THE STUDY OF PRIMARY PULM

ONARY HYPERTENTION, CLINICAL, ECHOCARDIOGRAPHY AND CATHETERIZATION ASSESSEMENT

Dr.Talaat A. Al-Jarrah FIBMS(PED.), DCH,FIBMS(CARDIOLOGY)*

Dr. Abdulhadi H. A. Al-Kabby CABP, FIBMS(PED.),FIBMS(CARDIOLOGY)**

Dr. Jasim Nasir Al Khalidi CABP, FIBMS(CARDIOLOGY)*

Abstract

BACKGROUND: A Retrospective study of 31 patients who diagnosed as a case of primary pulmonary hypertension (PPH) in Ibn-Albitar hospital for cardiac surgery, from July 1999 to April 2007, to study the clinical pattern of PPH in children and adult, who diagnosed as acase of PPH clinically and echocardiographically and confirmed by diagnostic cardiac catheterization**. Patient and Method**: This study excluded cases of secondary PAH and those without catheterization. Two cases excluded from PPH cases (one patent ductus arteriosus-eisenminger`s syndrome and other is large sinus venosus atrial septal defect). These data were collected from medical files or catheterization files, including:(age, gender, duration of symptoms before reaching diagnosis of PPH, number of hospital admissions, signs, and symptoms of PPH, echocardiographic findings), considering pediatric age group ≤ 18year and adult >18year, and the catheterization data were: way of reaching final diagnosis in catheterization, severity of PAH and mean of MRAP, MPAP) also morbidity and mortality. **Conclusions** :the pediatric cases tend to present earlier than adult cases, Females cases more than males cases. The duration of symptoms before catheterization was short, and it was shorter in adult cases. The most common symptoms in pediatrics are(cyanosis, fatigability, and extensional dyspnea), while in adult (exertional dyspnea, chest pain and fatigability).The most common signs in pediatrics are (normal physical examination, loud second heart sound and murmur)while in adult (murmur, dyspnea, loud second heart sound). The catheterization approach to reach definite diagnosis in most pediatrics (by normal pulmonary capillary wedge pressure) while in adult (by exclusion secondary causes). **Recommendations**: atrial septal defect-sinus venosus should be considered in exclusion list of secondary PAH, familial cases need genetic analysis, loud second heart sound is important clue for PPH, especially if associated with dyspnea on exertion. Pregnancy still wanted by certain families, and counseling for patients and their families regarding risk of pregnancy is essential.

*** Pediatric Cardiologist and Interventional Cardiologist in Nasiriyah Heart Center.**

**** Pediatric Cardiologist and Interventional Cardiologist in Ibn- Al Bitar Cardiac Center.**

Introduction

Definition and classification: is a disorder with no identifiable cause in which pulmonary artery pressure at rest is above the normal of (30 mmHg systolic and 18 mmHg diastolic) in adult at sea level [1][2][3]

Common causes of pulmonary arterial hypertension:

I. Pulmonary arterial hypertension: A-Primary pulmonary arterial hypertension:1-Sporadic.2-Familial (up to25%).B-Pulmonary arterial hypertension related to: 1-Connective tissue diseases(CREST syndrome, scleroderma). 2- HIV. 3- Congenital heart disease, Eisenminger`s syndrome. 4-Porto pulmonary hypertension.5-Anorexigens.6-Primary pulmonary hypertension of the newborn.

II. Pulmonary venous hypertension:

III. Disorders of the respiratory system:

IV. Chronic thromboembolic pulmonary hypertension.

V. Disorders directly affecting pulmonary vasculature[5][6].

Epidemiology: The actual incidence of PPH appears to be approximately 2 cases per million populations, [2].**Male: Female ratio:** is range 1: 2-4 [7] equal in children [1].**Age of Diagnosis**: Range: 2-56 year, Mean: 21-30 year[1].**Race:**No racial predilection [4].

Genetics: a hereditary disease inherited as AD trait with incomplete penetrance [2]

pathogenesis: The end stage was the plexiform lesion that represents one of three major histopathologic types of PPH in WHO – classification:

(1-plexogenic pulmonary arteriopathy,2-**Microthrombotic pulmonary arteriopathy** ,3-**pulmonary veno-occlusive disease**:

Clinical Feature: Interval between onsets of clinical features till reach diagnosis about 2 years [9] [10] [11]. Most common symptoms are : extensional dyspnea (86%),fatigue and lethargy(78 %),palpitation(78 %),angina, syncope, Reynaud's phenomenon, edema and less commonly; cough, hemoptysis, hoarseness of voice (Ortner's syndrome) [12].Cough may reach 95 % in study [13].

Physical Examination: It's quite variable [4]. Loud S2and paradoxical splitting of a second heart sound as high as 82 % [13], pulmonary regurgitation (Graham Steel murmur), tricuspid regurgitation murmur, elevated Jugular venous Pressure and exhibits 2 prominent crests, A and V wave and giant V-wave reach mandible [1].Other may have: heptomegally and positive abdomino-Jugular reflex [1].

Investigations: ***1-Electrocardiogram :***[1] ***2 - Chest X-Ray*** [4] [1]. ***3- Echocardiography:***[7]

[2]. **4-Ventilation Perfusion Scintigraphy:** [7].**5-Pulmonary Function test: 6-MRI:**[7].**7-Cardio pulmonary Exercise test:** [10]. [7], [11].**8-Connective tissue & Coagulation study:**[5]**9- Lung Biopsy:**[4][11]**.10-Catheterization:** of right side of heart. Although it is less valuable before be advances in other imaging but still it gold standard [7].It is absolute requirement for confirming the diagnosis of PPH and for guiding management these done by excluding secondary causes of PAH and to measure left ventricle filling pressure accurately.

ManagementI-**Generalmeasures:*A-Physical Activity:*** graded exercise capacity (e.g. by swimming is thought safer than isometric activity)[2].***B-Medication precaution:*** Certain medications should be avoided like vasoactive decongestant, cardio depressant antihypertensive drug ,and agent that interfere with warfarin (e.g. NSAID, Antibiotics) [11][7] and appetite suppressants are trigger PPH [2].***C-Oxygen Supplement:*** Should be supplemented in high attitude or unpressurised air craft [11].***D-Diet:*** Low sodium, and low fluid diet in right ventricular failure [4].***E-Pregnancy and General anesthesia:*** should avoid pregnancy [1] [7], so contraception is mandatory [11] [7],the best contraception is surgical sterilization [2], [7].***F-Patient Education***: about mortality is paramount [4].

II -**Medical therapy:** ***A-Digoxin:***in right ventricular failure [2], [7]. [11]. ***B- Diuretics:*** To manage peripheral edema[4].[11]. ***C-Anticoagulant therapy:*** Used due to that PPH patients are at risk of thrombosis [6]. [2].**(warfarin, Heparin)**[2] [6].***D-Vasodilators:*** to decrease PAP.**(Calcium-Channel Blockers**[2]**., prostaglandins and its analogues).*E-Endotheline Blockers (ET-Blockers):*1-Bosentan:** It is non selective ET-Blocker [2], with competitive, specific and orally given[4], used as first line in treatment of PPH [11].**2-Sitaxsentan:** selective ET- Blocker, selective to receptor A and it improves exercise capacity [2].**F-*Phosphodiesrase inhibitors:* Sildenafil:** [2], beneficial [6][11].

III -**Surgical Treatment:** ***A-Balloon Atrial Septostomy (BAS):*** It acts by increase right to left shunt, although it still is considered investigational [2]. ***B-Lung Transplantation (LT):*** consequently bilateral or double or single lung transplantation had been done successfully in PPH patient [2].***C-Heart-Lung transplantation (HLT*).**It performed successfully in patient with PPH for last 15 years [7].

Clinical course and prognosis: PPH is progressive disease without specific therapy[14], its clinical course is highly variable but with right ventricular failure the patient survival is 6 months [2].***Cause of death*** 1-Progressive right ventricular failure (47%). 2-Sudden death. 3-Other causes: pneumonia or bleeding[2]. ***Prognosis:*** Mean survival rate(SR) is less than 3 years of PPH patient who without appropriate therapy [15].Five-year survival rate for PPH is according to testing vasodilator drug [2].

Aim of study:

1- To study the clinical pattern of PPH in children and adult.

2- To detect best catheterization approach in diagnosis of PPH in pediatrics and adult.

Patient and Method: A Retrospective study in 31 patients who diagnosed as PPH in Ibn – Albitar Hospital for cardiac surgery, from July 1999 to April 2007.***Inclusion criteria:*** Any case diagnosed as PPH clinically and echocardiographically which had been confirmed by diagnostic cardiac catheterization. ***Exclusion criteria:*** 1- Precatheterization diagnosis of PAH cases secondary to other causes.2- Any PPH patient, who had been diagnosed clinically and echocardiographically without catheterization.

Method: Collecting the following data from medical files or catheterization files, catheterization done in all cases.In catheterization, and two cases excluded from PPH cases (one patent ductus arteriosus-eisenminger`s syndrome and other is large atrial septal defect-sinus venosus).

Following data are collected from files:1 – Regarding all cases: The final diagnosis were obtained whether PPH or PAH secondary to other causes. 2 – Regarding PPH cases: collection of (age, gender, duration of symptoms before reaching the diagnosis of PPH, No. of hospital admissions, signs and symptoms of PPH, echocardiography findings), considering pediatric age group ≤ 18year and adult >18year.3– In catheterization: the final diagnosis was confirmed by catheterization, severity of PAH-according to MPAP (mild>20mmHg, moderate>30mmHg and sever>45mmHg) [6] and mean of MRAP, MPAP).4 –The number of morbidity and mortality.5–Any case without enough data labeled as (NAD = Not Available Data).

Results: ***No. of patients:*** The diagnosis of PPH had been confirmed by catheterization in 29 patients, which is comparable with echocardiographic diagnosis, only 2 patients of them discovered as secondary PAH.

Table 1- The demographic data in patients with PPH.

	Pediatric (%)	Adult (%)	Total No. (%)
Patient No.	9(31%)	20(69%)	29
Gender:			
Male	2(6.89%)	5(17.2%)	7(24%)
Female	7(24.1%)	15(51.7%)	22(76%)
Male: Female ratio	1:3.5	1:3	1:3.14

(P-value=0.76)

Table (1) shows that no. of patients in pediatric age group was 9 (31%), and adult patients NO. =20 (69%),Male: Female ratio in general was (1:3.14). ***Familial PPH patients:*** One patient out of total 29 patients (3.44%) was 13 year; female who had strong family history of PPH with history of multiple family deaths for same disease.

Table 2- The duration of clinical features before diagnosis by cardiac catheterization in patients with PPH.

	Pediatrics (%)	Adult (%)	Total No. (%)
< 1 month	2 (33%)	6 (46 %)	8 (42 %)
1m.-1 y.	2(33%)	4(31%)	6(32%)
1 y.-2y.	2(33%)	3(23%)	5(26%)
Total No.	6	13	19
NAD*	3	7	10

*NAD: not available data. (P-value=0.96)

Table (2) shows that 46% of adult patients diagnosed in first month of clinical feature while in pediatrics the percentage are equal in all durations (<1month, <1year and >1year),no case diagnosed after 2 years of clinical symptoms.

Table 3 –The distribution of the patients according to number of admissions to hospital in patients with PPH.

	Pediatrics (%)	Adult (%)	Total (%)
Once	6 (67%)	14(70%)	20(69%)
Twice	3(33%)	5(25%)	8(28%)
Thrice	---	1(5%)	1(3%)

(P-value=0.51)

Table (3) shows that 20 patients (69%) admitted to hospital once, while 8 patients admitted twice (28%) and only one adult patient (3%) admitted three times.

Symptoms: shows that the pediatric symptoms (Bluish skin discoloration 67%, fatigability 50% and exertional dyspnea 33%) while the symptoms in adult (exertional dyspnea 77%, chest pain 55% and fatigability 44%).

Signs: the signs in pediatrics were ;loud second heart sound(37.5%)and murmur(37.5%) ,while in adult the physical signs include; murmur(53%),and loud second heart sound(33%).

Echocardiographic finding: the most common echocardiographic data in pediatrics and adult: right atrial dilatation (100%,84%),right ventricle dilatation(100%,89%), right ventricle hypertrophy (50%,26%) and pulmonary incompetence (50%,31%) respectively.

Table 4-The methods of diagnosis in patients with PPH .

	Pediatrics(%)	Adult(%)	Total(%)
By normal PCWP	5 (63%)	4 (23%)	**9(36%)**
By exclusion secondary causes of PAH	3 (37 %)	13 (77 %)	**16(64%)**
NAD*	**1**	**3**	**4**

*NAD: not available data. (P-value=0.07)

Table (4) shows that the diagnosis of PPH in adult and pediatric: by exclusion of secondary causes of PAH(37% and 77%) while by normal PCWP (63% and 23%) respectively.

Table 5- The severity of PAH in catheterization data in patients with PPH.

Age group	Pediatrics (%)	Adult (%)	Total No. (%)
Mild	---	---	---
Moderate	1 (12 %)	6 (32 %)	**7 (26 %)**
Sever	7 (88%)	13 (68 %)	**20 (74 %)**
NAD*	**1**	**1**	**2**

*NAD: not available data. (P-value=0.3)

Table (5) shows that thesever PAH in pediatric patients (88%) while in adult (68 %),and moderate PAH is (12 %) and (32 %) respectively.

Table 6- The mean of MRAP and MPAP in total cases of patients with PPH.

	Pediatrics	**Adult**	**Total cases**
Mean of MRAP(mmHg)	13.8	7.15	9
Mean of MPAP (mmHg)	75.6	62.8	70.7

Table (6) show that the mean of MRAP; in pediatrics (13.8 mmHg) and in adult (7.15 mmHg) while mean of MPAP is (75.6 mmHg) and (62.8 mmHg) respectively.

Fate of patient:that only 6 cases had known fate: 2cases died (one is pediatric patient and other is adult patient).One case get pregnancy.

Discussion:1- In this study that included 31 patients; 9 (31%) of them were pediatric cases(below 18 years) and 20(69%) were adult cases(more than 18 years); one case (3.4%)was 68 year old this not goes with (8%) in Rich's study [8].Peak of age: 20-40 year 13 cases (44.8%).Mean age: (26 year) old, and it is comparable with (29year) in Chinese study [16] and (23year) in Bangladesh's study [12] so PPH mean age follow Asian countries.2- Male: Female ratio in general (1:3.14), or in adult (1:3), goes with epidemiology of PPH (1:2-4:)[7].In pediatric male:female ratio (1:3.5), not goes with equal

ratio in Pietra`s study [1].3- Sixty nine percent of patients (no. =20) had history of one admission only, and this more in adult patients no. =14(70%) than pediatric patients No. =6(67%). First admission is for doing diagnostic cardiac catheterization, while second and third is for therapeutic purposes. 4-Duration of symptoms before catheterization (<1month, <1year and >1year) in pediatrics (2cases, 2cases, 2cases) and in adult (6cases, 4cases, 3cases) respectively, so its shorter in general (pediatric and adult cases), and more earlier presentation in adult (mostly less than one month duration), this not goes with Davinder`s study [9].5-The signs and symptoms: in adult cases were(exertional dyspnea 77%, chest pain 55% and fatigability 44%) it is approximated to Bangladesh's study (exertional dyspnea 77 %) [12].In contrast to the pediatric symptoms (bluish skin discoloration 67%, fatigability 50% and exertional dyspnea 33%).The signs in pediatric cases were; loud second heart sound(37.5%)and murmur(37.5%)while in the adult cases; murmur(53%),loud second heart sound(33%).6- The echocardiographic findings: it is approximated to Bossone'sstudy[17](in Michigan 1999):(right atrial dilatation,right ventricle dilatation,right ventricle hypertrophy,left ventricle dysfunction, pericardial effusion ,patent foramen ovale and pulmonary incombitance) are (89%,93%,33%,3%,11%,25%,and37%) respectively while in Bossone'sstudy[17] they are(92%,98%,43%,zero%,15%,24%,and 31%) respectively.7- The diagnosis of PPHby exclusion of secondary cases of PAH in (77%) of adult cases and it also used in pediatric cases (37%) and other cases were diagnosed by normal PCWP (63%) may be explained by different practice between adult and pediatrics.8-The mean of MRAP: in pediatrics (13.8mmHg), this goes with (12±6 mmHg) in Chinese study [16], while in adult cases it is not goes with this study [16]. The mean of MPAP: pediatrics (75.6mmHg) and in adult cases(62.8mmHg),the adult cases more approximated to Chinese study [16] (64±15 mmHg) than pediatric cases. The higher MRAP and MPAP in pediatric cases than adult cases, may be explained by delayed diagnosis due to non specific symptoms in pediatric cases.9-Only 6 cases with available data: 2cases died, one case get pregnancy may be because poor medical education or family desire to get a child.

Conclusions1-The pediatric PPH cases tend to present earlier than adult cases.2- The female cases present more common than the male cases.3- The shorter duration of symptoms to establish diagnosis by diagnostic catheterization in total cases, and it is shorter in adult cases.

4-The most common symptoms in pediatric cases (bluish skin discoloration, fatigability and exertional dyspnea), while they were in adult cases (exertional dyspnea, chest pain and fatigability). 5- The most common signs in pediatric cases were(loud second heart sound and murmur), while they were in adult (murmur and loud second heart sound).6-The loud second heart sound is important physical examination especially in patients who presented with dyspnea on exertion.7-The echocardiography is essential non invasive tool in diagnosis PPH cases, although echocardiography is not 100% sensitive for PPH diagnosis.8-The catheterization approach to reach definite diagnosis in the pediatric cases (by normal PCWP with PAH 63%, and by exclusion secondary causes of PAH 37%), while in the adult cases (by exclusion

secondary causes of PAH 77%, and normal PCWP with PAH 23%).9-The pediatric cases -in catheterization-tend to present with higher PAH than adult.10- The catheterization is essential to confirm diagnosis and to exclude secondary PAH cases.11-The pregnancy is still wanted by certain families.

Recommendations: 1-The atrial septal defect-sinus venosus type- should be considered in exclusion of secondary causes of PAH in addition to left to right shunt defects.2-The familial cases of PPH need more detailed investigations especially genetic analysis.3-The loud second heart sound must be kept in mind as important clue for PPH, especially if associated with dyspnea on exertion. 4-The pregnancy is still wanted by certain families, that necessitate more counseling to the patients and their families regarding risk of pregnancy.

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دراسة تقييم ارتفاع ضغط الشريان الرئوي ألأولي ، بواسطة العلامات السريرية، وفحص الايكو للقلب والقسطرة التشخيصية

د. طلعت علي الجراح* ، د. عبد الهادي حميد الكعبي ** ، د. جاسم ناصر الخالدي*

الخلاصة

دراسة استرجاعية لـ(٣١) مريض تم تشخيصهم(ارتفاع ضغط الشريان الرئوي الأولي) في مستشفى ابن البيطار لجراحة القلب، في الفترة من تموز ١٩٩٩ الى نيسان ٢٠٠٧.وشملت كل حالة شخصت(ارتفاع ضغط الشريان الرئوي الأولي) سريريا وبواسطة الايكو وتأكيده بالقسطرة القلبية التشخيصية، مستثنية: ارتفاع ضغط الشريان الرئوي الثانوي والأولي الذي لم يثبت قسطارياً ،مستثنيا حالتان(الأولى ناسور بين الشريانين الابهر والرئوي مع متلازمة أيزنمنكرز والثانية عدم كفاءة الصمام الاكليلي).البيانات التي جمعت من سجلات المرضى والقسطرة هي(العمر، نوع الجنس ، مدة الأعراض قبل التوصل الى التشخيص، عدد مرات دخول المستشفى ، علامات وأعراض المرض، وعلامات فحص الايكو)،معتبراً الفئة العمرية (للأطفال≥ ١٨ سنة والكبار> ١٨ سنة)، مع

بيانات القسطرة: طريقة التوصل إلى التشخيص النهائي في القسطرة ، وشدة ارتفاع ضغط الشريان الرئوي ومعدل (معدل ضغط الأذين الأيمن والشريان الرئوي) أيضاً معدلات المراضة والوفيات .تمت مقارنة هذه الدراسة مع اربع دراسات .الدراسة بينت ان الأطفال لديهم أعراض مبكرة، عدد الإناث اكثر من عدد الذكور، مدة الأعراض قبل إجراء القسطرة التشخيصية هي أقصر من المعدل العام للمرض، وهي أقصر في حالة البالغين. الأعراض الأكثر شيوعا في الأطفال (الازرقاق، قابلية التعب، وضيق التنفس نتيجة الجهد) ،أما في الكبار(ضيق التنفس نتيجة الجهد، ألم الصدر وقابلية التعب).العلامات الأكثر شيوعا في الاطفال(ارتفاع الصوت الثاني للقلب وطنين القلب)أما في الكبار(طنين القلب، وارتفاع الصوت الثاني للقلب).طريقة التشخيص النهائي بالقسطرة: معظم حالات الأطفال شخصت بواسطة(كون الضغط الرئوي الودجي طبيعي)بينما معظم حالات الكبار شخصت(باستثناء الأسباب الثانوية). توصي الدراسة : بعدم نسيان الفتحة بين الأذينين–النوع الوعائي من قائمة الأسباب الثانوية للمرض، الحالات العائلية تحتاج التحاليل الجينية لتأكيدها، التركيز على ارتفاع الصوت الثاني للقلب وخصوصاً المرتبط بضيق التنفس نتيجة الجهد، والحمل لا يزال مرغوباً به عند بعض الأسر مما يجعل تقديم المشورة للمرضى وأسرهم بشأن خطر الحمل على المريضة الحامل هو شيء أساسي.

*** مركز الناصرية للقلب / قسم تشوهات القلب الولادية.**

**** مركز ابن البيطار لجراحة القلب /قسم تشوهات القلب الولادية.**