Clinical study of patients with primary pulmonary hypertension (PPH)

Alaa A. Abbood AL-Kinani* **FIBMS (Cardio.)**

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Abstract:

Background: Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). Although there is some underestimation and overestimation of PAP between transthoracic Doppler echo (DE) and RHC, Doppler echo remains an indispensable screening tool for the assessment of PH.

Objective: clinical evaluation of patients with primary pulmonary hypertension (PPH) and assess vasoreactivity testing to identify patients who may benefit from long term therapy with calcium channel blockers (CCBs).

Patients and methods: This prospective study was performed in the cardiac catheterization division in Al-Zahraa teaching hospital in Al-Kut. We studied the prevalence of certain variables among forty two patients with PPH from "March 2014 to Nov 2016" including the clinical triggers, electrocardiographic (ECG) changes, Echocardiographic variables , RHC and vasoreactivity test with intravenous adenosine to identify acute positive responders and long term responders to CCB.

Results: A total of forty two patients, female to male ratio were 2.8:1 with a mean age of 38±10(years). Dyspnea is a common clinical trigger (85%). Abnormal ECG was found in (90.5%) of patients, the majority had right ventricular hypertrophy (RVH) (76.2%). Echocardiographically all patients had RVH. There was some differences in mean PAP (36±4.9mmhg) derived by DE from that obtained by RHC (47±4.78mmhg). RHC reveal that 6 patients (15.78%) were acute positive responders to intravenous adenosine and about 4 patients (66%) were long term responders to CCB during 3months follow up echocardiography.

Conclusions: There is some discrepancy in the mean PAP between Doppler echo and RHC within ±10 mm Hg for pulmonary artery pressure estimates. 15.7% of patients at RHC were acute positive responder to intravenous adenosine and half of them were long term responder to CCB.

Keywords: Clinical, pulmonary, hypertension

Introduction:

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition characterized by elevated mean pulmonary arterial pressure ≥25 mmHg at rest as assessed by echo study and RHC (1). Normal value of the mean PAP at rest is 14±3 mmHg, reaching up to 20 mmHg in selected cases (2). PAH is characterized by the pre-capillary PH and increase in pulmonary vascular resistance caused by inflammation, vasoconstriction, thrombosis, proliferative and obstructive remodeling of the pulmonary vasculature (3, 4). Clinically the symptoms of PAH are non-specific and include breathlessness, fatigue, weakness, angina, syncope, and abdominal distension(5). Electrocardiogram reveals that RV hypertrophy is present in 87% and right axis deviation in 79% of patients with IPAH. Supraventricular arrhythmias including atrial fibrillation and atrial flutter lead to further clinical deterioration and present mainly in advanced stage of disease (6). In IPAH chest x-ray is abnormal in 90% of patients and there is no correlation between the degree of PH and the extent of radiographic abnormalities (5).

* *Al-Zahraa teaching hospital in Al-Kut*
Email: dr-alaakinani@yahoo.com

Transthoracic echo should always be performed in the cases of suspected PH to measure certain echocardiographic parameters which correlate with RHC indices(7). Unfortunately, despite the strong correlation of the tricuspid regurgitation velocity and tricuspid regurgitation pressure gradient, Doppler estimation of PAP may be inaccurate in the individual patients(8). Echocardiographic criteria for diagnosis of PH include tricuspid regurgitation velocity >3.4 m/s, PA systolic pressure >50 mmHg, with or without additional variables suggestive of PH that include an increased pulmonary valve regurgitation velocity, increased RV and RA dimensions , interventricular septum abnormality, increased RV wall thickness, and dilated main PA(9). RHC is indicated in all patients with PAH to confirm the diagnosis, to evaluate the severity and to test the pulmonary vasoreactivity (I C) (1). When performed in experienced centers, RHC procedures have low morbidity (1.1%) and mortality (0.055%) rates(10). Vasoreactivity testing should be performed during RHC to select patients who are candidate for long term therapy with calcium channel blockers (CCBs) (1). Vasoreactivity test should only be performed with short acting and safe drug .The drug most currently used in acute testing

is NO, alternatively intravenous (i.v.) epoprostenol or i.v. adenosine may also be used (IIbC)(1). Follow up strategy is recommended every 3–6 months (1c) including clinical assessment, functional class, 6 minute walking test(6 MWT), echocardiography and RHC(11). Modern drug therapy and combination therapy leads to a significant improvement in patients' symptomatic status and a slower rate of clinical deterioration with 43% decrease in mortality and a 61% reduction in hospitalizations(12) .

Patients and Methods

This prospective study carried out in cardiac catheterization division in Al-Zahraa teaching hospital in Al-Kut .We studied 42 patients with PPH from "March 2014 to Nov 2016" after exclusion of other classes of PHT. The clinical triggers leading to referral to our cardiac clinic include onset of cardiopulmonary symptoms, loud p2 and or heart murmur , abnormal ECG and suspicion of coronary artery disease . Each patient had full history, clinical examination, ECG ,CXR, echocardiography, TEE, pulmonary function test ,CT angio and RHC. CT scan of chest(to exclude interstitial lung disease and emphysema) , blood test and immunology(to exclude connective tissue disease),US of abdomen(to exclude liver cirrhosis and/ or portal hypertension).

Definition of clinical variables:

1-Age (in years) and gender.

2-Clinical triggers: include history of chest pain , dyspnea, palpitation, fatigue and syncope.

3-ECG: RVH was analyzed from common diagnostic criteria for RVH, right atrial dilatation (RAD) and RT axis deviation from common diagnostic criteria for left and right atrial abnormalities and supraventricular arrhythmias including atrial flutter and fibrillation (13)

4-Echocardiography: Echo studies were performed with commercially available instruments GE Vived E9. A complete two-dimensional echo study was performed with parasternal, subcostal and apical four chamber views for evaluation of RV dimension ,RA dimension(8) and TAPSI(tricuspid annular plane systolic excursion)(14) . PA diameter assessed from parasternal short axis view(8). The TR velocity and pressure gradient was estimated with continuous wave Doppler for evaluation of PA systolic pressure = TR pressure gradient+ estimated RAP. Right atrial pressure (RAP) can be estimated based on the diameter and respiratory variation of the inferior vena cava although often a fixed value of 5 or 10 mmHg is assumed. Mean PAP = 0.61 * PA systolic pressure + 2 mmHg. (Definition of PH as mean PAP ≥25 mmHg) (15).

5-RHC: Right heart catheterization was performed in the cath lab (Philips cath lab) by femoral venous and arterial access and using 6F JL, JR, Pig tail and Gensini catheter. We measure the following parameters:

a- RA pressure

b- RV pressure

c- PAP (systolic ,diastolic and mean), mean PAP=(2*DP)+SP/3

d- PCWP (pulmonary capillary wedge pressure)

e- Venous and arterial oxygen concentration

f- CO(Cardiac output) :by Fick method using following equation . CO=VO2/(Ca-Cv) while VO2 is the oxygen consumption and its estimated as resting metabolic consumption of oxygen is 3.5 ml of O2 per kg per minute, or 125ml O2 per square meter of body surface area per minute. Ca arterial oxygen concentration and Cv is venous oxygen concentration.

g-PVR (Pulmonary vascular resistance):measured by PVR = 80*(PAP – PCWP)/CO, normal 100-200 dyn-s/cm5 (16).

h-Vasoreactivity test: by using iv adenosine 50-350 mg/kg/min over 2 minute with increment of 50mg /kg/min and repeat measurement of mean PAP,CO,PCWP,PVR. A positive acute response is defined as a reduction of mean PAP ≥10 mmHg with an increased or unchanged CO.(16) and decrease of PVR >33% ;ideally below 6 unit (17).

i-Follow up echocardiography: 3 months follow up echo for assessment of mean PAP in acute positive responder patients after giving CCB(60 mg diltiazem 3 times daily or amlodipine 2.5 mg daily as a starting dose and increasing gradually (18).

Statistical analysis: Standard statistical analysis was done using SAS program run in IBM computer. Proportion was tested by using the number (No.) and percent (%) for most clinical variables and Mean± SD for some echocardiographic and RHC variables.

Results:

A total of forty two patients with PPH had a mean age of 38.24±9.9 (years). Table 1 shows distribution of studied sample according to their age and gender and clinical triggers .Female to male ratio were 2.8:1. Dyspnea is a common clinical trigger (85%)

Table 1: Age, gender and clinical triggers of studied patients with PPH

Patients(N)	**42**
Age(mean± SD)	38.24±9.9
Gender	
Male	11(26.1%)
Female	31(73.8%)
Dyspnea	36(85%)
Chest pain	10(23.8%)
Fatigue	12(28.5%)
Syncope	4(9.5)

Table 2 shows the ECG variables in patients with PPH. Abnormal ECG was found in 38(90.5%) patients, while 4(9.5%) patients had normal ECG. The majority had RVH 32(76.2%).only 3 patients had supraventricular arrhythmia including AF and atrial flutter

Table 2: ECG variables in patients with PPH

Variables	N	%
Normal ECG	4	9.5%
RVH	32	76.2%
Right Atrial Dilatation	22	52.38%
Right Axis Deviation	27	64.28%
Atrial Fibrillation	2	4.76%
Atrial flutter	1	2.38%

Table 3 shows the echocardiographic variables of patients with PPH. All patients had mean PAP >30 mmhg . RVH was found in majority of patients

Table 3: Echocardiographic data of patients with PPH

Variables	(Mean± SD)
Mean PAP(mmhg)	36±4.9
RVH(mm)	7.7±1.6
RV dilatation(mm)	37.76±2.25
RA dilatation(mm)	48.76±2.25
TAPSE(mm)	25.16±4

Table 4 shows RHC and vasoreactivity test in Thirty eight patients with PPH. Majority of patients had mean PAP ≥ 40 mmhg . PVR are elevated in majority of patients reaching more than 400 dyne-sec.cm−5. All patients had normal cardiac output and PCWP. RVSP are equal to PASP. 6 patients 15.78% were acute positive responders to iv adenosine .

Table 4: Right heart catheterization and vasoreactivity test of Thirty eight patients with PPH

Variables	N (38)
RA pressure(mmhg)	11.9±1.71
RV pressure(mmhg)	47±5.14
Mean PAP(mmhg)	47±4.78
PCWP(mmhg)	9.2±1.6
Cardiac output(L/min)	4.3±1.7
PVR(dyne-sec.cm^{-}**5)**	599±207
Vasoreactivity test	**N(%)**
Positive responders	6(15.78)
Negative responders	32(84.21)

From comparing table 3 and 4, there was differences in mean PAP derived by Doppler echo (36±4.9mmhg) and mean PAP obtained by RHC (47±4.78mmhg).

Table 5 show three months echo follow up of acute positive responders by RHC .Four of six patients (66.66%) revealed decrease of mean PAP to normal or near normal value (positive responders) after giving CCB for three months.

Table 5: Three months echocardiographic follow up of acute positive responder patients with PPH

Long term responder to CCB N(%)	
Positive responder	4(66.66)
Negative responder	2(33.33)

Discussion:

This study focused on clinical evaluation of patients with PPH including history, examination, ECG, echocardiography and RHC with vasoreactivity test .The present study estimated that high prevalence of the disease in females and in patients younger than 50 years of age and this agreed with a study done by Rich S et al(19) . Initial reports from the National Institutes of Health in the 1980s reported the mean age at diagnosis of PAH was 36 years and the female-to-male ratio was 1.7 to 1. Interestingly, the age at diagnosis and gender distribution of PAH may be evolving as more studies report a mean age at diagnosis of 50 years and higher female-to-male ratios. The reason for these shifts remains unclear (20). The present study demonstrates that large number of studied samples are presented with dyspnea (85%) . In our study almost (76.2%) of patients presenting with demonstrable echocardiographic evidence of PH had RVH criteria on ECG and (64.28%) had RAD ,(9.5%) had normal ECG and these data agreed with Rich S et al(21) and Tongers J et al(22) , they explained this by the absence of these findings does not exclude the presence of PH or severe hemodynamic abnormalities and the sensitivity and specificity of ECG for detecting significant PH was (55%) and (70%) respectively. Supraventricular arrhythmia including atrial fibrillation and flutter found in nearly 7% in our study and this often resulting in clinical deterioration, RV failure and increased mortality as Tongers J et.al said (22). Although there is some discrepancy of PAP between transthoracic Doppler echo and RHC in our PH patients, Doppler echo remains an a screening tool for the assessment of PH; however, we should not be entirely depend on Doppler pressure measurement alone in the initial evaluation of patients with suspected PH. In patients with severe TR The use of the simple usual method for pressure estimation may lead to underestimation of pulmonary artery systolic pressure. Consequently, estimation of PAP based on Doppler transthoracic echocardiography measurements is not suitable for screening for mild, asymptomatic PH(8). PASP was affected by age, BMI, sex, wall thickness, and ejection fraction (23). Moreover, it cannot be assumed that Doppler echo does not replace RHC for definitive hemodynamic assessment of known or suspected PH (24). Right heart catheterization was performed on 38 patients with PH .We document that those patients had PPH from normal range of CO, normal range of mean PCWP and absence of intracardiac shunt (25). There is some discrepancy in mean PAP from DE with 95% accuracy limits within ±10 mm Hg for pulmonary artery pressure estimates (15). From vasoreactivity test during RHC , only 6 patients (15.7%) had positive acute responder to intravenous adenosine and this agreed with Galiè_N[1]et.al and Zuo_XRet.al who showed that acute vasoreactivity testing with intravenous adenosine was safe and able to screen responders to CCB therapy in patients with IPAH(26) and only those patients in whom a reduction of PVR of ≥ 20% is associated with a decrease in PAP of ≥ 20% should be considered as responders to the acute test . In clinical studies only 20-30% of the patients are short term responders and vasoreactivity test with short acting agent during

RHC are recommended to select patients who may respond to long-term treatment. (27). Tonelli_AR demonstrates that a positive vasoreactivity test predicts a better response to (CCB) and improved survival. He found that a positive acute test was observed in about 10-15% of patients with idiopathic PAH and approximately half of these patients experienced long term response to CCBs. A positive acute test may select patients with an earlier or less aggressive form of disease, which may carry a better prognosis(28). All acute responders were subsequently treated with high dose CCB monotherapy and 3 months follow-up echocardiography demonstrate that 4 of 6 patients (66.6%) (10.6% of all patients) showed sustained long term response to CCB by decrease mean PAP to normal or near normal value and this agreed with Sitbon O et.al who demonstrate that long term CCB responders represent <10% of IPAH patients evaluated in a pulmonary vascular referral center(29).

Conclusions:

Most of our patients were symptomatic and dyspnea was the most common symptom (85%).There is some discrepancy in mean PAP between DE and RHC within ±10 mm Hg for pulmonary artery pressure estimates. 15.7% of patients at RHC were acute positive responder to IV adenosine and half of them were long term responder to CCB.

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