intracardiac pressures, enthusiasm for placement of Swan–Ganz catheters has dwindled over the past decade on account of complications that include infection, cardiac perforation, and tamponade. In addition, the use of Swan-Ganz Cathters is commonly used in the sick population so that it requires measuring the use of a catheter.[14]

In healthy populations, measurements can be performed noninvasively using Doppler echocardiography in an outpatient setting that is more cost-effective. Doppler echocardiography is generally acknowledged to be a noninvasive alternative to Swan–Ganz catheterization. Hitherto, a number of noninvasive Doppler echo measurements of left ventricular (LV) filling pressure, right atrial pressure, and cardiac output and the changes following load interventions have correlated closely with measurements made by Swan–Ganz catheterization.[13]

Pulmonary vascular resistance (PVR) is a hemodynamic variable that contributes to the management of patients with advanced cardiovascular and pulmonary conditions. Based on the formula issued by Abbas et.al , doppler echocardiography may provide a reliable, non-invasive method to determine PVR using mean pulmonary artery pressure and pulmonary artery wedge pressure (PAWP) or cardiac output. The weakness of this formula is there must be a pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP) and mean pulmonary artery pressure (MPAP) value. However, the formula is directly related to transpulmonary pressure gradient (Δp) and inversely related to transpulmonary flow (Qp).[13]

The term PAWP is used interchangeably with pulmonary capillary wedge pressure and pulmonary artery occlusion pressure in the general literature.[10] Non-invasive measurement of PAWP is useful for the evaluation intravascular fluid volume and pressure status to identify diastolc dysfunction. Nagueh formula can be used for calculation of PAWP from the Doppler derived mitral E/e' ratio. PAWP is usually equal to the left atrial pressure and hence the left ventricular filling pressure. E' (Ea) has been considered as a preload independent index of left ventricular relaxation. Nagueh formula uses mitral E velocity during early diastolic flow corrected for the influence of left ventricular relaxation (E/e' ratio) to estimate the mean PAWP. Nagueh formula: PAWP = 1.24 [E/e'] + 1.9. Ea was taken from the lateral mitral annulus in the pioneering study of Nagueh SF et al. patients had invasive measurement of PAWP and simultaneous Doppler echocardiography.[9]

In addition, the formula proposed by Vladislav et.al also plays a role in determining PAWP using echocardiography. In his research tricuspid regurgitation velocity (TRV), average E/e′ ratio, LV ejection fraction (LVEF), RV fractional area change (RVFAC), IVC diameter, and left atrial volume index (LAVi) were found to be independent predictors of PAWP ratio without any evidence of multicollinearity between variables. The model accurately identified patients with precapillary, isolated postcapillary, and combined PH, with no cases of undetermination and outperforming current echocardiographic algorithms, by using variables routinely acquired in echocardiographic laboratories.[15]

This present study compared PAWP with the value predicted using standard tissue Doppler measurement method validated by Nagueh et al.[9] and it is found that PAWP derived using these 2 methods has fair correlations, suggesting that this method will give similar results to the tissue Doppler method in most examples. Diastolic dysfunction significantly associated with pulmonary artery wedge pressure

measured using proposed formula (R = 0.240, p value = 0.030). These results emphasize the pathophysiologic process of passive pulmonary hypertension; namely, that increased left atrial pressure will necessitate a higher driving pressure across the pulmonary capillary bed.[11] At present, echocardiography is the only non-invasive technique that allows estimation of pulmonary and LV filling pressures in HF).

Precisely defining the role of OSA in the origin of some cardiovascular complications has been difficult for several reasons. One limitation

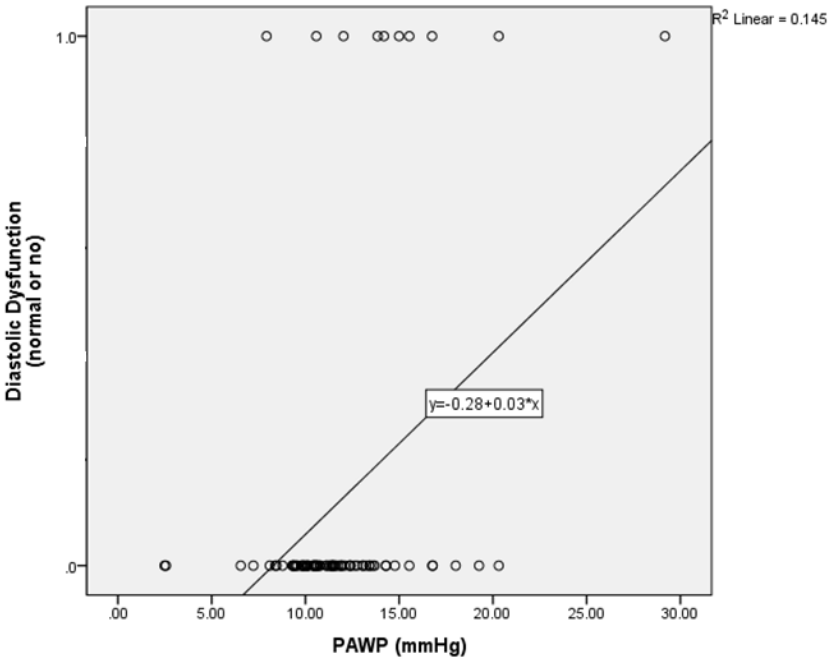

Figure 3. Spearman Correlation between PAWP and Diastolic Dysfunction

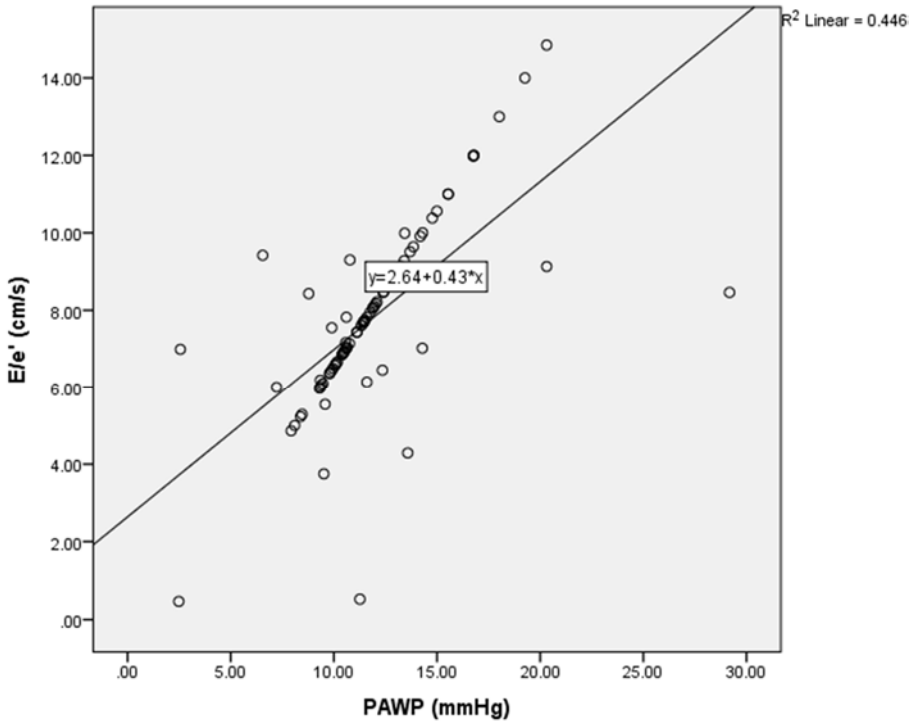

Figure 4. Pearson Correlation between PAWP and E/e'

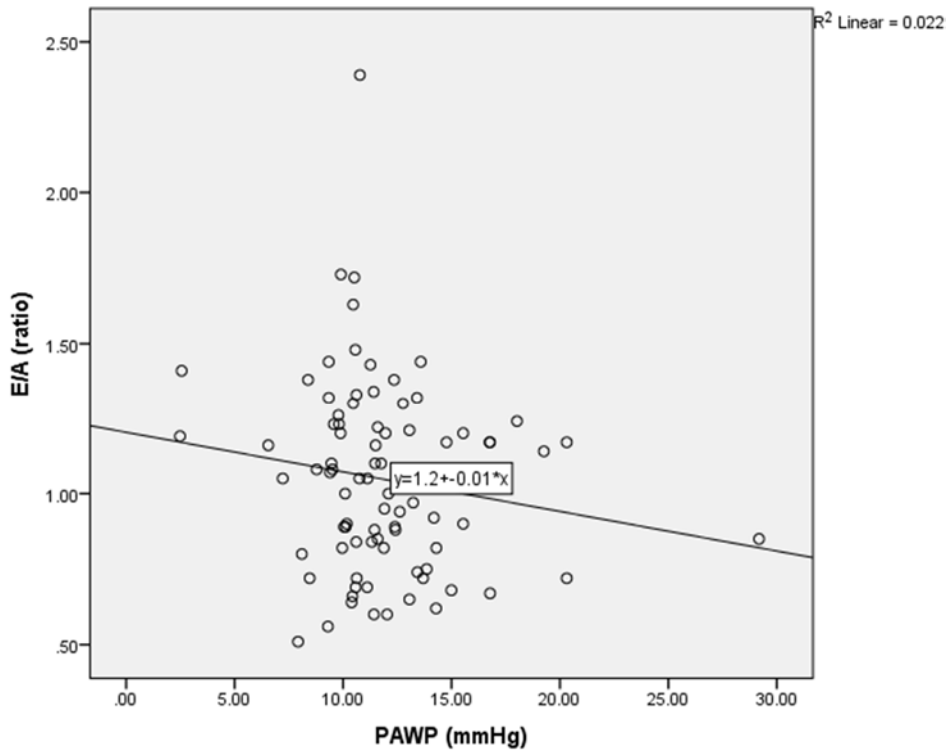

Figure 5. Pearson Correlation between PAWP and E/A

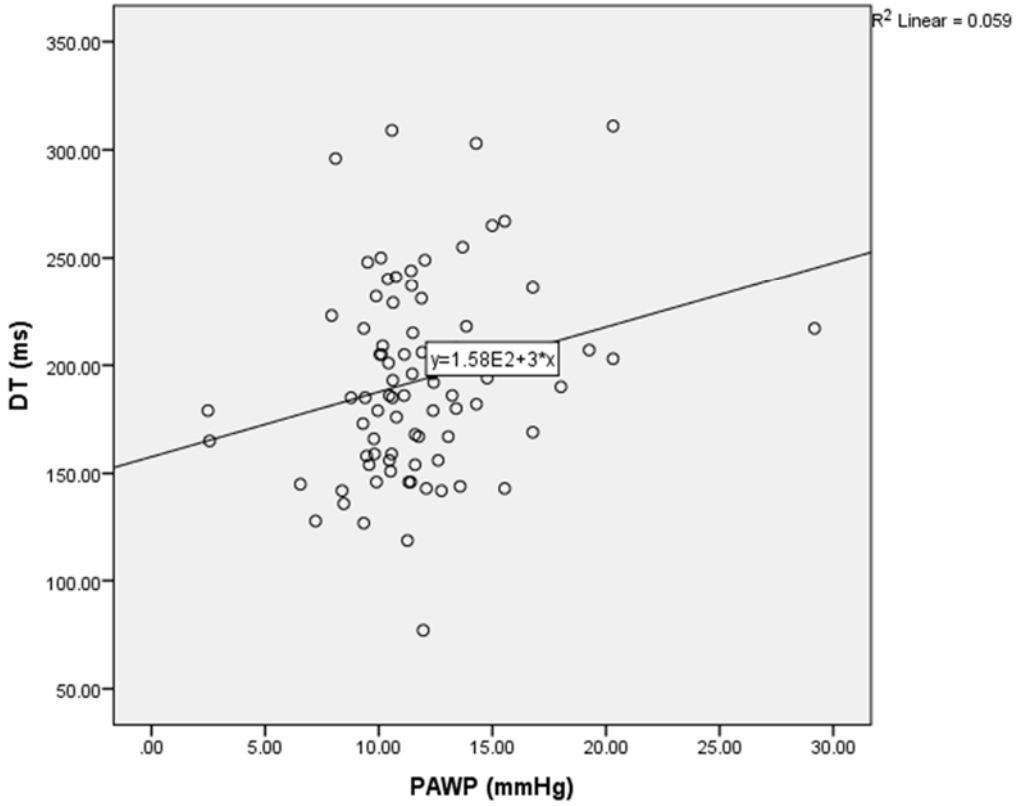

Figure 6. Pearson Correlation between PAWP and DT

Table 5. Comparison between The New PAWP Formula, Nagueh Formula, and Abbas Formula [16]

	The New PAWP Formula	Nagueh et al. Formula	Abbas et al. Formula
Formula	P_{LA} = 18,525 x V_A^2 mmHg (V_A^2 on m/s)	PCWP = 1,24* (E/ e') + 1,9. e' = (e'$_{lat}$ + e'$_{med}$) /2.	PVR= TRV/TVI$_{RVOT}$ x10 + 0,16
Research Population	Obese with Obstructive Sleep Apnea patients	Heart failure patients	Cardiovascular and pulmonary disease patients
Strengths	This formula has more complete parameters and does not require tricuspid regurgitation to be used	This formula does not require tricuspid regurgitation to be used	This formula had been validated by the Swan-Ganz catheter
Weaknesses	This formula had not been validated by the Swan-Ganz catheter	Other echocardiographic and even invasive measurements should be used to supplement the E/e' parameter in some cases.	This formula requires a tricuspid regurgitation condition on patients

has been the various methods by which the diagnosis of pulmonary hypertension is made in studies of subjects with OSA, many by way of Doppler echocardiography, with varying pulmonary artery pressure thresholds.

This study used echocardiographic procedures to assess the impact of OSA on cardiovascular function and structural without symptoms of heart failure. Subjects with OSA jshowed a decreased in E/A ratio, higher LA volume and deceleration time compared with subjects with no OSA. All subjects with OSA manifest diastolic dysfunction, while none of the subjects without OSA have abnormal diastolic function. However, this difference was not statistically significant between the two groups. Various mechanisms might explain the presence of diastolic dysfunction in OSA patients. Patients who experience chronic hypoxemia, which might result in abnormalities of myocardial relaxation because of myocyte hypoxia due to intracellular calcium transport disturbances.[16]

The results of this present study suggest that subjects with OSA have changes in pulmonary hemodynamics. Obstructive sleep apnea can be assimilated to a Müller's maneuver, which is an inspiratory effort against a closed glottis, and the PAWP reflects the changes in intrathoracic pressure; the latter may decrease by as much as 30 mmHg during an OSA, with a subsequent fall of PAWP which decreases to negative values.[17]

These results are in accordance with the research conducted by Solin et al. which analysed sleep-disordered breathing with hemodynamic parameters. From this study, the group with sleep disorders had higher PCWP and pulmonary artery pressure (PAP) values compared to the control group or the group without sleep disorders.[18] Other studies have also shown that PAWP experienced significant changes during the cycle in patients with OSA.

It has been shown that OSA patients might have an increased in left ventricular mass, and alterations of the neurohumoral system might contribute to the elevation of pulmonary artery pressures and PCWP in patients with OSA.

Diastolic dysfunction is a condition with increased resistance to filling of the left ventricle, leading to an inappropriate rise in the diastolic pressure-volume relationship and causing symptoms of pulmonary congestion during exercise. The potential mechanisms leading to changes in cardiac structure and function in patients with OSA have been studied in animal models. Fletcher et al demonstrated ventricular hypertrophy in rats exposed to short bursts of repetitive hypoxia over an extended period and that intermittent severe hypoxia can lead to a sustained rise in BP within 35 days.[4] Diastolic dysfunction leads to elevated left atrial filling pressures which are transmitted to the pulmonary venous system. Long standing elevation in pulmonary venous pressures leads to secondary changes in pulmonary vascular resistance.

CONCLUSION

The pulmonary artery wedge pressure (PAWP) is a surrogate marker of left atrial pressure and chronic airflow obstruction is the most important cause of pulmonary artery remodelling, that

can lead to diastolic dysfunction. This study has proved echocardiography can be replaced invasive cardiac catheterization to assess LV filling with high feasibility and good accuracy to estimate LV filling pressure that leads to diastolic dysfunction.

The new mathematical formula based on echocardiographic variables had a good accuracy because it can estimated indirectly the LA pressure and PAWP which can described the stage of diastolic dysfunction and it could be readily applied in daily clinical practice.

Obstructive sleep apnea is one of the health problems that may lead to cardiovascular complications. This study showed that patients with OSA have a higher risk of cardiovascular remodeling than those without. Obscure cardiac comorbidities may be present in patients with significant OSA. It is highly recommended for patients with OSA to have routine echocardiogram, as development of cardiovascular morbidities is common and proper treatment should not be delayed.

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